

3 Splice

Definition

One edge of the splicing reaction.

► Alternative Splicing and Glial Maturation

5 Untranslated Region (5 UTR)

Definition

The 5' region of the mRNA that is not translated into protein. It extends from the transcription start site to the translation ATG start site, and contains regulatory sequences that control mRNA stability and translation efficiency.

14-3-3

Definition

A large family of acidic adaptor proteins of ~30 kDa that mainly (but not solely) interact with phosphoserine or -threonine sites on target proteins to facilitate their activity. 14-3-3 proteins have 9–10 alpha helices, generally form homo- or heterodimers, and contain a number of common modification sites (e.g. phosphorylation, divalent cation binding, and so forth) to regulate their activities, interactions, and localizations.

► Synaptic Proteins and Regulated Exocytosis

65-kDa Synaptic Vesicle Protein

► Calcium Binding Proteins

2074v Alpha1-Beta1 and Alpha6-Beta1-Integrin

Definition

Integrins are a family of alpha-beta-heterodimers, comprising of different beta chains that associate with different alpha chains. Integrins primarily mediate cell adhesion and recognize a variety of ligands including extracellular matrix proteins, cell surface proteins and plasma proteins.

A1-A7 Cell Groups (Noradrenergic Cell Groups)

Definition

A1-A7 is the original designation for separate catecholamine cell groups located in the brainstem by the use of fluorescent histochemical methods. The numbering began in the medulla and continued into the forebrain. Groups A1-A7 are located only in the medulla, and are noradrenergic.

► Cellulae noradrenergicae/A1 – A7

A8-A17 Cell Groups (Dopaminergic Cell Groups)

Definition

A1-A17 is the original designation for separate catecholamine cell groups located in the brain by the use of fluorescent histochemical methods. The numbering began in the medulla and continued into the forebrain. Groups A8-A16 are dopaminergic, and reside primarily in the midbrain and hypothalamus. Another dopaminergic cell type, A17, appears in the retina.

Abducens Nucleus

Definition

A nucleus which contains both motoneurons and interneurons. The motoneurons send direct projections to the lateral rectus muscles. The interneurons send projections via the medial longitudinal fasciculus to the contralateral medial rectus motoneurons neurons.

A δ , C-Fibers

Definition

Small-diameter myelinated (conduction velocity 2–30 m/s, diameter below $\leq 4 \mu\text{m}$) or unmyelinated (conduction velocity $\geq 2 \text{ m/s}$, diameter $\geq 1-2 \mu\text{m}$) afferent nerve fibers.

► Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Abducens Internuclear Neuron

Definition

Neurons located within the abducens nucleus which project to the contralateral medial rectus motoneurons to produce conjugate eye movements.

► Accommodation–vergence Interactions
► Near Response Neuron
► Saccade-Vergence Interactions

Abducens Nerve (VI)

Synonyms

► N. abducens (N. VI); ► Abducent Nerve (VI)

Definition

Abducens nerve (VI) has a purely motor function and innervates the lateral rectus muscle of the eyeball, generating an abduction movement of the eyeball (hence the name) Nucleus: nucleus of abducens nerve.

Skull: superior orbital fissure.

Damage to the nerve causes inversion of the ipsilateral eyeball towards the nose. This produces diplopia (double vision), increasingly so the more the two visual axes deviate from each other. Looking in the direction of the respective eye reduces the severity of the diplopia.

► Nerves

Absence Epilepsy

Definition

Absence (petit mal) seizures are a group of epileptic syndromes typically starting in childhood or adolescence and characterized by a sudden brief lack of attention (indicated by a stare or cessation of behavior) and mild automatic movements (fluttering of eyelids or facial twitches) for some seconds to minutes. The ►electroencephalogram shows typical three-per-second spikes and waves. Absence ►epilepsies are generalized, i.e. the whole ►neocortex shifts into a state of sleep-like oscillations.

► Electroencephalography

Absolute Temperature

Definition

A (positive) temperature scale postulated by the second law of thermodynamics. It is physically related to the laws of ideal gases.

► Mechanics

Absolute Threshold

Definition

The lowest intensity of sensory stimulation that can be detected.

- Sensory Systems

Abstract Entity

Definition

Something that exists but is not spatiotemporally located, e.g. universals (whiteness, horsemanship), numbers or states of affairs.

- Possible World
- Property

Absolute Threshold in Acoustics

Definition

This characterizes the lowest level of sound that a listener can reliably detect and is sometimes referred to as threshold of audibility. The units are typically reported in dB sound pressure level (SPL).

- Psychoacoustics

Abundance of Degrees of Freedom

Definition

An apparent excess of elemental variables (cf. redundancy); the term assumes that elemental variables (degrees-of-freedom) are not eliminated in voluntary movements, but they are all used to stabilize important task-related performance variables (principle of abundance).

- Coordination
- Redundancy

Absorption (Sound Absorption)

Definition

Change in sound energy into some other form, usually heat, in passing through a medium or striking a surface.

- Acoustics

Abventricular Division

Definition

Any cell divisions that occur outside the ventricular and subventricular zones.

Abstinence Syndrome

Definition

The abstinence syndrome (synonym: withdrawal symptom) is observed after withdrawal of a drug to which a person is addicted. For example, the abstinence syndrome after alcohol withdrawal is characterized by

- tremor, nausea, tachycardia, sweating and sometimes hallucinations.

ACC

Definition

Anterior cingulate cortex.

Acceleration

Definition

The time-derivative of the velocity vector of a specific particle. For a material body, at each instant of time there exists an acceleration field, namely an acceleration vector assigned to each particle of the body.

- Mechanics
- Measurement Techniques

Definition

The accessory nucleus (Edinger-Westphal) is the parasympathetic nuclear component of the oculomotor nucleus.

It contains the somas of the preganglionic parasympathetic fibers and innervates the sphincter muscle of pupil as well as the ciliary muscle. It receives its afferents from the pretectal area of the ipsi- and contralateral side. Its efferents course in the ipsilateral oculomotor nerve to the second neuron in the ciliary ganglion.

- Mesencephalon

Accessory Nerve (XI)

Synonyms

- N. accessorius (N.XI)

Definition

The accessory nerve has two parts:

- Accessory nerve (XI), cranial roots: these fibers arise from nucleus ambiguus and innervate the pharynx and larynx muscles and course together with the vagus nerve (X). Skull: Foramen jugulare.
- Accessory nerve (XI), spinal root: it arises from a nuclear column in the cervical cord (spinal root nucleus of accessory nerve) and innervate the sternocleidomastoid muscle and the trapezius muscle.

Skull: Foramen magnum.

Dysfunction of the accessory nerve (XI) results in accessory paralysis rendering it more difficult to lift the arm above shoulder level (trapezius muscle), and turning the head to the unimpaired side is possible only after having successfully contended with resistance (sternocleidomastoid muscle).

- Nerves

Accessory Nucleus of Oculomotor Nerve

Synonyms

- Accessorius n. Oculomotorii

Accessory Neuromast

Definition

Supernumerary neuromasts found only in teleosts. Most likely sensitive to fluid velocity and may mediate rheotaxis in teleosts.

- Evolution of the Mechanosensory and Electrosensory Lateral Line Systems

Accessory Olfactory Bulb

Definition

Specialized region adjacent to the dorsocaudal main olfactory bulb receiving input from the vomeronasal organ. Axons of vomeronasal sensory neurons are bundled in the vomeronasal nerve and terminate in accessory olfactory bulb glomeruli where they form synapses with the dendrites of mitral cells, the first-order relay neurons in the accessory olfactory system.

Axons from vomeronasal sensory neurons expressing the same vomeronasal receptor converge onto a small number of glomeruli in the accessory olfactory bulb.

- Accessory Olfactory System
- Evolution of Olfactory and Vomeronasal Systems
- Vomeronasal Organ (Jacobson's Organ)

Accessory Olfactory System

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Synonyms

Vomeronasal system; Vomeronasal pathway

Definition

Second olfactory pathway found in addition to the ►main olfactory system in terrestrial vertebrates. Initiating in the neuroepithelium of the vomeronasal organ, the ►accessory olfactory system is specialized in the detection of pheromones. The accessory olfactory system converges and synergizes with the main olfactory system to control behaviors and hormonal changes triggered by chemosensory cues.

Characteristics

Vomeronasal Organ

In addition to the main ►olfactory epithelium (OE), a second chemoreceptive structure can be found at the base of the nasal septum in most terrestrial vertebrates. This structure is called ►vomeronasal (or Jacobson's) ►organ (VNO) and is specialized in the detection of ►pheromones [1]. Pheromones are chemical cues that are released by animals and act on members of the same species to regulate populations of animals and their social interactions by eliciting stereotyped behaviors and neuroendocrine alterations.

Pheromonal effects in mammals range from intermale aggression to reproductive behaviors and endocrine changes [1]. In rodents, pheromones can influence the onset of puberty as well as the length of the estrus cycle in females, and cause a surge in serum testosterone levels in males. In the ►Bruce effect, implantation failure results from exposure of a female mouse to the urine of a male genetically different from the inseminating male, coupling a pheromone effect with the detection of "individuality cues." Male pheromones can also stimulate female courtship behaviors, as well as receptive posturing (lordosis). Vice versa, female pheromones can act on males to stimulate mounting behavior, increased intromission attempts, and ultrasonic vocalizations associated with courtship. Experimental ablation of the VNO has shown that it contributes to most if not all of these pheromone effects [1].

Due to advances in molecular biology and genetic engineering of mice, the molecular architecture of the mouse VNO in particular has emerged in great detail [2]. The mouse VNO is a bilateral tubular structure contained in a cartilaginous capsule, which is connected to

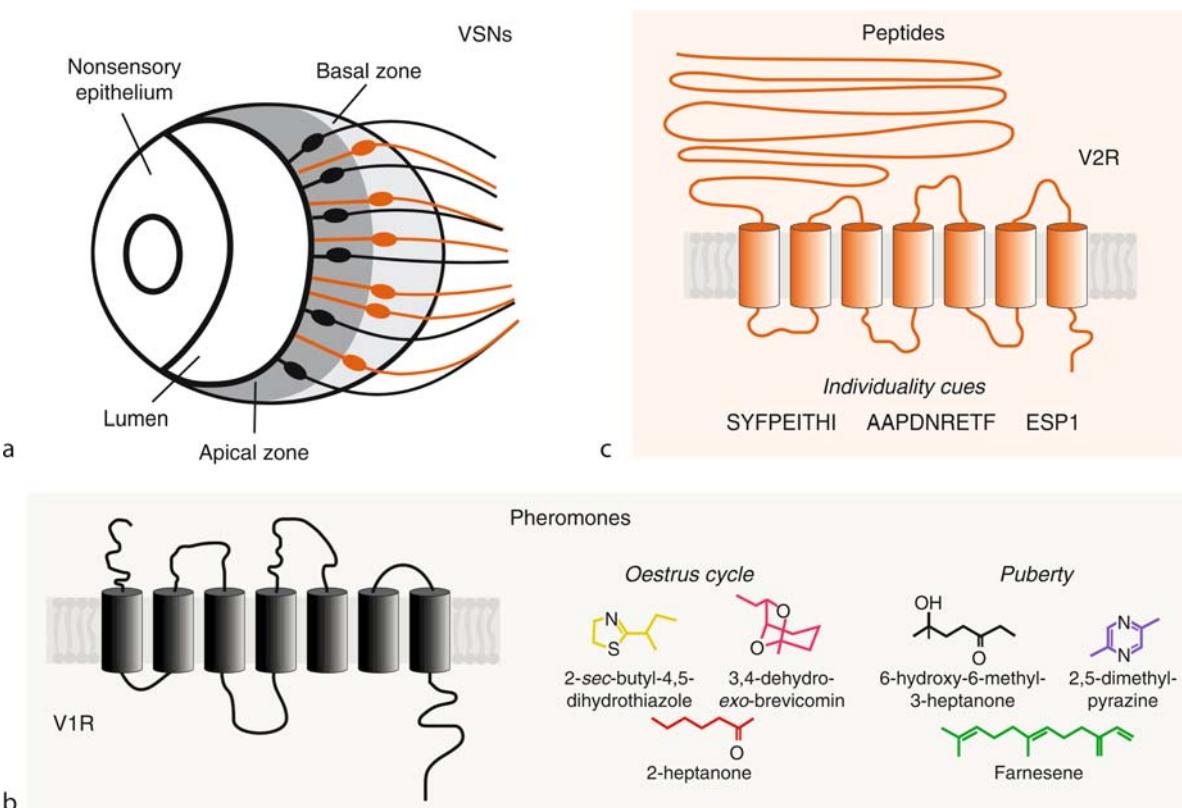
the nasal cavity via a narrow duct [1] (Figs. 1a and 2b). Stimulus access to the VNO depends on a vascular pumping mechanism that is activated in situations of novelty.

The VNO contains two populations of bipolar ►vomeronasal sensory neurons (►VSNs), which appear to be specialized in responding to different types of ►ligands (Fig. 1) [2]. Each VSN expresses members of two large families of ►vomeronasal receptors (VRs), the V1Rs and V2Rs (Figs. 1b and c). VRs are seven-transmembrane-domain ►G-protein-coupled receptors (►GPCRs) and members of each family are diverse in amino acid sequence, suggesting that they may recognize a variety of different sensory ligands [3]. It appears that each VSN may express only one V1R or V2R gene and that ~500–1000 VSNs express the same VR [2].

Expression of V1Rs and V2Rs is anatomically confined to specific zones in the VNO ►neuroepithelium (Fig. 1a). Members of the V1R family are exclusively expressed by VSNs located in the apical zone (Figs. 1a and b) and appear to be specialized in the detection of pheromones [4]. Each of the few mouse pheromones identified so far (Fig. 1b) is detected with high specificity by a unique small subset of VSNs in the apical V1R positive zone (Figs. 3a and b), suggesting that VSNs are very narrowly tuned. However, it is not known whether a given pheromone is recognized by one or multiple VRs, and only one VR-ligand pair has been identified so far [2]. A mouse line lacking a cluster of V1R genes has clearly established their contribution in the detection of some pheromones [5].

In contrast, members of the V2R family are specifically expressed by VSNs located in the basal zone of the epithelium and appear to be specialized in the detection of individuality cues such as peptides (Figs. 1c and 3d, e) [2]. A small number of VSNs respond to two different ►major histocompatibility complex (MHC) class I peptides [6] as well as to a sex-specific peptide secreted from exocrine glands [2] (Figs. 1c and 3e) and all of them are located in the basal V2R positive zone (Fig. 3d). MHC class I peptides are fragments of intracellular proteins which are presented on the cell surface by MHC class I molecules. This process is called ►antigen presentation and enables cytotoxic T cells to identify and selectively eliminate those cells that are synthesizing foreign or abnormal proteins. MHC-peptide complexes can be shed from the cell surface and their fragments appear in urine and other body fluids, which can get access to the VNO [6]. It has been shown, that MHC peptides can function as individuality signals during social recognition offering a molecular basis to explain the pregnancy block in the Bruce effect [6].

Chemosensory signal transduction in VSNs is distinct from that in ►olfactory sensory neurons



Accessory Olfactory System. Figure 1 Molecular architecture of the vomeronasal organ. (a) Schematic representation of a rodent vomeronasal organ (coronal view). Vomeronasal receptors of the V1R family (Fig. 1b) are expressed by sensory neurons in the apical zone (black) whereas V2R family members (Fig. 1c) are expressed by sensory neurons in the basal zone of the epithelium (orange). (b) V1Rs are seven-transmembrane-domain GPCRs that appear to be specialized in detecting pheromones (pheromone colors correspond to Fig. 3a and b). (c) V2R GPCRs contain a long N-terminal extracellular domain and appear to be specialized in the detection of peptides such as the mouse strain specific MHC class I peptides SYFPEITHI and AAPDNRETF (see Figs. 3d and e) and exocrine-gland secreting peptide 1 (ESP1).

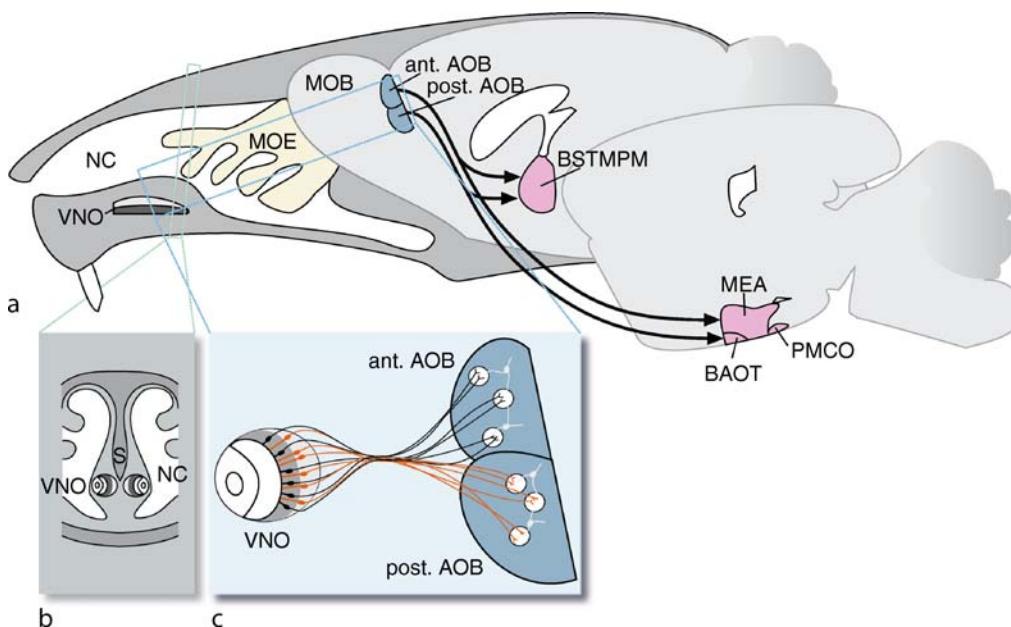
(►OSNs), but poorly understood. V1R and V2R positive VSNS express different G proteins, $G_{\alpha i2}$ and $G_{\alpha o}$, respectively, however a direct role in VSN ►sensory transduction still needs to be demonstrated. Signal transduction in VSNS involves a diacylglycerol-activated cation channel, which partially depends on TRPC2, a VNO-specific member of the Trp family of ►calcium channels [7].

From Vomeronasal Organ to Accessory Olfactory Bulb: Segregation and Convergence

Each VSN projects one single ►axon to the ►accessory olfactory bulb (►AOB), which is a specialized region adjacent to the dorsocaudal main ►olfactory bulb (MOB). VSN axons are bundled in the vomeronasal nerve and terminate in anatomically discrete synaptic units called ►glomeruli where they form synapses with the ►dendrites of AOB ►mitral cells, the first-order relay neurons in the accessory olfactory system [1].

Neurons that express V1R/ $G_{\alpha i2}$ or V2R/ $G_{\alpha o}$ synapse in the anterior or posterior part of the AOB, respectively, maintaining the anatomical segregation observed in the VNO [1] (Fig. 2c). This raises the possibility that signals generated by the V1R and V2R families are eventually targeted to brain regions that mediate different behavioral and physiological effects.

Axons from ~500–1000 VSNS expressing the same VR converge onto a small number (6–30) of glomeruli in the AOB [7] (Fig. 2c). This wiring pattern is similar but not identical compared to that in the MOB where axons of olfactory sensory neurons (OSNs) expressing the same ►odorant receptor (OR) converge onto 1 or 2 glomeruli at two specific locations in the MOB [3]. AOB mitral cells can have from one up to six dendrites contacting multiple glomeruli innervated by neurons expressing the same V1R or V2R [2]. Therefore convergence in the AOB is achieved by dendritic convergence of mitral cells.



Accessory Olfactory System. Figure 2 The rodent accessory olfactory system. (a) Schematic representation of a rodent nasal cavity and brain (lateral view). AOB mitral cells project to vomeronasal and extended amygdala. For abbreviations, see text. (b) Schematic representation of a coronal section through a rodent nose. The VNO is a bilateral tubular structure located at the base of the nasal septum. (c) VSNs that express the same V1R or V2R converge on a small number of glomeruli in the accessory olfactory bulb (AOB). The apical layer of the epithelium projects to the anterior part of the AOB whereas the basal layer projects to the posterior part. Adapted from [2].

Accessory Olfactory System Signaling Beyond the Bulb

Sensory signals generated in the VNO follow neural pathways separate from those that carry odor signals from the OE [1]. OE signals are transmitted to the MOB, and then relayed through the primary ►olfactory cortex to higher cortical areas involved in conscious ►perception as well as ►limbic areas controlling basic drives and ►emotions [3]. In contrast, VNO signals are relayed through the AOB to regions of the ►amygdala and ►hypothalamus implicated in behavioral and physiological effects of pheromones. Although the general projections of the accessory olfactory system are known, the individual cells and neural circuits that mediate pheromonal effects on behavior and physiology have not been identified. Only recently some new techniques using genetically engineered mouse models have started to reveal individual neurons in the hypothalamus that appear to integrate ►chemosensory information.

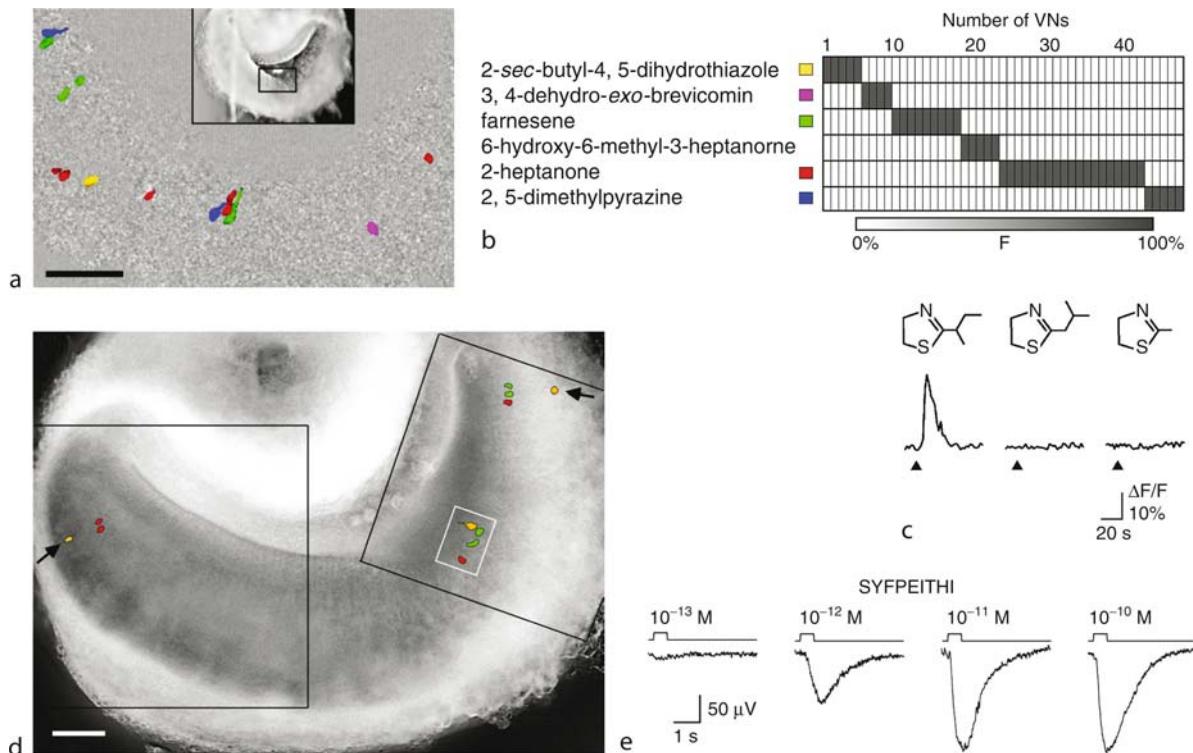
How are signals generated by VSNs relayed beyond the bulb? AOB mitral cells project to the medial amygdaloid nucleus (MEA) and posteromedial cortical amygdaloid area (PMCO; which taken together are referred to as the vomeronasal amygdala), as well as to the bed nucleus of the accessory olfactory tract (BAOT) and the posteromedial bed nucleus of the stria terminalis (BSTMPM, also called “extended amygdala”) (Fig. 2a).

All of these connections are bidirectional suggesting ►feedback loops [2].

It is not known whether the V1R/V2R segregation observed in VNO and AOB is preserved in connections beyond the bulb. Although differential projections from the distinct AOB zones to the vomeronasal amygdala were observed in some species, this segregation could not be confirmed in the mouse [1]. Several studies of neural activation in rodents, however, suggest some functional segregation within the vomeronasal amygdala itself [1].

Information from the vomeronasal amygdala to the medial hypothalamus is sent both by direct projections and via a relay in the BSTMPM [1]. Therefore the BSTMPM receives vomeronasal information both by direct innervation from AOB ►mitral cells and via a relay in the vomeronasal amygdala, suggesting a prominent role in the integration of accessory olfactory signaling [2]. It is not known whether accessory olfactory signaling involving a particular chemosensory stimulus can bypass any of these relay nodes. The BSTMPM is also a prominent part of a sexually dimorphic forebrain circuit including the MEA and several nuclei in the hypothalamus [2].

It is not yet known if signals relayed by AOB mitral cells representing two different VRs converge onto the same neuron(s) in the vomeronasal amygdala or



Accessory Olfactory System. Figure 3 Chemosensitivity of vomeronasal sensory neurons. (a) VSN activation map produced by successive stimulation with each of the six ligands listed in B (each at 10^{-6} M). Each ligand activated a unique, nonoverlapping subset of VSNs. Inset, low-power transmitted light image of the VNO slice; black box, imaged area. Scale bar, 50 μm . (b) Summary of the tuning profiles of 47 VSNs responding to the six ligands. For each VSN, the magnitude of the Ca^{2+} response was plotted as a percentage of the maximal response to a given chemical. Dark grey, 100%; white 0%. Without exception, VSNs responded to only one of the pheromones tested. Thus, computed tuning curves were identical for all VSNs that responded to the same pheromone. (c) Two structural analogues of 2-sec-butyl-4,5-dihydrothiazole, isobutyl-4,5-dihydrothiazole and methyl-4,5-dihydrothiazole, were unable to evoke a Ca^{2+} response in VSNs (each tested at 10^{-6} M). Adapted from [4]. (d) Spatial representation of peptide-induced activity in VNO sensory epithelium using an acute slice preparation. Shown are reconstructed VSN response maps for the MHC class I ligands AAPDNRETF (10^{-12} M, green) and SYFPEITHI (10^{-12} M, red). Cells responding to both peptides are shown in yellow. Black arrows indicate peptide-sensitive neurons that are localized at the base of the epithelium. Black boxes: imaged areas. Scale bar, 100 μm . (e) Ultrasensitive detection of the MHC class I ligand SYFPEITHI by VSNs. Traces are summed field potentials evoked by brief pulses of increasing concentrations of ligand. Adapted from [6].

BSTMPM or if a stereotyped map represents vomeronasal input in the amygdala.

Ultimately, VNO signals are relayed to specific neurons in the hypothalamus, which initiate and control the behavioral and hormonal responses triggered by pheromones. At the center of hypothalamic control of reproduction are ►GnRH neurons, which regulate the reproductive endocrine status in mammals. Recent studies using ►transneuronal tracers have shown, that GnRH neurons appear to integrate both vomeronasal [8] and main olfactory signals [8,9]. In addition, these studies have revealed feedback loops between the neuroendocrine hypothalamus and both the main and accessory olfactory systems [8], suggesting that the

animal's neuroendocrine status might modulate its susceptibility to chemosensory cues.

Multiple Level Convergence and Synergism of the Main and Accessory Olfactory Systems

Because the main and accessory olfactory systems consist of anatomically separated chemosensory epithelia (Fig. 2a) with different molecular profiles and parallel largely non-overlapping projections, strict functional dichotomy was postulated with each olfactory system specialized in distinct behavioral domains [1]. However, experimental evidence is accumulating that hints at complementary roles of the two olfactory systems and it is important to point out that accessory

olfactory signaling is not functionally equivalent to pheromone signaling [2].

Several experiments across species have shown that pheromone signals are not exclusively perceived by the VNO, but can also be processed by the main olfactory system [2]. Consistent with this, 2-heptanone (Fig. 1b), the only ligand matched to a particular VR (V1Rb2) so far, is also recognized by an olfactory receptor (mOR912–93; [2]). Vive versa, some odorants can also stimulate VSNs [2]. In addition, both the main and the accessory olfactory bulbs are stimulated by both pheromones and general odorants in mice [2]. Furthermore, the two MHC class I peptides recognized by VSNs were recently shown to stimulate OSNs at equally low concentrations, consistent with numerous studies demonstrating participation of the main olfactory system in MHC-related behaviors [2]). Thus, both OE and VNO can contribute to olfactory recognition of pheromones, odorants and peptides.

Convergence of the main and accessory olfactory systems could potentially also occur at different levels in the brain [1,2]. For example, the MEA in hamster has been shown to share extensive bidirectional connections with the cortical nucleus of the amygdala (ACO), which receives information from the MOB but not AOB [1]. In addition, convergence could occur in the hypothalamus, for example in GnRH neurons, which apparently receive information from both olfactory systems [8].

Potential synergism of both olfactory systems is evident in the analysis of reproductive behavior in hamster where complete removal of the olfactory bulbs (bulbectomy) in hamsters completely eliminates mating whereas VNO or OE ablation alone have more subtle effects [1]. Therefore it appears that both olfactory systems can converge and synergize to express reproductive behaviors and hormonal changes triggered by chemosensory cues in rodents.

Do Humans Have a Functional Accessory Olfactory System?

Fueled by significant public interest, pheromonal communication in humans is controversially debated [7]. Both anatomical and molecular evidence clearly speaks against the existence of a functional human accessory olfactory system. Although an embryonic structure resembling a VNO and a fetal AOB have been identified, they degenerate before birth [1]. A ►vomeronasal pit has been described in some adults, however this structure is not connected to the brain. In addition, no AOB has been found in adults. On the molecular level, hallmarks of the rodent accessory olfactory system are missing in humans. The V2R family is not found in the ►human genome, the V1R repertoire is reduced from 150 functional genes in mice to five in humans and the gene encoding the human TRPC2 channel is a ►pseudogene [7].

The apparent absence of a functional accessory olfactory system in humans does however not imply that humans do not have pheromonal communication. Some chemosensory effects like synchronized estrus in women living in close proximity are well documented [7]. Presumably these more subtle pheromonal effects in humans are mediated by the main olfactory epithelium. Consistent with this, a family of putative pheromone receptors expressed in the main olfactory epithelium has recently been identified [10].

►Evolution of Olfactory and Vomeronasal Systems

References

1. Halpern M, Martinez-Marcos A (2003) Structure and function of the vomeronasal system: an update. *Prog Neurobiol* 70:245–318
2. Boehm U (2006) The vomeronasal system in mice: from the nose to the hypothalamus- and back! *Semin Cell Dev Biol* 17:471–479
3. Buck LB (2000) The molecular architecture of odor and pheromone sensing in mammals. *Cell* 100:611–618
4. Leinders-Zufall T, Lane AP, Puche AC, Ma W, Novotny MV, Shipley MT, Zufall F (2000) Ultrasensitive pheromone detection by mammalian vomeronasal neurons. *Nature* 405:792–796
5. Del Punta K, Leinders-Zufall T, Rodriguez I, Jukam D, Wysocki CJ, Ogawa S, Zufall F, Mombaerts P (2002) Deficient pheromone responses in mice lacking a cluster of vomeronasal receptor genes. *Nature* 419:70–74
6. Leinders-Zufall T, Brennan P, Widmayer P, SPC, Maul-Pavicic A, Jager M, Li XH, Breer H, Zufall F, Boehm T (2004) MHC class I peptides as chemosensory signals in the vomeronasal organ. *Science* 306:1033–1037
7. Dulac C, Torello AT (2003) Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nat Rev Neurosci* 4:551–562
8. Boehm U, Zou Z, Buck LB (2005) Feedback loops link odor and pheromone signaling with reproduction. *Cell* 123:683–695
9. Yoon H, Enquist LW, Dulac C (2005) Olfactory inputs to hypothalamic neurons controlling reproduction and fertility. *Cell* 123:669–682
10. Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. *Nature* 42:645–650

Accessory Optic System

Definition

A subcortical visual pathway that is responsible for the analysis of optic flow that results from self-motion.

►Optic Flow

Accessory Subunits of Ion Channels

Definition

Most of the pores forming subunits of ion channels are complexed with additional, accessory subunits that can influence key properties of ion channels, such as trafficking and targeting of ion channels to specific cell membrane components. Accessory subunits can also modulate channel gating, such as the activation or inactivation properties of voltage-gated ion channels.

► [Ion Channels from Development to Disease](#)

Accommodation of the Lens

Definition

Increase in the refractive power of the lens of the eye.

Accommodation–Vergence Interactions

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Definition

In this context, accommodation refers to the change in the refractive power of the crystalline lens of the eye. A unit of refractive power is the Diopter, which is the reciprocal of the focal length measured in meters. Positive accommodation decreases the focal length of the lens, allowing near objects to be seen clearly, while negative accommodation or relaxation of accommodation increases the focal length for viewing more distant objects. Vergence, or vergence angle, refers to the angle between the lines of sight of the two eyes in the horizontal plane. Clinically, vergence angle is usually expressed in terms of prism diopters. A prism diopter is the deviation of light by one cm at a distance of one meter, and is $\sim 0.57^\circ$. Convergence ([►Convergent eye movement](#)) is an increase in vergence angle, and occurs when viewing a near object with both eyes. Divergence ([►Divergent eye movement](#)) is a decrease in vergence angle. Accommodative convergence (AC) is the increase in vergence angle which occurs when the lens

accommodates to view a nearer object. The AC/A ratio is the change in vergence angle for each Diopter of accommodative demand. Convergence accommodation (CA) is the increase in lens accommodation which occurs when the eyes converge. The CA/C ratio is the amount of accommodation (in Diopters) associated with a given change in convergence (usually measured in prism diopters).

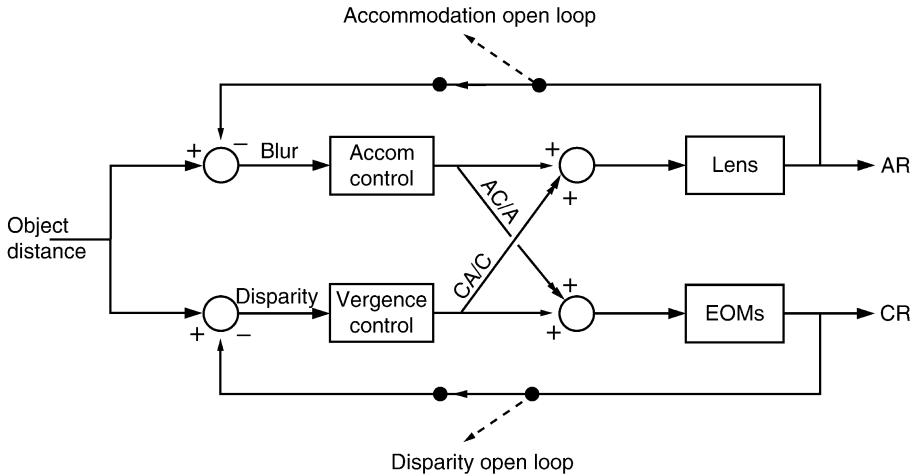
Characteristics

Upstream Events/Conditions

The primary stimulus for [►accommodation of the lens](#) is optical blur caused by a mismatch between the distance to the object of regard and the refractive power of the lens. Since blur decreases the spatial frequencies of the image, any element in the visual system which is tuned to spatial frequency can be used to detect blur. Indeed, many neurons in the visual cortices show such sensitivity. In operation, accommodation is modeled as a negative feedback system (top half of [Fig. 1](#)) the goal of which is to minimize blur [1]. The primary stimulus for horizontal ocular vergence is binocular disparity, which is the difference between the locations of an image on the two retinas. Many neurons in the primary visual cortex, the first point in the geniculo-striate system at which inputs from the two eyes are combined [2], are sensitive to absolute horizontal binocular disparity, and so could provide a useful disparity error signal. Single binocular vision requires that binocular disparity be reduced to a fraction of a degree. Like the accommodative system, the vergence system is modeled as a negative feedback system (bottom half of [Fig. 1](#)). It is important to note that for both the accommodation and vergence systems, the subtraction of the accommodative or vergence response from the demands imposed by the visual stimulus is geometric and not neural.

Interactions Between Systems

The observations that accommodation by itself drives vergence and vergence responses drive accommodation suggest a simple cross linking of these systems, as indicated by the crossed arrows in the [Fig. 1](#). The strengths of these cross-links are given by the AC/A (accommodation to vergence drive) and CA/C (vergence to accommodation drive) ratios. Control system analysis indicates that as long as the product of AC/A and CA/C, measured in equivalent units (Diopters for accommodation and Meter Angles for vergence) is less than unity, the system is stable. Indeed, the accommodative and vergence systems work in a synergistic manner via these cross-links to facilitate responses to changes in the distance of visual objects. Both psychophysical [1] and neurophysiological studies [3] have supported this model.



Accommodation–Vergence Interactions. **Figure 1** Representation of the dual-interaction model of accommodation and vergence. Both the accommodation (upper half of figure) and the disparity vergence (lower half) systems are controlled by negative feedback. The input to both controllers is Object Distance. For the accommodative controller, the error signal is optical blur, arises from the mismatch (difference) between Object Distance and the Accommodation Response (AR). The blur-driven accommodative controller (Accom Control) produces an output proportion to this error to drive the neurons controlling the crystalline lens (Lens) and thus changes the AR. The accommodative system can be made open loop by placing pinholes in the optical path which eliminates blur, regardless of the relationship between the Object Distance and the AR. This is shown schematically by a switch represented by the dashed arrow at top. A similar system is used for the disparity vergence system; except that the error signal for the controller (Vergence Control) is binocular disparity, which is the difference between the vergence demand imposed by Object Distance and the Convergence Response (CR). The output of the vergence controller goes to the extraocular muscles (EOMs) which adjust vergence angle. This feedback loop can be opened (dashed arrow at bottom) by any manipulation which eliminates binocular viewing of the target, such as occluding one eye. The accommodation-vergence interaction is due to cross-links by which some fraction of the output of the accommodative controller is added to output of the vergence controller (accommodative convergence, downward angled arrow), and some fraction of the output of the vergence controller is added to the output of the accommodative controller (convergence accommodation, upward angled arrow). The strengths of these cross-links is assessed by the AC/A and CA/C ratios. In order to measure the AC/A ratio, the disparity feedback system must be open loop, and measurement of the CA/C ratio requires that the accommodative feedback system be open loop.

Although not indicated by the Fig. 1, there is some flexibility associated with these cross-links. For example, if a subject is required to binocularly view a target at a given distance through base-out prisms, a greater demand is placed upon the systems to converge than to accommodate. Subjects have some limited ability to dissociate the convergence and accommodative responses. However, if the convergence demand imposed by the prisms is too great, the subjects will experience blurring of the target, caused by the excessive driving of the accommodative system by the vergence systems via the AC/A cross-link. If the change in vergence demand by the prisms is gradual and takes place over a time course of minutes, prism adaptation may occur. Prism adaptation may be considered as a change in the vergence offset or bias in the relationship between accommodation and vergence [4]. Adaptation with base-out prisms causes the eyes to be more converged for a given level of accommodative demand. Prism adaptation is also called phoria adaptation,

because it is measured as a change in the phoria. There is some evidence for adaptation of accommodation when accommodative and vergence demands are mismatched, but the degree of adaptation appears to be modest.

In addition to the changes in bias or offsets, the AC/A and CA/C ratios can be modified. Prolonged viewing of targets using periscopic spectacles which simulate a larger inter-ocular distance results in an increase in the AC/A ratio and a corresponding decrease in the CA/C ratio [5]. Optical manipulations which effectively decrease the inter-ocular distance decrease the AC/A ratio and increase the CA/C ratio, although the observed changes are more modest. For adults, the inter-ocular distance is constant, and so are the AC/A and CA/C ratios for a given individual, although there are differences in the ratios among people. The capacity to increase the AC/A ratio with increasing inter-ocular separation is probably important during childhood growth.

Downstream Events/Conditions

Although both the vergence and accommodative control systems strive to minimize error, this is rarely realized. Error within the vergence systems is termed binocular disparity. If it is small enough to permit single vision (i.e. less than about 0.25°) this error is termed “fixation disparity.” Larger binocular disparities lead to double vision, or ►diplopia, which generally results in the suppression of one eye’s image by the nervous system. Errors in accommodation seem to be more readily tolerated, and the mismatch between the accommodative demand and the eye’s response is termed “accommodative lag.” With aging, there is a progressive loss of the ability to accommodate (presbyopia), which is believed to be due to the gradual loss of elasticity of the crystalline lens.

Involved Structures

The neuronal circuits for both accommodation and vergence are believed to be located in the midbrain. Although it seems likely that visual cortical inputs provide the sensory inputs to this mechanism, the pathways are not known. Neuronal signals related to accommodation and vergence are found on midbrain near response cells (►Near response neurons). Most near response cells have a firing rate which is proportional to both accommodation and vergence. Many also have a signal related to vergence velocity, and presumably, to accommodation velocity as well. A subset of near response cells has been shown to project to the ►medial rectus subdivisions of the oculomotor nucleus, the site of medial rectus motoneurons, which are needed to generate convergence of the eyes [3]. Near response cells may also project to the Edinger-Westphal nucleus to control accommodation, but this has not been demonstrated. Neurons in the abducens nucleus are also involved in ocular vergence, but neither direct nor indirect projections from near response neurons to the abducens nucleus have been shown. Lens accommodation is effected by the action of the ciliary muscle of the eye, which has both parasympathetic and sympathetic inputs. Parasympathetic input, which appears to be more important for accommodation, is relayed from the midbrain Edinger-Westphal nucleus via the ciliary ganglion.

Methods to Measure This Event/Condition

The most commonly used measure of the interaction between accommodation and vergence is the AC/A ratio. This is measured by first opening the vergence feedback loop (see dashed arrow in lower half of Fig. 1). This is done by dissociating vision in the two eyes, often with a hand-held occluder, so that they do not see the same object at the same time. Typically, a clinician will measure the subject’s phoria while viewing a distant target. The phoria is the deviation of the non-viewing eye from the target. The phoria will

then be re-measured while the subject views a near target. The AC/A is calculated as the ratio of the change in phoria to the change in accommodative demand. A typical AC/A ratio value is 4 prism diopters per Diopter, or about 0.6 Meter Angles (MA) per Diopter. Note that this describes a stimulus AC/A ratio; in that the subject’s accommodative response is not measured. The accommodative response can be measured, but this is rarely done in clinical settings. The CA/C ratio must be determined independently, since it cannot be calculated from the AC/A ratio. To measure the CA/C ratio, it is necessary to open the accommodative feedback loop (dashed arrow on top half of Fig. 1), which can be done by having the subject view a target through optical pinholes. Convergence can be elicited by placing base-out prisms in the optical path as the subject views a target binocularly. The associated change in accommodation, which can be measured using retinoscopy or by means of an optometer, is expressed as a ratio of accommodative change per unit of vergence change. When expressed in equivalent units, the CA/C ratio is usually around 0.7 D/MA. This corresponds to about 0.1 Diopters per prism diopter. Due to the specialized optical equipment needed to measure the CA/C ratio, it is rarely done in clinical settings.

References

1. Hung GD, Semmlow JL (1980) Static behavior of accommodation and vergence: computer simulation of an interactive dual-feedback system IEEE Trans. BME 27:439–447
2. Freeman RD (2004) Binocular interaction in the visual cortex. In: Chalupa LM, Werner JS (eds) The visual neurosciences. MIT, Cambridge, MA, pp 765–778
3. Zhang Y, Mays LE, Gamlin PDR (1992) Characteristics of near response cells projecting to the oculomotor nucleus. J Neurophysiol 67:944–960
4. Henson DB, North R (1980) Adaptation to prism-induced heterophoria. Am J Physiol Opt 57:129–137
5. Miles FA, Judge SJ, Optican LM (1987) Optically induced changes in the couplings between vergence and accommodation. J Neurosci 7:2576–2589

Accumbens Nucleus

Synonyms

►Nucl. Accumbens

Definition

At the site where the corpus striatum borders on the septal nuclei is situated the accumbens nucleus (septal),

which has a structure similar to the corpus striatum, but has unusually intensive fiber connections to the limbic system and hence is viewed as being a link in emotion/motivation and movement.

- Telencephalon

neurons are primarily located in the basal forebrain and brainstem. Acetylcholine acts at nicotinic and muscarinic acetylcholine receptors.

- Acetylcholine Receptors
- Autonomic Ganglia
- Basal Forebrain
- Cholinergic Brainstem
- Neuromuscular Junction

Accuracy Versus Speed Rule

Definition

- Fitts' Law.

- Eye-Hand Coordination

Acetylation of Nucleosomal Histones

- Histone Acetylation in the Developing Central Nervous System

Acetylcholine (ACh)

Definition

Acetylcholine (ACh) is a classical neurotransmitter found both in the central nervous system (CNS) and the peripheral nervous system (PNS). Cells that produce acetylcholine are referred to as cholinergic. Acetylcholine formed the basis for early studies of synaptic transmission which led to the formation of key principles of chemical neurotransmission. The transfer of the acetyl group from acetyl-coenzyme A to choline is a single step process that forms acetylcholine and is dependent on the enzyme choline acetyltransferase (ChAT). Acetylcholine is inactivated by the enzyme acetylcholinesterase, which converts acetylcholine to choline and acetic acid. Choline is transported back into the presynaptic terminal where it is used to synthesize acetylcholine. Acetylcholine is released from both somatic motor nerve terminals (at the neuromuscular junction) and autonomic preganglionic terminals, as well as at synapses in enteric ganglia and some central synapses. In the central nervous system, cholinergic

Acetylcholinesterase

Definition

Enzyme that breaks down acetylcholine at the synapse.

- Evolution of Subpallial Cholinergic Cell Groups

N-acetyl-5-methoxytryptamine

- Melatonin

AchR

Definition

Acetylcholine Receptor.

- Acetylcholine

Achromatopsia

Definition

Color blindness resulting from damage to cortical visual area V4.

- Visual Neuropsychology
- Visual Perception

Acid-Sensing Ion Channels

Definition

Acid-sensing ion channels (ASICs) are members of the epithelial sodium channel (ENaC)/degenerin (DEG) family, characterized by two transmembrane domains and a large cysteine-rich extracellular domain. ASICs are expressed in neurons, and function as extracellular proton-gated cation channels, preferably permeable to Na^+ .

- Taste Bud

Acinopterygians

Definition

The subclass of Osteichthyes, the bony fishes, that comprise the ray-finned fishes. These include five major clades: the cladistians (reedfishes, or bichirs), chondrostean (paddlefishes and sturgeons), ginglymodi (gars), halecomorphi (the single species *Amia calva*, the bowfin), and teleosts (the very large radiation of bony fishes).

- Evolution of Brain: at Invertebrate–vertebrate Transition

Acoustic Labyrinth

- Cochlea

Acoustic Neurinoma

Definition

Tumor arising from the nerve sheath cells. Other terms to describe this entity include acoustic schwannoma, neurilemoma, acoustic neuroma. This tumor arises on the cranial nerve VIII (acoustic). It is presumably formed by Schwann cells (or their progenitors).

Schwannoma arises eccentrically within the nerve, displacing the axons and sparing the nerve. This feature makes nerve-sparing surgery possible in some cases.

Tissue architecture of the tumor is characterized by dense or loose structures named Antoni A or B respectively. Acoustic schwannoma corresponds histologically to WHO grade I. Malignant progression of acoustic schwannoma is extremely rare. Clinical presentation typically includes tinnitus (ringing in the ear) and hearing loss. Magnetic resonance imaging (MRI) is the study of choice for detection of this tumor and usually reveals well-circumscribed, sometimes cystic and enhancing mass. Treatment modalities employed include observation, surgical resection and/or radiotherapy. Bilateral acoustic schwannomas are the hallmark of a neurogenetic disease Neurofibromatosis type 2.

- Gliomas
- Schwann Cell

Acoustic Sensillum

- Invertebrate Ears and Hearing

Acoustic Striae

Definition

Fiber tracts that emerge from the cochlear nucleus containing the axons of neurons projecting to higher auditory centers.

- Cochlear Nucleus

Acousticolateralis Organ

- Electroreceptor Organs

Acousticolateralis System

- Evolution of the Mechanosensory and Electrosensory Lateral Line Systems

Acoustics

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Definition

►Acoustics is the study of ►sound [1,2]. Sound is produced when an object vibrates causing a pressure wave to propagate through a medium (e.g., air) to a receiver.

Characteristics

As acoustics is the study of sound [1,2], it is the study of how objects produce sound through vibration. An object must have mass and inertia in order to vibrate. A spring attached to a weight may serve as a model for a vibrating object, with the weight representing the properties of mass and the spring the properties of inertia. When the weight is pulled away from or pushed past its resting point, the spring will cause the weight to vibrate. A force moves the object and the spring applies a restoring force. These forces can be expressed as the moving force, $F = ma$, and the restoring force, $F = -sx$, where m is mass, s is stiffness, and a and x are acceleration terms. In a frictionless world with no ►resistance, the two forces offset each other when the weight vibrates resulting in $ma + sx = 0$. This equation has as one of its solutions $a(t) = A \sin[(s/m)t + \theta]$, where s , m are defined as above, $a(t)$ is the instantaneous displacement of the weight as a function of time, t is the time in seconds, A is the peak distance that the weight moves, and θ is the ►starting phase (in radians) that describes the position of the start of the vibration relative to the weight's resting position.

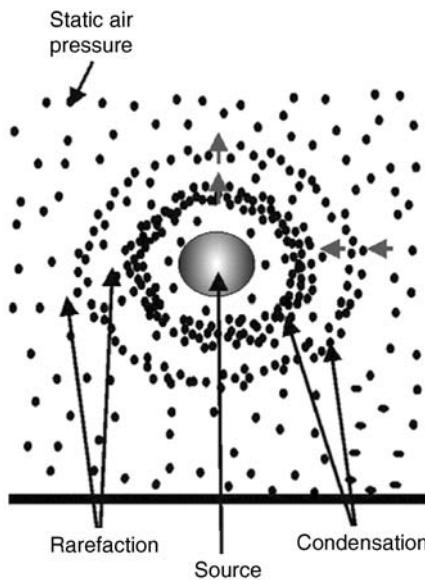
Hence, a sinusoidal (sin) function describes the motion of the free vibration of the weight and spring. The formula $a(t)$ can be rewritten as $a(t) = A \sin(2\pi ft + \theta)$, where A is the peak amplitude, f is ►frequency (for the mass and spring $f = 1/(s/m)$), t is the time, and θ is the starting phase. Such a sinusoidal vibration produces a ►simple or pure-tone sound. The frequency of vibration (f) is expressed in ►Hertz (►Hz), in which "n" Hz means that the object has gone through "n" vibratory ►cycles in one second. When friction is included, the sinusoidal pattern of vibration becomes a damped pattern in which the amplitude of vibration decreases over time, at a rate that is proportional to the amount of resistance.

Vibrating objects then impart their pattern of vibration to the molecules within a medium (e.g., air). As air is the medium for sound transmission for most animals, we will consider the transmission of sound through air. Air consists of molecules in constant random motion. When

a vibrating object moves in one direction, air molecules are pushed in the same direction (assuming no frictional forces). The molecules next to the vibrating object are compressed together as the object moves outward from its resting state, creating an area of greater air-molecule density. As the density of air molecules increases, the pressure increases creating an area of ►condensation. As the vibrating object moves in the opposite direction (back toward its resting state), the air molecules fill the space vacated by the vibrating object moving in the opposite direction. As the vibrating object moves back past its resting state, an even larger vacated area is generated for the air molecules to fill. Now the density of air molecules has decreased, lowering the pressure, and generating an area of ►rarefaction.

The mere presence of molecules in air creates ►static air pressure, which is proportional to the density of molecules. The changes in pressure due to the vibrating object are changes in this existing static air pressure. Imagine a photograph of the air molecules taken when the object was vibrating, freezing the density pattern at a moment in time (Fig. 1).

The molecules appear to cluster at some points in space (condensation) and spread farther apart at other places (rarefaction). The molecular motion at a condensation tends to be away from the source, and the motion at a rarefaction tends to be toward the source. As an object vibrates, it causes a sound pressure wave with alternating areas of condensation and rarefactions to radiate out from the source in a spherical



Acoustics. Figure 1 A depiction of a sound wave and areas of condensation and rarefaction of increased and decreased pressure (above and below the static air pressure) as the wave motion forces the air molecules to move away from and toward the vibrating source.

manner. The distance between successive condensations or rarefactions is the ►wavelength (λ) of sound; $\lambda = c/f$, where c is the speed of sound in meters/second, f is the frequency, and λ is expressed in units of distance (e.g., meters). The speed of sound in air is approximately 345 m s^{-1} , although it can vary as a function of temperature, density, and humidity.

A propagating wave produces instantaneous changes in pressure $p(t) = mv / tAr$, where m is the mass, v is the velocity, t is the time, and Ar is the area. The root-mean-square (rms) pressure (p) describes an average pressure. Since force, $F = mv / t$, then, $p = F / Ar$. As a vibrating object exerts a force, this means that the force moves an object through some distance. This is a definition of work. Energy (E) is the ability to do work. Power (P) is the rate at which work is done. Therefore $P = E/T$, where T is the time in seconds over which the work is done. ►Sound intensity (►I) is a measure of sound power, $I = p^2/p_0c$, p is the rms pressure, p_0 is the density of the medium, and c is the speed of sound in the medium. Sound pressure is usually expressed in units of micropascal (μPa) and sound intensity in units of watt/cm².

Given the very large range over which sound intensity can vary (especially in terms of the range for hearing), a logarithmic relationship is often used to measure sound ►level in terms of sound intensity and sound pressure. The ratio of two sound intensities (I_1 and I_2) expressed in ►decibels (►dB) is $10 \log I_1 / I_2$. As $I = p^2/p_0c$, then the formula for decibels in terms of pressure (p) is decibel (dB) = $10 \log I_1 / I_2 = 20 \log (p_1 / p_2)$. The decibel (dB), therefore, is 10 times the log of the ratio of two intensities, two powers, or two energies and 20 times the log of the ratio of two pressures. Two conventions are commonly used to define decibels in relative terms. Experiments conducted in the 1930s determined that a pressure of $20 \mu\text{Pa}$ was the smallest sound pressure required for the average young adult to detect the presence of a mid-frequency pure tone. When decibels are expressed relative to $20 \mu\text{Pa}$ (i.e., $p_2 = 20 \mu\text{Pa}$), they are expressed as decibels of ►Sound Pressure Level (dB SPL), and they indicate the decibel level relative to the softest sound that humans can detect. ►Sensation Level (dB SL) is referenced to the least intense sound a particular subject can detect in a particular experimental situation (for example, at a particular frequency). Decibels of ►Hearing Loss (dB HL) is a measure like dB SL, in that dB HL is expressed relative to standardized levels required for listeners with normal hearing to detect tones of different frequencies.

The sound wave propagates out from the source in a spherical manner. Since sound intensity is inversely proportional to area, and the area of a sphere is proportional to its radius squared, sound intensity decreases as function of the square of the distance from

the source. This inverse relationship between sound intensity and distance is referred to as the ►inverse-square law. Thus, for each doubling of the distance from the sound source, sound intensity decreases by a factor of 4, or about 6 dB ($10 \log 4 = 6.02 \text{ dB}$) assuming the sound wave does not encounter any obstacles as it radiates out from the vibrating source.

The sound pressure wave can encounter objects as it travels from its source. The sound wave can be reflected from the object, absorbed at the boundary of the object, transmitted through the medium of the object, or ►diffracted around the object. The amount of reflection depends on the difference between the characteristic ►impedance of the original medium in which the sound wave is traveling and that of the object the sound wave encounters. ►Characteristic impedance (►Z_c) is defined as $Z_c = p_0c$, where p_0 is the density of the medium and c is the speed of the sound in the medium. Notice that Z_c is the same as the denominator of the definition of sound intensity, i.e., $I = p^2 / Z_c$. The greater the characteristic impedance of the object, the greater the magnitude of the sound wave that is reflected from the surface of the object.

Sound is diffracted around objects whose diameters are approximately equal to or less than the wavelength of the sound wave. The level of sound on the side of an object opposite the direction in which the sound travels may be less than that on the side that the sound wave encounters first. That is, objects can produce a sound shadow. Since wavelength is inversely proportional to frequency, the higher the frequency of the sound wave, the greater the amount of attenuation due to the sound shadow.

The reflections of sound waves traveling in enclosed spaces (e.g., in a tube) can produce a pattern of reflections that can both reinforce and cancel the pressure waveform. Under appropriate conditions, a ►standing wave can be created. A standing wave creates areas of increased pressure within the enclosed spaces (►antinodes), interspersed with areas of decreased pressure (►nodes). The fundamental frequency (f_0) of the standing wave is related to the length of the enclosed space (e.g., $f_0 = c / (2L)$, where c is speed of sound, L is length of enclosed space, when the enclosed space is closed or opened at both ends).

The reflections from surfaces in enclosed spaces like rooms can reinforce each other and the combined reflected sound wave can last a long time after the originating sound has ceased. In this case, ►reverberation is produced and the time it takes the reverberant sound level to decrease 60 dB from the original sound level is the ►reverberation time of the room. Reverberation time is proportional to the size of the room and inversely proportional to the amount of sound that is absorbed by the surfaces of the room.

Sound may be analyzed in several ways. The time waveform representing the relationship between sound pressure or intensity and time may be converted into a frequency-domain representation using a mathematical procedure known as the ►Fourier transform. Using the Fourier transform, any ►time-domain waveform can be represented by the sum (or integral) of a set of simple sinusoidal time-domain components.

For ►periodic time-domain waveforms, the discrete Fourier transform is

$$f(t) = 1/2A_o + \sum [a_n \cos(n\omega_o t) + b_n \sin(n\omega_o t)]$$

for $n = 0$ to ∞ ,

where $f(t)$ is the time-domain waveform, A_o is a DC shift in the baseline of the time-domain waveform, $\omega_o = 2\pi f_o$, f_o is the fundamental frequency of the periodic complex time-domain waveform, and a_n and b_n are magnitude constants expressed in terms of amplitude or power.

For non-periodic waveforms the Fourier transform is $f(t) = 1/2\pi \int f(\omega) e^{j\omega t} d\omega$, over the integral from $-\infty$ to $+\infty$, where $f(t)$ is the time-domain waveform, $f(\omega)$ is ►frequency domain transform, j is complex number ($\sqrt{-1}$), and $\omega = 2\pi f$. The exponential ($e^{j\omega t}$) is related to a complex form of the trigonometric sinusoidal function.

Thus, either the time-domain or the frequency domain description of the sound waveform provides a unique and complete characterization of the waveform. In the frequency domain, the sinusoidal components are described by ►spectra. The ►magnitude spectrum indicates the magnitude (pressure or intensity) of each sinusoidal component as a function of its frequency (e.g., for discrete Fourier transforms of “n” components, the magnitude spectrum is the relationship between $C_n = \sqrt{(a_n^2 + b_n^2)}$ and $n\omega_o$). The ►phase spectrum indicates the starting phase of each sinusoidal component as a function of its frequency (e.g., for discrete Fourier transforms of “n” components, the phase spectrum is the relationship between the arctangent (a_n/b_n) and $n\omega_o$). Thus, the magnitude and phase spectra completely and uniquely describe the waveform. If sound is to be described in terms of pressure variations over time, then the time-domain waveform is used. If it is important to know the frequency components of the sound, then the frequency-domain description is used.

Any system that analyzes sound can be described as linear or nonlinear. A ►linear analysis system means that the spectrum of the sound would only change in the sense that the amplitudes and starting phase of the input spectrum might change, but the frequency components at the output of the analysis system are the same as those of the input spectrum. In a ►nonlinear system, there may be frequency components at the output of the analysis system that were not present in the input.

For instance, if the input to a nonlinear analysis system was a spectrum of two sinusoidal components with frequencies f_1 and f_2 ($f_1 > f_2$), then a nonlinear system of the form $y = x^n$, where x is the sum of the components with frequencies f_1 and f_2 , can produce nonlinear ►distortion components at mf_1 , mf_2 , $(m-1)f_1 + (p-1)f_2$, and $(m-1)f_1 - (p-1)f_2$, where $m = p = 1$ to n , $m \neq p$. If $n = 2$, then the output spectrum would contain frequency components at f_1 and f_2 (the input components), $2f_1$, $2f_2$ (►harmonics), $f_1 + f_2$ (►summation tones), and $f_1 - f_2$ (►difference tones). Since the additional sinusoidal components would be added to the input components, the time-domain description of the output of a nonlinear system is distorted relative to the input.

Filtering may be used to estimate the magnitude spectrum of a complex time-domain waveform. A ►filter is a device or function that passes the frequency components of a sound within the ►passband of the filter without altering their magnitude. The magnitudes of frequency components with frequencies that lie outside of the passband are attenuated. For instance, a bandpass filter with a 500-Hz to 1,000-Hz passband and a 6-dB/octave ►roll off would not change the magnitude of the frequency components with frequencies between 500 and 1,000 Hz. The magnitude of components with frequencies greater than 1,000 Hz, or less than 500 Hz, would be reduced by 6 dB for each ►octave (doubling) of the component’s frequency away from 500 or 1,000 Hz (e.g., components at two octaves below 500 Hz, 125 Hz, and two octaves above 1,000 Hz, 4,000 Hz, will have magnitudes at the output of the filter that are 12 dB less than they were at the input to the filter).

In the example above, if a ►complex sound input to the filter had frequency components in the range of 500–1,000 Hz, the filter output would be greater in level than if the complex sound only had frequencies above 4,000 Hz. Thus, the output of each filter in a bank of bandpass filters can estimate the relative magnitudes of the frequency components in a complex sound. The accuracy of the estimate depends on the density of filters, the width of the passbands of each filter (the width of the passband is related to the ►Q of the filter, where Q is the ratio of the filter’s center frequency and its bandwidth), and steepness of the roll offs of each filter. Thus, a bank of bandpass filters may be used to estimate the magnitude spectrum of a sound.

The description of sound and its analysis provided above covers the major aspects of sound that affect auditory processing. The auditory system is sensitive to the pressure wave and how any objects that it encounters as it travels from its source to the ears of a listener affect it. Both the time and frequency domain descriptions of sound are coded by the auditory periphery. A filter bank is often used to model the frequency analysis performed by the biomechanics of the inner

ear. The auditory system is nonlinear at almost every stage of processing and is remarkably sensitive to the acoustic properties of vibrating objects.

References

1. Rossing T (1990) The science of sound, 2nd edn. Addison-Wesley, Reading, MA
2. Yost WA (2007) Fundamentals of hearing: an introduction 5th edn. Academic, San Diego, CA

Acquisition in Classical Conditioning

Definition

Learning about the predictive relation between a conditioned stimulus (CS) and an unconditioned stimulus (US) follows a negatively accelerated acquisition curve. A common index of acquisition is the ability of the CS to elicit a conditioned response. Control procedures are used to ensure that the change in behavior to the CS is due to learning about the CS-US relation and not to experience with the events per se. In the unpaired control procedure, the same number of CSs and USs is presented as in the paired condition but they are never contiguous in time; in the random control procedure, the probability of an US is unchanged by the presence or absence of the CS.

- Theory on Classical Conditioning

Across-Neuron (also: Across-Fiber) Pattern Code

Definition

Hypothesis stating that neural information is represented by spatiotemporal patterns of activity and amounts of activity in populations of nerve fibers and central neurons rather than in the activity of individual neurons. For example, since the three types of retinal cones respond broadly, albeit differentially, to overlapping ranges of light wavelengths, any individual wavelength is represented by a specific ratio of activities across the different cone types.

- Color Processing
- Photoreceptors
- Sensory Systems

Actin

Definition

Actin filaments (microfilament) are a major structural component of the cellular cytoskeleton. The monomeric globular form (G-actin) polymerizes to form long helical filaments (F-actin), 7–9 nm in diameter. All subunits are oriented in the same direction resulting in a structural polarity where the ends of the filament are different. The structural polarity has important functional implications where the barbed end (+ end) of the filament has a faster rate of growth than the pointed (- end). Actin is also the name of one of the two contractile proteins implicated in muscle contraction. Actin (sometimes also referred to as the thin filament) consists of two chains of serially linked actin globules that are wrapped around each other in a helical fashion. Actin also contains tropomyosin, a long fibrous protein that lies in the groove formed by the actin chains and three sub-units of troponin, troponin T, I and C. Tropomyosin and troponin are regulatory proteins associated with controlling cross-bridge binding to actin.

- Force Depression/Enhancement in Skeletal Muscles
- Molecular and Cellular Biomechanics
- Sliding Filament Theory

Actin-associating Protein Kinase (Akt)

Definition

Akt, also known as protein kinase B (PKB) is involved in intracellular signaling. Its roles include glucose metabolism and cell survival. Akt regulates cell survival and metabolism by binding to and regulating downstream effectors such as transcription factors and anti-apoptotic molecules.

- Neurotrophic Factors in Nerve Regeneration

Actinopterygians

Definition

Sistergroup of sarcopterygians, include all ray-finned fishes, i.e., bichirs (*Polypterus*) and the reedfish

(Calamoichthys), together forming the cladistians, the sturgeons (chondrostean) the gars (Lepisosteus; gin-glymodes) and the bowfin (Amia; halecomorphs), as well as the manifold modern ray-finned fishes, the teleosts.

- Evolution of the Brain: In Fishes
- Evolution of the Telencephalon: In Anamniotes

Action, Action-Theory

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Synonyms

Action; Behavior; Doing; Action-theory; Philosophy of action

Definition

Usually an action is defined as something which is done by an agent for a reason, where the reason explains the action. But here, at the latest, agreement comes to an end and various action-theories start.

Description of the Theory

There is no single action-theory but a variety of theories which address a number of closely interrelated topics that shape what is usually called ►philosophy of action. Although many of these topics had already been discussed in traditional philosophy (notably by Aristotle, Hume, Kant), these discussions were then usually regarded as part of moral philosophy. Philosophy of action as a discipline of its own came up in the middle of the twentieth century (helpful collections of classical papers in action theory are [1,2]).

The Central Question: What are Actions?

The main target of any action-theory is to give an adequate account of ►what actions are. An action is something we do, not something that merely happens to us, like rotating with the earth or catching a cold. Yet, not everything done is properly called an action. Warming the seat of a chair or outwearing one's shoes are things we do, but they are not actions. Neither is it an action if someone trembles when he is scared or blinks when something is approaching his eyes. Hence, actions are to be distinguished from things that happen to us and also from mere behavior, particularly reflexive behavior.

In order to account for the difference, actions are usually regarded as events each of one of which is a person's doing something for a reason, where the person's having the reason explains why they did the thing. In ordinary language the term "reason" is used in two different ways to explain actions: reasons are either states of affairs that speak in favor of the action (The reason I phone you is that your uncle died) or reasons are mental states that motivate the action (The reason I phone you is that I want to invite you for dinner). Both kinds of reasons (so called ►external and ►internal reasons) have been used to specify what actions are.

The idea that reasons basically are external reasons, i.e. states of affairs in the environment of the agent, and that actions are the agent's ►response to them was proposed, among others, by Georg Henrik von Wright [3]. But this view faces a number of serious problems: First, usually we would only regard such responses as actions if the agent also realizes the specific features of the environment, i.e. if she has the respective internal reason as well. Secondly, we would still take them to be actions even if the features do not in fact obtain, as long as the agent mistakenly assumes that they do. And thirdly, it is not quite clear how an adherent of this approach could account for the explanatory power of reasons.

Because of these problems and because it is initially so plausible that we are agents because we have minds, the received understanding of action in modern action theory is ►mentalistic, which means that the specific difference between actions and other doings is located in the mental attitudes the agent has towards her doings. Actions are done, because the agent wants, wills or intends them to occur. Mentalistic proposals differ with respect to the mental attitudes they take to be crucial and/or with respect to what they regard as the proper relationship between these attitudes and the respective actions.

The classical mentalistic view is ►volitionalism, according to which actions have to be preceded by volitions or ►acts of will that trigger the action. Volitionalism arguably originates in the early Christian adaptation of antique concepts of agency, particularly in the writings of Augustine. However, in recent philosophy of action volitionalism met at least two serious problems: first, there are many everyday, routine actions, which we seem to perform without a preceding act of will, and secondly volitionalism seems to imply that volitions are actions too, which would presuppose that they in turn are preceded by another act of will, and so on, ad infinitum. Despite these difficulties there are still defenders of volitionalism.

The dominant mentalistic alternative to volitionalism is the so-called ►belief-desire thesis. According to this view it is characteristic of actions that they are

performed because the agent has a desire (or more generally: a pro-attitude) towards doing something and believes that what she does is of the desired kind. The agent might e.g. phone her friend because she wants to invite him for dinner and believes that phoning him is a way to invite him. In the terminology of the leading proponent of this view, Donald Davidson, the belief-desire pair is called the action's ►primary reason [4]. Actions are things done for primary reasons.

However, the belief-desire thesis, too, faces an obvious problem: it seems to account merely for ►intentional actions, leaving all kinds of unintentional, involuntary, inadvertent actions unexplained. If the agent phones her friend because she mistook his number for the number of her parents, she does not act on a primary reason for phoning him, yet her phoning him is neither just something that happened to her nor a mere behavior, it is a mistaken, misguided action. What is therefore needed is a two-step account of actions: they are either intentional (i.e. done for a primary reason) or they are performed by doing something else intentionally.

For some time, roughly between 1970 and 1990, the metaphysical question of how to understand this by-locution played an important role in action theory (for an overview see [5]). According to Davidson and others “by” only relates different descriptions of the same, numerically identical action. Hence, in their terminology, actions are intentional only under a certain description (►coarse grained account). According to authors like Alvin Goldman and Jaegwon Kim on the other hand “by” always or at least sometimes relates different, numerically distinct actions (►fine-grained accounts). These views were usually combined with ontological claims as to whether actions are events at all, whether they are restricted to bodily movements or could also comprise some other events, or whether actions should in the last analysis be seen as internal, mental phenomena: e.g. strivings, tryings or decisions.

The ontological debate in action theory also focused on the problem of how to account for so called ►negative actions, i.e. omitting something or letting something happen. On the one hand it seems to be beyond doubt that part of what we intentionally do belongs to this negative kind (e.g. if we abstain from smoking because it is unhealthy), on the other hand negative actions seem to be ontologically unreal, because in a sense the agent is not doing anything at all.

The intentionality of actions also gave rise to the question, whether a pair of beliefs and desires is really sufficient for an action to occur or whether it is necessary to have an ►intention in advance of one's action. The proposal to augment the belief-desire thesis by an additional mental component, the agent's intention or choice, has the advantage to preserve the initial plausibility of volitionalism with a good chance for avoiding some of its difficulties. However, the

proposal it is still faced with the problem that particularly routine acts seem not to be preceded by such an attitude. Yet in any case, even if not all actions presuppose intentions separate from the agent's primary reasons, it is an important task in action theory to account for the role an agent's intentions play, since intentions are crucial for understanding ►planned, ►complex and ►joint actions [6]. Authors disagree though on what intentions are and particularly whether they could be reduced to other kinds of intentional attitudes.

Other mental phenomena also play an important role for agency. Actions are not only performed for reasons or intentions, we also act on e.g. fury, love, fear, or shame. Sometimes we even act just for fun or “for nothing.” What this shows is that, at least, action theory has to take into account other mental antecedents of actions that add to action explanations, although some authors go further and regard the existence of such ►arational actions as a refutation of the belief-desire thesis and of its too rationalistic view of actions.

Despite their differences all mentalistic approaches agree in the idea that for a doing to be an action it is not sufficient that the agent has the respective mental antecedents, the doing must also be explained by them. This leads to a second major topic in the philosophy of action, the character of action explanations.

Action Explanations

Action explanations combine two ideas: first the action is described as, in a sense, being ►adequate (or fitting) to the explanantia, and secondly it is described as happening because of its adequacy.

The first idea is easily illustrated by explanations based on the agent's acts of will, volitions, intentions or decisions. The action fulfills what is expressed in the content of the respective attitude. The agent's phoning her friend fits to her preliminary intention, because phoning him is what she intended to do.

Primary reasons fit the action in showing it as being reasonable, in the sense that the agent could have concluded from the reasons she has that it is somehow favorable to perform the action. The agent's desire to invite her friend together with her belief that this could be done by phoning him speak in favor of phoning him. The idea that reasons allow for a special sort of inference to the respective action goes back to Aristotle who called inferences like these ►practical syllogisms. Obviously there is something to the idea that action explanations have such a quasi-logical structure, but there is widespread disagreement as to whether practical inferences could be valid at all, whether they follow a special kind of (deontic) logic and which form a conclusion of a practical syllogism has. Is it, e.g. a value judgement, an expression of intention or perhaps the action itself?

Moreover, pointing out the primary reason of an action seems to be quite a feeble kind of explanation. Since agents usually have many competing desires which they cannot fulfill simultaneously, simply saying that there was a reason in favor for the agent's action doesn't explain why it was just this desire she satisfied and not any other. So one might wonder why we are at all interested in an agent's reasons.

One way to cope with this question is to regard the agent's intentional states as constituting something like a ►hierarchical structure, ordered according to the strength of her desires and the subjective probability of her beliefs. Reason explanations would then carry an implicit presumption that the reasons mentioned were on top of this hierarchy. Seen in this light the agent is a perfectly ►rational being and reasons explain an action because from the agent's perspective every action is displayed as the very rational thing to do.

Obviously, this view has difficulties in coping with familiar cases of ►irrationality, e.g. instances of weakness of will, and also with agency in dilemmatic cases. Moreover, as Rational Choice Theory and Game Theory have made vivid, it is sometimes awfully complicated to figure out how to behave rationally, hence it would be surprising if every human agent could be regarded as a perfectly rational being.

But besides these difficulties there is the second idea that for an occurrence's being an action it may not be sufficient that it is rational in the light of the agent, but that it also has to be caused by the agent's intention.

When this topic was discussed in the mid twentieth century by, among others, Ludwig Wittgenstein, Gilbert Ryle and G.E.M. Anscombe there was widespread agreement that because reason explanations aim at an ►interpretation (or an understanding) of the action they could not at the same time be causal explanations. The most prominent argument for this view was the so called logical connection argument, according to which the connection between a reason for doing something and the resultant action is incompatible with the logical independence requisite for cause and effect.

During the sixties these arguments were criticized very effectively, most prominently by Davidson. Since then it is the received view that reason explanations are a special kind of causal explanations. This causalistic view fits well with different approaches to the mind body problem that were developed in these days in the ►philosophy of mind, e.g. identity theory and functionalism. But there are still authors who doubt that reason explanations are causal and defend alternative views (►interpretative or ►teleological approaches).

One reason for being skeptical about the causalistic approach is that there are cases where although intentional attitudes rationalize as well as cause something the agent does, what she does isn't an action. A student, e.g. who wants to avoid an examination may try so hard

to find a way of getting around it that she absentmindedly runs into a car on the street and spends her time in the hospital instead of being examined. Although the student certainly knows that having a car accident is a suitable means for avoiding an examination, and although her want to avoid the examination also has caused the accident, the accident still was not an intentional act of her. Some authors regard such cases of so called ►wayward causal chains as evidence against causalism. What they show in any case is that there is more to the explanatory value of reason explanations than just rationalization and causation. Speaking metaphorically, the causation has to take the right route, and it is a widely discussed topic in today's action theory how to unwrap this metaphor.

Agents

Another reason for being reluctant to accept the standard causal account of action explanations is that it may threaten our ►freedom and responsibility (►Will, freedom of). The suspicion that taking reasons to be causes of actions would leave us no real freedom of choice has led some authors (most prominently Roderick Chisholm) to the view (foreshadowed in ancient conceptions of causality) that instead of the agent's intentional attitudes the agent herself should be regarded as the cause of the action.

But although most action theorists are reluctant with regard to such a special kind of ►agent causality, many agree that the standard belief-desire thesis underestimates the role of the agent, as far as full-fledged human agency is concerned. What is usually assumed to be missing is some sort of complexity that distinguishes agents like us from simpler (e.g. animal) agents. Moreover most authors agree that the crucial difference is to be found in features that are usually associated with concepts like ►personality and ►autonomy (►personal autonomy). These features in turn are either located in the reflective structure of the intentionality of persons (e.g. Harry Frankfurt's conception of second order volitions in [7]), or in a special capability of valuing (e.g. Charles Taylor's distinction between weak and strong evaluations in [8]).

Parallel to this debate about the characteristics of paradigmatic full-fledged human agents there is also a discussion about borderline cases of ►non-human agency. In accordance with common sense most authors agree that at least higher mammals are agents, but some authors are willing to concede agency to lower animals, plants and perhaps even artifacts as well. A rather different and also widely discussed question is concerned with corporate agency. While animals typically raise worries whether they are sophisticated enough for being agents, corporations, in a sense, are obviously very smart, but on the other hand they seem to be too lofty entities for counting them as true agents.

Why Action Theory?

There are several good reasons for being interested in the results of action theory. Action theory is part of ►anthropology i.e. the study of human nature. In particular, there are strong connections with the philosophy of mind. On the one hand actions are typically characterized by their mental antecedents, therefore most problems in action theory can only be solved by taking into account the nature of these antecedents. On the other hand, many influential characterizations of mental states in the philosophy of mind refer to their behavioral output (e.g. behaviorism, functionalism), so that presumably any plausible theory of the mind has to offer an account of actions as well (for an overview see [9]).

The findings of action theory also have strong bearings on ►ethical issues. For one thing ethics is obviously interested in the problem of freedom of the will since free will is usually regarded as a prerequisite of moral responsibility, and for another there are some important distinctions in moral theory that rely on corresponding differences in action theory, most prominently the difference between actively doing something and letting something happen or omitting something, which e.g. is at the basis of the distinction in medical ethics between killing a patient and letting him die. Another distinction that is relevant for applied ethics is the one between causing something and merely accepting it as a side effect, which, e.g. is sometimes employed for drawing the line between permitted and forbidden killings of civilians in warfare. Both distinctions have to be elucidated in action theory in order to estimate their ethical impact in moral philosophy [10].

References

1. White A (ed) (1968) The philosophy of action. Oxford University Press, Oxford
2. Mele A (ed) (1997) The philosophy of action. Oxford University Press, Oxford
3. von Wright GH (1971) Explanation and understanding. Routledge, London
4. Davidson D (2001) Essays on actions and events, 2nd edn. Oxford University Press, Oxford
5. Pfeifer K (1989) Actions and other events. New York, Bern, Frankfurt, Peterlong, Paris
6. Bratman M (1999) Faces of intention. Cambridge University Press, Cambridge
7. Frankfurt H (1988) The importance of what we care about. Cambridge University Press, Cambridge
8. Taylor C (1985) What is human agency? In: Taylor C. Philosophical Papers 1. Cambridge University Press, Cambridge. pp 15–44
9. Kim J (2005) Philosophy of mind, 2nd edn. Harper collins, Boulder
10. Steimbeck B, Norcross A (1994) Killing and letting die, 2nd edn. Fordtton University Press, New York

Action Potential

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Synonyms

Discharge; Impulse; Spike

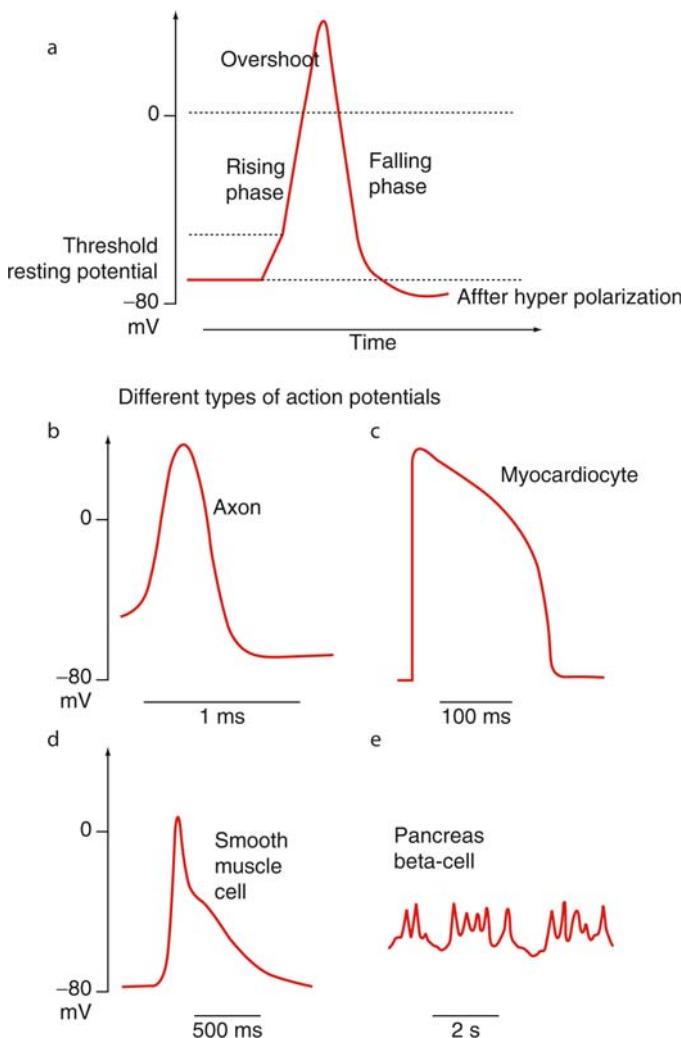
Definition

The action potential is the active electrical response of an excitable cell membrane to a stimulus, reflected in a fairly stereotyped change in membrane potential from a resting value (negative inside) to a depolarized (either positive or less negative inside) value and back. The durations of action potentials range from a few milliseconds in neurons to hundreds of milliseconds in cardiac, gastric and intestinal cells. The underlying mechanism consists of voltage-dependent opening of Na^+ , Ca^{2+} and K^+ channels. The response is initially depolarizing due to opening of Na^+ and/or Ca^{2+} channels, and subsequently repolarizing due to delayed opening of K^+ channels.

Characteristics

The action potential represents membrane mechanisms, that yield an electrical signal, which propagates over long distances. The signal originates from an encoding process that converts graded, non-propagating ►receptor potentials or synaptic potentials into action potentials (►Sensory Systems).

Various examples of action potentials (red lines) in different cells are displayed in Fig. 1. Most of them are pulses (also called “impulses” or “spikes”) of fairly short duration, on the order of 1–3 ms (Fig. 1a, b) except for those in heart or smooth muscle cells (Fig. 1c, d). A spike (Fig. 1a) evolves from a ►resting membrane potential of about -50 to -90 mV, (►Membrane Potential – Basics), depolarizes at a steep rate and reaches a peak which, depending on the resting potential from which it arises, ranges from a much less negative value than at rest (typically -10 mV to -5 mV) to a positive voltage (►overshoot). In cardiac Purkinje fibers, myocytes and some cells of the gastro intestinal tract, the action potential has a prolonged plateau phase (Fig. 1c), while in neurons and skeletal muscle cells, rapid repolarization brings the action potential back close to the resting potential, where a ►delayed depolarization or protracted ►afterhyperpolarization (AHP) may follow (Fig. 1a, b). Some neurons, such as



Action Potential. Figure 1 (a–e) Intracellular records of membrane and action potentials (red lines).

(a) Schematic representation of an action potential with its phases. (b) The action potential measured in a squid axon is a prototype of the fast action potential produced by nerve or muscle fibers. It is about 100 times faster than the action potentials of heart muscle cells. In heart and smooth muscle cells (c,d), the rising phase of the action potential is carried by Na^+ currents through Na^+ channels, while the prolonged plateau phase is mediated by Ca^{2+} currents through Ca^{2+} channels. E: Endocrine cells such as the pancreatic β -cells also produce action potentials, which are mediated by Ca^{2+} and trigger exocytosis of the hormone (in this case insulin) (Adapted from ref. [1]).

the ▶motoneurons innervating skeletal muscle fibers, may have pronounced (several mV deep) and long-lasting (50–200 ms) afterhyperpolarizations.

The Squid Giant Axon

The basic processes underlying the generation of the axon action potential were studied and described by Hodgkin, Huxley (A.L. Hodgkin, A.F. Huxley, Nobel Prize of Physiology or Medicine 1963) and coworkers, including B. Katz (Nobel Prize of Physiology and Medicine (1970)). The giant axon of the squid turned out to be a favourable structure because its size (diameter 0.5–1 mm) and robustness allowed it to be removed

from the animal, placed in a bath and subjected to varying extracellular compositions. Its size allowed insertion of relatively bulky longitudinal electrodes, and because of membrane durability it was possible to squeeze out the intracellular content and replace it with solutions of varying composition (▶Intracellular Recording).

Processes Underlying the Squid-Axon Action Potential Need for Extracellular Na^+

The squid-axon experiments showed that the depolarization (rising phase) of the action potential results from a regenerative increase in Na^+ conductance, beginning

with the observation that reducing extracellular Na^+ concentration diminished the amplitude and rate of depolarization. Subsequently, current measurements were made with the ►voltage-clamp technique, which identified voltage- and time-dependent properties associated with the action potential.

Voltage-Dependent Currents

Voltage changes during the action potential are associated with several different currents:

- Na^+ and K^+ conductances and the ensuing currents show complicated dependencies on both time t and time-varying membrane potential $V(t)$:

$$I_{\text{Na}}(V, t) = g_{\text{Na}}(V, t) [V(t) - E_{\text{Na}}], \quad (1a)$$

$$I_K(V, t) = g_K(V, t) [V(t) - E_K], \quad (1b)$$

These dependencies lead to a fast ionic current $I_{\text{ion}}(V, t)$ through the membrane, composed of Na^+ and K^+ currents:

$$I_{\text{ion}}(V, t) = I_{\text{Na}}(V, t) + I_K(V, t) \quad (2)$$

- Although small and relatively insignificant in the squid axon, a so-called leakage or ►leak current through other ion channels must be taken into account, if only for corrective purposes [2]:

$$I_L(V, t) = g_L(V, t) [V(t) - E_L]. \quad (3)$$

- Fast voltage changes during the action potential generate ►capacitative currents I_C due to charging and discharging the membrane capacitance C_m :

$$I_C(t) = C_m \cdot dV(t)/dt \quad (4)$$

- The total current during the action potential would thus be:

$$I_{\text{tot}}(t) = I_{\text{Na}}(V, t) + I_K(V, t) + I_L(V, t) + I_C(t) \quad (5)$$

The superposition of various time-and voltage-varying currents was difficult to disentangle using the more conventional methods of the time. The invention of the voltage-clamp technique (►Intracellular recording) made it possible to separate and analyze voltage- and time-dependent properties of the action potential.

Voltage Clamp

The basic idea of the voltage-clamp technique is as follows. Rather than studying the naturally occurring action potential with its complicated time- and voltage-dependent currents, abrupt step-like changes in membrane potential from an initial “holding” potential V_h to a final test potential V_f are utilized. The fundamental principle is to keep the membrane potential constant before and after the step by injecting, via a second intraxonal electrode, currents into the axon. These currents

would, of necessity, have the same magnitude, but the opposite polarity of those elicited by the voltage step.

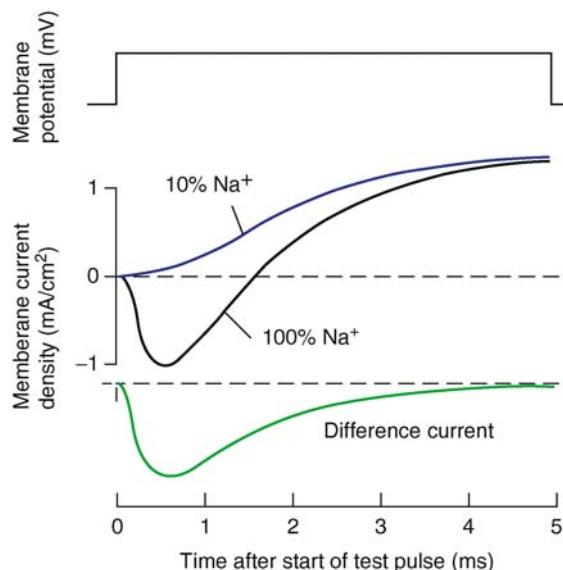
The method was revolutionary for its time, introducing a number of advantages:

1. The transient capacitative current I_C (Eq. 4) is isolated because it only occurs during a very brief time (order of microseconds), whereas the slower ionic currents persist and can be measured independently of I_C .
2. The membrane potential can be “clamped” at various, constant test levels, at which the time course of the voltage-dependent net current [$I_{\text{net}}(t)$] can be followed.
3. Varying the voltage-step size reveals the dependency of ion conductances on membrane potential.
4. Conditioning voltage steps and holding potentials permit measurements of time- and voltage-dependent properties of ion channel activation and inactivation.
5. Changes in extra- and intracellular ion concentrations, and/or elimination of specific ion conductances with ion channel neurotoxins, can be used in conjunction with voltage-clamp protocols to elucidate the relative contributions of $I_{\text{Na}}(t)$ and $I_K(t)$ to $I_{\text{net}}(t)$.
6. The experimental arrangement for voltage-clamping the squid axon has the further advantage of producing a uniform space clamp, because an identical transmembrane potential change is impressed across the entire length of the membrane. The result is that current changes due to longitudinal current spread between regions of different membrane voltage cannot contaminate transmembrane current flow through voltage-gated ion channels.

Na^+ and K^+ Currents Elicited by Depolarization

An example of a voltage-clamp experiment is shown in Fig. 2. The membrane is abruptly depolarized from an initial holding potential of -65 mV by 56 mV to -9 mV (upper trace). This evokes an initial capacitative current (not shown) that is very brief and precedes an inward-outward sequence of slower currents (middle panel, lower trace). Provided this latter sequence is ionic, various manipulations should demonstrate its nature and composition.

Replacing about 90% of the external Na^+ with choline, an impermeant ion, renders the Na^+ concentrations inside and outside the axon approximately equal and, according to the Nernst equation (►Membrane Potential – Basics), brings E_{Na} to about zero. If, after the step, the membrane potential is then held at 0 mV , no net Na^+ current should flow, and the remaining current should be due to K^+ (Fig. 2, middle panel, blue line labelled “10% Na^+ ”), as verified by the observation that its magnitude is altered by varying extracellular K^+



Action Potential. **Figure 2** Classical ion substitution method for studying the ionic basis of voltage-clamp currents. The axon is depolarized from -65 mV by 56 mV to -9 mV (top trace). With normal seawater (100% Na^+), the typical curve (black line in the middle panel) results. Reducing the external Na^+ concentration to 10% of normal results in the blue line (labeled “ 10% Na^+ ”) in the middle panel. The difference between these two curves (green line in lower panel) corresponds to the current carried by Na^+ . $T = 8.5^\circ\text{C}$ (Adapted from ref. [3]).

concentration (not shown). The K^+ current is slowly activated by depolarization, directed outward, has a slow time course, and remains activated throughout the depolarization. The difference between the K^+ current (blue line) and the mixed current (Fig. 2, middle panel, black line labelled “ 100% Na^+ ”) is plotted in the bottom trace (green line labelled “Difference current”) and corresponds to the current carried by Na^+ (► [Intracellular Recording](#)). It is an inward current that peaks within 1 ms and then decays over a few milliseconds despite continued depolarization. Hence, the Na^+ current is quickly activated, but subsequently ► [inactivates](#) automatically (see below).

Dependence of Na^+ and K^+ Currents and Conductances on Depolarization Amplitude

The precise dependence of these currents on the amplitude of the voltage steps and, hence, the steady state potential, can be established [4] by stepping the membrane from a holding potential (say -65 mV) to various end-potentials. The late K^+ current increases as the depolarizing steps increase. By contrast, the early Na^+ current first increases, but subsequently decreases with increasing depolarization, is absent at $+52\text{ mV}$ (corresponding approximately to the Na^+ equilibrium

potential), and is reversed in sign (directed outward) at $+65\text{ mV}$. The Na^+ and K^+ currents can be transformed into the underlying conductance changes by using Eqs. 1a, b. Like the currents, these conductance changes depend on the amplitude of the voltage step. While the K^+ conductance remains elevated with continuing depolarization, the Na^+ decays on its own. This process is due to ion channel inactivation (see below).

Pharmacological Identification of Na^+ and K^+ Conductances

The above results indicate that the squid giant axon must possess (at least) two voltage-dependent conductances with different, very specific properties. Indeed, voltage-clamp experiments have shown that they also have very different pharmacological sensitivities. The neurotoxins ► [tetrodotoxin](#) (TTX) or ► [saxitoxin](#) (STX) and local anaesthetics such as procaine, cocaine and tetracaine block voltage-gated Na^+ current but leave the K^+ current intact. On the other hand, ► [tetraethylammonium](#) (TEA) as well as cesium ions block K^+ currents but not sodium currents [5].

Ion channels that carry Na^+ Current Inactivate during the Time Course of the Action Potential

Voltage-clamp experiments such as those described above pointed to two processes that bring about the fall of the action potential from its peak: inactivation of the Na^+ conductance and late development of the K^+ conductance. If both Na^+ activation and inactivation during an action potential are triggered by depolarization, the two processes must be timed in such a manner as not to cancel each other. Inactivation should have a slower time course that allows it to follow activation. By the same token, any degree of antecedent inactivation should suppress a second activation (see below), and preceding membrane potential changes should influence the amount of Na^+ activation. These predictions have been confirmed in pulse-conditioning experiments and have functional consequences on discharge properties during bursts of action potentials (see below).

In voltage-clamp experiments on squid giant axons, depolarization from -65 mV to -21 mV elicits the usual inward-outward sequence of currents. However, when the voltage step to -21 mV is preceded by a short-lasting, smaller depolarization of 14 mV (conditioning pre-pulse), the inward current is much reduced. Conversely, when a hyperpolarizing pre-pulse of 31 mV is applied, the step depolarization elicits a much stronger inward current. A plot of normalized inward current vs. amount of conditioning potential change shows that at the normal resting potential, about one-third of the Na^+ current is inactivated. The functional consequence is that antecedent membrane hyperpolarization decreases the degree of inactivation and therefore

increases action potential amplitude, while residual membrane depolarization has the opposite effect.

The time course of recovery from Na^+ inactivation has been worked out in paired depolarizing pulse paradigms, where the pulses are delivered at varied intervals. They show that the Na^+ system recovers from inactivation with an approximately exponential time course and a time constant on the order of 5 ms, with the time constant depending on the holding potentials [5].

At the peak of an action potential and during the subsequent decline toward resting potential the Na^+ channels exhibit reduced depolarization-dependent permeability, from which recovery occurs gradually over several milliseconds. This period of reduced channel reactivity characterizes the ►refractory period. At peak membrane depolarization and shortly thereafter, Na^+ permeability cannot be activated at all, however strong the depolarization. This is called the absolute refractory period. During the subsequent relative refractory period, Na^+ permeability can be increased by relatively large degrees of membrane depolarization.

Proteolytic enzymes such as pronase or papain applied intracellularly impair or remove Na^+ inactivation, leading to long-lasting Na^+ activation during prolonged depolarization [5].

Consequences of Na^+ Inactivation

The impact of membrane depolarization on both activation and inactivation of Na^+ conductance has profound functional consequences. The sequence of Na^+ activation and inactivation:

1. Limits action potential frequency. Since an action potential is followed by an absolute refractory period, there is a minimal interval at which one action potential can follow the preceding one. This minimal interval defines the maximal rate of occurrence of action potentials.
2. Leads to accommodation. When a nerve fiber is slowly depolarized by a ramp-like rather than a step-like waveform, the Na^+ inactivation may have time enough to develop in step with Na^+ activation. Slow depolarization – even to very high levels – may thus not elicit action potentials, but rather completely prevent their generation.
3. Has clinical implications. Nerve, muscle and gut paralysis can result from long-lasting depolarization (►depolarization block).

The Hodgkin–Huxley Model of the Action Potential

Voltage-clamp experiments revealed that the Na^+ and K^+ conductances that give rise to the action potential vary with membrane potential and time. A successful attempt at quantitatively describing these dependencies and mathematically model the squid-axon action potential was made by Hodgkin and Huxley [6]. They

were able to reconstruct the shape of the action potential and its underlying ion conductance changes, as shown in Fig. 3. The “HH equations” and variations thereof are still used to model neuron bioelectrical properties.

Channel Gating Currents

Hodgkin and Huxley [6] suggested that channel opening should be associated with the movement of charged particles within the membrane. This was subsequently demonstrated in voltage-clamp experiments with computer averaging and subtraction techniques [7].

Single-Channel Currents

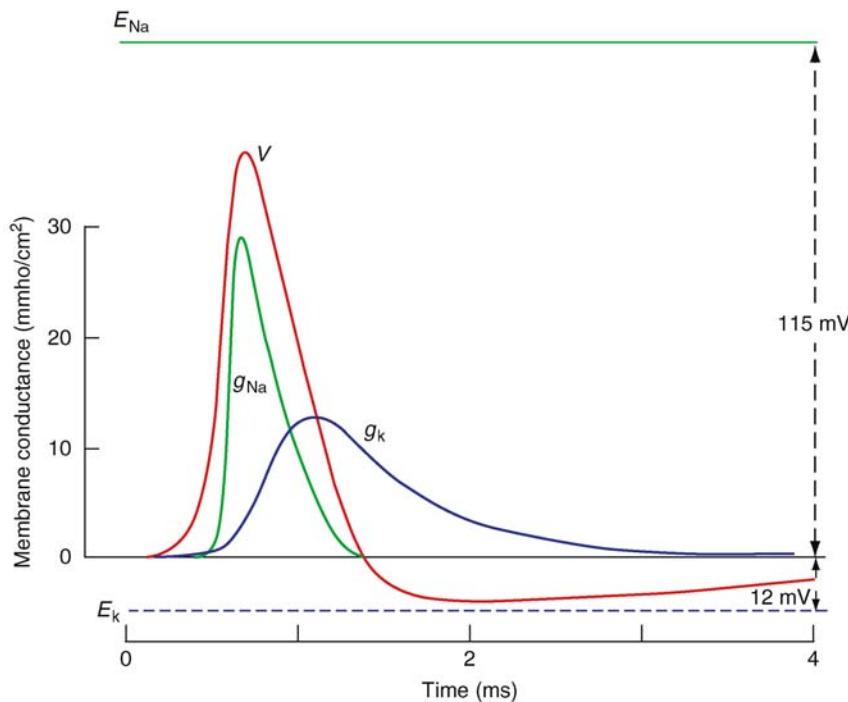
Within the last 25 years, it has become possible to voltage-clamp small patches of cell membrane and record single-channel currents with the ►patch-clamp technique (►Intracellular Recording). Single-channel inward currents appear at varying times after step depolarization, but most often close to the beginning. When hundreds of individual recordings are averaged, the average inward current has a time course comparable with that of the inward Na^+ current shown in Fig. 2 (green line in lower panel: “Difference curve”). Experiments such as these have revealed some interesting properties of single ion channels. They indicate that channel behavior is probabilistic; the current reflects the probability of being open. The Na^+ current recorded with gross electrodes (Fig. 2) results from the superimposed activity of many Na^+ channels.

Action Potentials in Central Neurons

The squid axon is a relatively simple system devoted to conducting action potentials along the axon (►Action Potential Propagation), and probably for this reason can be content with two major ion conductances. Central neurons, however, have much more varied signal-processing functions and therefore express complex repertoires of ion channels, endowing them with a plethora of firing behaviors. Thus, individual neurons in the mammalian brain typically express several subtypes of ►voltage-dependent Na^+ channels, ►voltage-dependent Ca^{2+} channels, ►voltage-dependent K^+ channels, ► Ca^{2+} -activated K^+ channels (►Neuronal potassium channels), ►hyperpolarization-activated, ►non-selective cation channels, and more. The different combinations of channels enable diverse action potential shapes and firing patterns. Action potential amplitude, shape and firing rate are particularly important at presynaptic axon terminals, where they co-determine – via the amount of presynaptic Ca^{2+} influx – the amount of released ►neurotransmitter [8].

Contribution of Na^+ Currents to Action Potentials

In central neurons, very much like in the squid axon, the rising phase of the action potential is generated by very fast activation and inactivation of voltage-dependent



Action Potential. **Figure 3** Reconstruction of the action potential. The time courses of the propagated action potential and underlying ionic conductance changes computed by Hodgkin and Huxley [5] from their voltage-clamp data. The constants used were appropriate to a temperature of 18.5°C. The calculated net entry of Na^+ was 4.33 pmole/cm², and the net exit of K^+ was 4.26 pmole/cm². The calculated conduction velocity was 18.8 m/s (Adapted from ref. [6]).

Na^+ channels, although the detailed kinetics may vary between different types of neuron and even between different parts of a neuron [8].

Contribution of Ca^{2+} Current to Action Potentials

Although individual mammalian neurons typically express at least four or five types of voltage-dependent Ca^{2+} channels, inward Ca^{2+} currents contribute little to the action potential upstroke because of their slow activation kinetics, whereby they start to be activated near the peak of the action potential and are maximal during the repolarization phase. In addition to initiating intracellular signalling pathways, the action potential-evoked Ca^{2+} influx influences action-potential shape and firing pattern. Conversely, since the activation and inactivation kinetics of the Ca^{2+} channels are strongly voltage-dependent, the shape and width of the action potential determines the amount of evoked Ca^{2+} influx and thereby, at presynaptic terminals, the amount of neurotransmitter released [8].

Among the Ca^{2+} channels expressed are low-voltage-activated T-type channels (Cav3 family channels) and high-voltage-activated channels including L-type (Cav1.2 and Cav1.3), P/Q-type channels (Cav2.1), N-type (Cav2.2) and R-type (Cav2.3) channels.

Pharmacological blockade of Ca^{2+} channels often broadens the action potential and lengthens discharge duration, because Ca^{2+} influx leads to opening of large-conductance Ca^{2+} -activated K^+ channels (BK channels) that promote membrane repolarization. Small-conductance Ca^{2+} -activated K^+ channels (SK channels) are also coupled to Ca^{2+} influx. They activate too slowly to affect action-potential repolarization, but they do contribute to the following afterhyperpolarization (AHP; below) [8].

Contribution of K^+ Current to Action Potentials

Central neurons express a huge variety of voltage-gated K^+ channels, only a fraction of which activate appreciably during the action potential. Significant contributions to action potential repolarization are commonly made by Kv3 family and Kv4 family channels mediating the A-type current (I_A). In some fast-spiking neurons (below), Kv3-mediated current appears to be the major current flowing during repolarization. In glutamatergic neurons of hippocampus and cortex, repolarization is mediated by at least three types of K^+ currents: the BK Ca^{2+} -activated K^+ current (above), and two purely voltage-dependent currents, I_A and I_D . I_A shows relatively rapid inactivation

and is, in cell bodies and dendrites, mostly mediated by the Kv4 family channels. I_D is activated by sub-threshold depolarizations, inactivates slowly and is blocked by ►4-aminopyridine, which broadens action potentials. In some neurons, high rates of firing lead to broadening of action potentials that probably results from cumulative inactivation of K^+ channels, and may facilitate synaptic transmission by increasing Ca^{2+} influx in presynaptic terminals [8].

Afterdepolarization

In many neurons (e.g., pyramidal cells of hippocampus and cortex), the fast phase of action potential repolarization is followed by a delayed depolarization, either attached to the fast phase as a slow phase or as a hump intercalated between a fast transient and a subsequent afterhyperpolarization. The origins of ►afterdepolarization may be passive and/or active. That is, an action potential in the cell soma may recharge the dendritic tree with its large surface area and ►capacitance (electrical), which takes time. This electrotonic mechanism may be amplified by active dendritic conductances, whose activation is often delayed and slower than that of the somatic conductances. Active ionic currents contributing to afterdepolarization include ►persistent Na^+ currents, ►resurgent Na^+ currents, R-type and T-type Ca^{2+} currents, and currents due to ►non-selective cation currents [8].

Afterhyperpolarization (AHP)

While in the squid axon, the afterhyperpolarization (Fig. 3) is generated by the merely slowly inactivating voltage-dependent K^+ conductance activated during the action potential, afterhyperpolarizations in mammalian central neurons are more complex. First, they may show different phases: fast, medium and slow. Second, the contributing K^+ channels include BK and SK channels and Kv7 channels mediating the ►M-current. BK-channel-mediated afterhyperpolarizations are usually brief, while SK-channel-mediated ones can last up to seconds [8].

Repetitive Firing

Many central neurons discharge action potential over a wide range of frequencies and with various patterns, to which many factors already discussed may contribute. For example, if the hump-like intermittent afterdepolarization is fast and large enough, it may elicit new spikes and thus burst firing [8]. On the other hand, the depth and duration of afterhyperpolarization (reduced excitability) co-determines the firing pattern, e.g., in skeleto-motoneurons [9].

The rates and patterns of repetitive firing are also influenced by several sub-threshold currents that flow between action potentials and accelerate or slow the approach to threshold. Such currents include the

steady-state “persistent” Na^+ current, I_A and I_D K^+ currents, the I_h current carried by ►hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, and currents carried by low-voltage-activated (T-type) Ca^{2+} channels [8].

The ►A-type K^+ current (I_A) activates and inactivates at sub-threshold voltages. During the post-spike hyperpolarization, I_A inactivation is partially removed; during the subsequent depolarization, I_A first activates and slows the approach to threshold, and then inactivates enabling threshold crossing. The I_D current plays a similar role but inactivates more slowly [8].

Most central neurons possess TTX-sensitive and insensitive, voltage-dependent, steady-state “persistent” inward Na^+ current flowing at voltages between -65 and -40 mV, which significantly influences sub-threshold membrane potential changes and thus the firing rate and pattern of discharge [8].

One function of low-voltage-gated (T-type) Ca^{2+} currents is the generation of ►rebound bursting following hyperpolarization (e.g., after a prolonged inhibitory synaptic input), which removes its inactivation [8].

Many central neurons fire spontaneously (without overt excitatory inputs) and fairly regularly, and are called “►pacemakers”. In some of these neurons, the “persistent” Na^+ current plays the major role to drive membrane potential to threshold, in others it is the I_h current. In dopaminergic midbrain neurons, a sub-threshold Ca^{2+} current appears to drive pacemaker activity [8].

Fast-Spiking Neurons

Neurons capable of firing at high rates for prolonged periods, e.g., cerebellar ►Purkinje cells, often possess voltage-gated K^+ channels of the Kv3 family, whose fast and steeply voltage-dependent activation and inactivation kinetics allow them to produce narrow action potentials and short refractory periods suitable for fast repetitive firing. In some types of central neurons, this mechanism may be supported by a special “resurgent” Na^+ current, which activates transiently upon repolarization after inactivation due to strong depolarization and is sensitive to tetrodotoxin (TTX) [8].

References

- Ruppertsberg JP (1996) Ion channels in excitable membranes. In: Greger R, Windhorst U (eds) Comprehensive human physiology. From cellular mechanisms to integration. Springer, Berlin Heidelberg, New York, pp 267–282
- Keynes RD, Aidley DJ (1991) Muscle and nerve, 2nd edn. Cambridge University Press, Cambridge
- Hodgkin AL (1958) Ionic movements and electrical activity in giant nerve fibres. Proc R Soc Lond B 148:1–37

4. Hodgkin AL, Huxley AF, Katz B (1952) Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*. *J Physiol (Lond)* 116:424–448
5. Hille B (1992) Ionic channels of excitable membranes, 2nd edn. Sinauer Associates, Sunderland, MA
6. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol (Lond)* 117:500–544
7. Armstrong CM, Bezanilla F (1974) Charge movement associated with the opening and closing of the activation gates of the Na channel. *J Gen Physiol* 63:533–552
8. Bean BP (2007) The action potential in mammalian central neurons. *Nat Rev Neurosci* 8:451–465
9. Kornell D (1992) Organized variability in the neuromuscular system: a survey of task-related adaptations. *Arch Ital Biol* 130:19–66

Action Potential Conduction

► Action Potential Propagation

Action Potential Propagation

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Synonyms

Action potential conduction

Definition

Movement of the action potential along the cell surface.

Characteristics

The evolutionary pressure to develop the ►action potential resulted from the inability of graded local membrane potential changes to electronically spread across the cell surface over wide distances (►Electrotonic Spread). Self-evidently, the action potential holds its promise to do exactly that, otherwise it would not have evolved. The mechanisms underlying the propagation along muscle fibers and axons are surprisingly simple: amplification of ►graded potential changes into much larger, all-or-none action potentials and electrotonic spread. Action potential propagation

along a nerve or muscle fiber occurs automatically as a consequence of the axonal cable structure (►Cable Theory).

Continuous Action Potential Propagation along an Axon or Muscle Fiber

First consider a smooth muscle or nerve fiber. The mechanism, somewhat simplified, is as follows.

Propagation Mechanism

Since charging or discharging of a capacitor takes some time, expressed in the time constant, the substantial depolarization-induced ionic (Na^+) currents are delayed. The amount of current needed to unload the membrane capacitor by a certain amount depends on the capacitor's surface, which increases linearly with fiber radius, and so the capacitative current required for depolarization should increase by a given amount. But note that the amount of source current also increases linearly with the fiber radius because the number of opening Na^+ channels does.

Conduction Velocity

In axons like the squid axon, the conduction velocity v is related to the ►space constant (►Cable Theory) for electrotonic spread. The reason is simple: The farther the local currents reach out in front at any moment, the more advanced are the membrane regions that are depolarized to threshold for action potential generation the next moment. Thus:

$$v \propto \lambda = \sqrt{R_M/R_i} \quad (1)$$

where R_M is the membrane resistance and R_i is the longitudinal resistance of the fiber interior.

Since, with r being the fiber radius,

$$R_M \propto 1/(2\pi r) \quad R_i \propto 1/(\pi r^2)$$

$$v \propto \sqrt{r} \quad (2)$$

One means of increasing the conduction velocity is therefore to increase the fiber diameter. This means is used especially by invertebrates. For example, the squid giant axon innervates the mantle musculature whose rapid contraction ejects water in the squid's flight reaction. Clearly, a high action potential conduction velocity has a high survival value, and therefore the axon has evolved to reach fiber diameters of 0.5–1 mm and maximal conduction velocities of up to ca. 20 m s^{-1} (depending on ambient temperature).

In higher organisms, however, the evolutionary pressure on the complexity and speed of neural information transmission increases dramatically, requiring an ever-increasing number of fast parallel signal channels. For example, the human optic nerve contains about 1 million

nerve fibers, many of them conducting several times faster than the squid giant axon. These values cannot be achieved with the squid solution of producing “giant” axons. Just imagine how the human optic nerve would look like if made up of giant axons of appropriate conduction velocities. The problem for Nature therefore was to invent a more efficient method that would allow for an increase in velocity without a proportional increase in space as well as metabolic and other costs.

Saltatory Action Potential Propagation along an Axon

Since the conduction velocity is related to cable properties of the axon, a possible solution to the above problem would be to change one or the other cable parameter appropriately. A possible mechanism would be to increase the ►length constant $\lambda = \sqrt{R_M/R_i}$ by increasing R_M , that is, by thickening the membrane somehow (►Cable Theory).

Myelination

The solution Nature came up with is a ►myelin sheath. In the peripheral nervous system, myelin sheaths are built by ►Schwann cells, in the central nervous system they are built by ►oligodendrocytes, this different origin having implications for diseases and restoration of function after injury. A myelin sheath is built by repetitively wrapping the cell membranes of a Schwann cell or oligodendrocyte around an axon, in which process the cytoplasm is squeezed out. Thereby a stretch of axon of 0.5–2 mm length becomes covered by a multi-layered stack of membranes, adjacent stretches being separated by gaps of 1–2 μm . These gaps are called ►nodes of Ranvier and the stretches in between internodes. There may be as many as 100 myelin wrappings between two nodes of Ranvier, producing a sheath as thick as 2 μm [2].

The myelin sheath is a good insulator. With 100 double-membrane layers in the sheath, the Ohmic resistance of the sheath to perpendicular current flow is 200 times higher than that of the single cell membrane. By contrast, because the capacity of a capacitor is inversely proportional to the distance of the plates, the capacity of the myelin sheath and, hence, the amount of charge stored across it for a particular potential difference, is 200 times smaller than that of the single membrane layer. The amount of charge stored on an internodal region of 2 mm length is only about half that stored in a single 1–2 μm ►node of Ranvier [2]. The reduced charge capacity and the higher resistance to transmembrane current flow cause resting and action potentials to be generated only at the nodes.

Saltatory Conduction

When a node is depolarized during an action potential, local circuit currents depolarize the next one ahead,

without discharging the internodal region. The excitation thus hops from node to node rather than coursing continuously through all membrane regions, this mode of propagation being called ►saltatory conduction (saltare, Latin for to leap, dance). The conduction velocity v is determined by a number of factors [2], but largely by the length of the ►internode, which is approximately proportional to the fiber diameter. In myelinated nerve fibers, the conduction velocity is linearly correlated with outer fiber diameter, with the proportionality constant (Hrush factor) being about 6 m/s per μm in cats, where maximal conduction velocities are on the order of 120 m s^{-1} for a fiber of 20 μm diameter. For comparison, according to the square-root rule (1), an unmyelinated squid axon of 20 μm diameter would have a conduction velocity of 4 m s^{-1} [2]. It should be noted that conduction velocity in myelinated and unmyelinated fibers also depends directly on temperature, because the operation of channels does. Na^+ channels, for instance, open more slowly at lower temperatures [2]. This is an experimental means of slowing nerve conduction in human and animal experiments.

Saltatory conduction confers several advantages:

1. Economy of space: A myelinated frog nerve fiber of 10 μm diameter has the same conduction velocity as an unmyelinated squid axon of 500 μm diameter, but 2,500 10- μm fibers can be packed into the volume of a squid giant axon. A mammalian muscle nerve typically contains on the order of 2,000 large-diameter (10–20 μm) fibers and is about 1 mm thick. If the nerve were composed of the same number of unmyelinated fibers of the same conduction velocities, its diameter would lie between 3.5 and 4 cm [2].
2. Economy of energy expenditure: The ► Na^+/K^+ pump that generates and maintains the resting potential is needed only at and close to the nodes of Ranvier, amounting to an immense saving of metabolic energy.
3. High safety factor for conduction: The current density discharging the capacitor at the narrow nodes of Ranvier is so high as to easily secure action potential generation.

In the central nervous system, the “white matter” is characterized by high concentrations of myelinated axons, while the “gray matter” contains lower concentrations of myelin.

Problems with Myelination

The myelin sheath has been an extremely useful invention of Nature to dramatically enhance information transmission and processing capabilities in the nervous system. However, as all good inventions, it has its drawbacks. These are indicated by limits to regeneration after injury (►Regeneration) and various neurological diseases involving myelin.

Axon Regeneration and Its Limits

Prerequisites for functional recovery following axonal interruption (axotomy) in the nervous system are [3]:

1. Survival of the injured neuron.
2. Axon regrowth of sufficient length to reach its target.
3. Axon guidance and path-finding such that the appropriate connections are reformed.
4. Formation and maintenance of functional synapses.

Functional recovery following injury differs dramatically in the peripheral and the central nervous system (►Regeneration). If a peripheral nerve is injured so that some or all of its axons are severed, it usually regenerates by sending out new processes. Thus there is a robust growth of injured axons within the peripheral nervous system of vertebrates and in some regions of the central nervous system of lower vertebrates [3]. This is facilitated by the nerve sheath being intact or resutured surgically. By contrast, axon regeneration is much less likely in the central nervous system. In the central nervous system of adult mammals and higher vertebrates, neurons that survive axotomy extend their axons only a short distance (approximately 1 mm). The reasons for this are multiple and complex, from physical or molecular barriers built by glial scarring at the lesion site, to the possibility that the normal myelinated environment contains potent growth inhibitors or lacks growth-promoting molecules. However, combined approaches raise the possibility of overcoming these problems [4].

Demyelination Disorders

The importance of myelin for normal nervous system operation is attested to by a number of demyelination diseases, two of which are the ►Guillain-Barré syndrome and ►Multiple sclerosis.

Ephaptic Transmission

Demyelination disorders may impair fast action potential propagation, but also lead to non-synaptic contacts between nerve fibers with pathological transfer of electrical impulses.

Composition of Peripheral Nerves

Peripheral nerves are composed of nerve fibers of different degree of myelination, diameter and conduction velocity. Using both histological and electrophysiological techniques, nerve fibers have been classified as shown in Table 1.

Back-Propagation of Action Potentials

In many neurons, action potentials originate close to the origin of the centrifugal axon and then not only travel down the efferent axon, but also ‘back-propagate’ retrogradely into the dendritic tree. These back-propagating action potentials are supported by active, ►tetrodotoxin-sensitive, ►voltage-dependent Na^+ channels and possibly ► Ca^{2+} channels, and decrease in amplitude but increase in width, the further they travel into the tree. The extent of this decremental back-propagation varies widely between different types of central neurons, different specimens of the same sort, and possibly different dendritic branches of individual cells. Back-propagation depends on cell morphology and densities of dendritic ion channels, modulatory influences provided by excitatory and inhibitory inputs and ►neuromodulators [8].

Several functions have been proposed for back-propagating action potentials, among which are [8]:

1. Short-term changes in ►synaptic efficacy due to the back-propagating action potential’s drastic effects on membrane potential and voltage- and

Action Potential Propagation. Table 1 Properties of different peripheral nerve fiber groups (Data from [5–7])

Group		Function	Diameter (μm)	Conduction velocity (m s^{-1})
I	A α	Ia afferents from muscle spindle endings (stretch)	ca. 12–20	ca. 70–120
		Ib afferents from Golgi tendon organs (force)		
		Motor efferents to skeletal muscles		
II	A β	Afferents from cutaneous mechano-receptors (pressure, touch, vibration)	ca. 6–12	ca. 30–70
		Afferents from secondary muscle spindle endings (stretch)		
II	A γ	Motor efferents to muscle spindle (intrafusal ca. 2–8 muscle fibers)	ca. 2–8	ca. 15–30
III	A δ	Afferents for mechano-, chemo-, thermo- and nociception	ca. 1–5	ca. 5–30
		Preganglionic sympathetic efferents		
IV	C unmyelinated	Afferents for mechano-, chemo-, thermo- and nociception	0.1–1.3	ca. 0.6–2
		Postganglionic sympathetic efferents (motor to glands and smooth muscle)		

- time-dependent dendritic ion channels, whereby the properties of synaptic conductances are changed.
2. Long-term changes in synaptic efficacy. It has been proposed that back-propagating action potentials change synaptic efficacy on a long-term time base. Long-term increases in synaptic efficacy often depend on increased Ca^{2+} influx, which may elicit a cascade of metabolic events. The rises in intra-dendritic Ca^{2+} concentrations occur following (i) activation of ►voltage-dependent Ca^{2+} channels due to the back-propagating action potential, (ii) activation of postsynaptic ►N-methyl-D-aspartate (NMDA) channels during depolarization [8]. Thus, nearly coincident pre- and postsynaptic activity and consequent intra-dendritic Ca^{2+} increases would be expected to strengthen excitatory synapses.
- The extent of action potential back-propagation into the dendritic tree is not invariant, but depends on several variables, such as interactions between synaptic inputs and postsynaptic activity and modulatory factors. Appropriately timed excitatory inputs to distal dendrites may enhance action potential back-propagation, and inhibitory (e.g., GABAergic) inputs suppress it [8]. Locally operating inhibitory inputs may control the routes of action potential propagation through the dendritic tree and thereby the action of action potentials on other synaptic inputs. Depending on where in the soma-dendritic tree the inhibition operates, it may differentially influence the propagation of excitatory synaptic currents to the action potential-generating site. Inhibition at the soma would globally shunt excitation originating in vast spaces of the dendritic tree, while local inhibition in the dendrites would counteract excitation originating peripherally to the site of inhibition. The converse may now hold for back-propagating action potentials. Synaptic inhibition acting at the soma may prevent or attenuate back-propagating action potentials and, hence, quench their effects on synaptic inputs widely distributed in the dendritic tree, while local dendritic inhibition may have subtle and selective local effects.
- Recurrent inhibition in the spinal cord is among the types of inhibition influencing action potential back-propagation in ►motoneurons. It has been proposed that recurrent inhibition might provide a mechanism involved in regulating, calibrating and adapting the patterns and quantitative characteristics of excitatory reflex inputs to motoneurons during the stance phase. It could do so by influencing the degree of retrograde invasion of the motoneuron dendritic trees by back-propagating action potentials [9].

References

1. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol (Lond)* 117:500–544
2. Woodbury JW (1965) Action potential: properties of excitable membranes. In: Ruch TC, Patton HD (eds) *Physiology and biophysics*. W.B. Saunders Comp, Philadelphia London, pp 26–58
3. Zwimpfer TJ, Guest JD (1999) Grafting of peripheral nerves and Schwann cells into the CNS to support axon regeneration. In: Windhorst U, Johansson H (eds) *Modern techniques in neuroscience research*. Springer, Berlin Heidelberg New York, pp 379–409
4. Maier IC, Schwab ME (2007) Sprouting, regeneration and circuit formation in the injured spinal cord: factors and activity. *Philos Trans R Soc Lond B Biol Sci* 361:1611–1634
5. Afifi AK, Bergman RA (1980) *Basic neuroscience*. Urban & Schwarzenberg, Baltimore Munich
6. Boyd IA, Davey MR (1968) *Composition of peripheral nerves*. Livingstone, Edinburgh
7. Stein RB (1980) *Nerve and muscle: membranes, cells and systems*. Plenum, New York
8. Waters J, Schaefer A, Sakmann B (2005) Backpropagating action potentials in neurones: measurement, mechanisms and potential functions. *Prog Biophys Mol Biol* 87:145–170
9. Windhorst U (2007) Muscle proprioceptive feedback and spinal networks. *Brain Res Bull* 73:155–202

Action Representation

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Definition

The brain represents actions and this information is used to prepare and execute voluntary movements. Action representations are also drawn upon when we imagine a movement or when we observe and understand actions of others. As regards the underlying brain structures, action representations involve brain activity in the frontal and parietal lobes.

Characteristics

Different Pathways for Perception and Action

Action and perception mutually depend on one another (e.g. when we look for a pen on our desk we first need to detect it visually before picking it up) and it is not evident that the underlying mechanisms can in fact dissociate. Visual input from the retina first reaches occipital cortex and the visual information is then further processed in the ventral and dorsal streams of the brain. Ungerleider and Mishkin [1] postulate that the dorsal stream, from the occipital primary visual areas to the inferior parietal lobule, is involved in the perception

of where objects are in space, whereas the ventral stream, which ends in the inferior temporal cortex, is associated with the perception and recognition of objects. In line with this view, the dorsal and ventral streams are referred to as the “where-stream” and the “what-stream” respectively. It has been suggested that the two streams differ primarily in terms of the output they provide [2]. Indeed, the output provided by the dorsal stream plays an important role in action related processes. Patients with lesions to the posterior parietal cortex (dorsal stream) have an impaired capacity to execute spatially accurate movements to visual targets despite the preserved capacity to correctly estimate the size of the target (optic ataxia) [3]. Lesions to the ventral stream, however, leave intact the ability to act appropriately whereas perceptual judgments are impaired.

Indeed, appropriate actions need not necessarily rely on a perfect perception of a visual target. Studies on visual illusions provide further evidence, an example of which is the Ebbinghaus-illusion: two identical circles appear different in size when one of them is surrounded by set of larger circles (leading to a relative decrease in perceived size) and the other one is surrounded by a set of smaller circles (leading to a relative increase in perceived size). Interestingly, this visual illusion shows up much weaker when measuring the finger grip as participants prepare to pick up the central circle [4]. Thus, the grip aperture turns out to be more adequate to the real size of the circle and thus depends less on the confounding visual context. The representations guiding our movements are provided by a neural substrate that does not completely overlap with those representations involved in visual perception.

Action Observation

One of the most remarkable findings in recent neurophysiological research is the discovery of a population of visuo-motor neurons in the ventral premotor cortex [5]. These neurons were discovered in the macaque monkey’s frontal area F5 (corresponds to area 44 in humans) and have been called “►mirror neurons” as they fire when a goal-directed action is executed and during observation of the same action performed by another agent. These findings gave rise to a new view on how actions are represented. It has been suggested that the mere observation of a motor act causes the observer’s motor system to resonate [5]. Motor representations are thus used to understand the meaning of an observed motor action. Moreover, the premotor areas containing mirror neurons are not driven by the visual input alone as they are still activated when the final part of the observed action is hidden. In this context, intended actions are yet another important factor, which was studied by Iacoboni et al. [6]. In that study participants viewed videos displaying grasping

movements. The video clips showed the action of grasping a cup in the absence of any other object, and exactly the same action in the presence of two different situational contexts: (i) displaying filled cups and cookies as before having tea, and (ii) an after tea setting with empty cups and crumbs. It was the context conditions, which specified the intention of the grasping movement (either for drinking or cleaning up). The activity of premotor areas increased in the context conditions, thus indicating that these neurons do not only fire when we recognize an action but they also take into account the goal behind a specific movement. It has been proposed that these neurons specifically code the “why” of an action. Furthermore, the mirror neuron system is not only involved in the understanding of an action per se, but also in the understanding of body postures or faces expressing emotions. It has been suggested that we infer emotions of others on the basis of an internal simulation.

Imagined Actions

Neuroimaging and behavioral studies on improvements of motor skills showed similar results when participants imagined actions as compared to when the movements were executed (for a review on this topic see [7]). For example, imagined and executed actions are both principally controlled by the contralateral hemisphere and mental practice can improve both the accuracy and the velocity of an action as well as muscular strength. Moreover, heart and respiration rates are also increased during mental rehearsal of an action and this provides further support for the involvement of at least partly the same underlying mechanisms. According to Jeannerod [7] imagined movements can be conceived as covert actions, which involve several action-related mechanisms (with the difference being the non-execution of the action itself). Cerebral lesions provide yet another approach to explore whether and to what extent motor execution and ►motor imagery share the same mechanisms. It has been shown that brain lesions leading to an impaired capacity to execute specific body part movements also affect the capacity to imagine a movement of the same body part. Moreover, the use of mental practice has been shown to improve motor performance after peripheral or cerebral lesions.

Motor representations can also be involved in other mental imagery abilities such as ►mental rotation. For example, when participants have to judge the laterality of pictures of hands shown in different orientations on a screen (is this a left or right hand?), they mentally rotate a representation of their own hand to line it up with the stimulus hand. In this case, a motor strategy is used automatically to process visual stimuli (pictures of hands).

As regards the underlying neuronal representation it has to be pointed out that not only frontal brain areas

play a role in motor imagery tasks. The parietal cortex is involved in predicting through mental imagery the time necessary to perform an action. Sirigu and colleagues [8] investigated the involvement of the parietal cortex in patients with unilateral lesions. They imagined a thumb-finger sequence with either hand. The patients' ability to mentally represent the sequence was impaired when compared to the actual motor performance. The key role the parietal cortex plays in monitoring motor intentions is also supported by a more recent study comparing patients with parietal and cerebellar lesions [9]. Patients were asked to indicate both the onset of a finger movement, and the moment when they have decided to move. Parietal patients were unable to discriminate the onset of movement from the moment in which they felt the urge to move, whereas cerebellar patients behaved like healthy control subjects. Parietal patients also showed a much less pronounced progressive and negative rise in the cortical potentials originating in contralateral motor areas before motor onset. This is supposed to be the neuronal correlate of the decision to initiate a motor preparation. It has therefore been suggested that the parietal cortex might be involved in a conscious self-monitoring of the motor intentions originating within the prefrontal areas.

The Self-Other Distinction

It has been claimed that the experience of oneself being the cause of an action and the representation of the ►bodily self are related. Gallagher [10] distinguished between a “sense of ownership” and a “►sense of agency.” We refer to the former as the feeling of the body belonging to ourselves. The sense of ownership appears to rely strongly on the afferent sensory input. The sense of agency is based on the ability to recognize oneself as the source of one's own actions, thoughts, and intentions. Therefore, the ►efferent information stream of centrally generated commands plays an important role and constitutes the awareness of having initiated an action. Afferent and efferent information are simultaneously involved when people execute actions and it is therefore not easy to isolate their relative contributions to the representation of a coherent bodily self. Imagine, however, someone grasped your forearm and moved it up and down. There is no reason to doubt that you will still consider yourself being the owner of your forearm even though you are not executing its movement and thus are lacking any sense of agency. Interestingly, it has been shown that the contribution of efferent information helps to better recognize one's own movements when proprioceptive and visual information are not conclusive. Clinical cases suggest dissociations in the reverse direction such as the alien hand syndrome (patients attribute to others their own body parts despite preserved motor functions).

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References

1. Ungerleider LG, Mishkin M (1982) Two visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW (eds) Analysis of visual behavior. MIT Press, Cambridge, pp 549–586
2. Milner D, Goodale MA (1995) The visual brain in action, Oxford University Press, Oxford
3. Himmelbach M, Karnath HO (2007) Optic ataxia: a gateway to the human visual action system. In: Mast FW, Jänecke L (eds) Spatial processing in navigation, imagery and perception. Springer, Berlin Heidelberg New York, pp 85–105
4. Haffenden AM, Goodale MA (1998) The effect of pictorial illusion on prehension and perception. *J Cogn Neurosci* 10:122–136
5. Rizzolatti G, Fogassi L, Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2:661–670
6. Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G (2005) Grasping the intentions of others with one's own mirror neuron system. *Plos Biology* 3(3):e79
7. Jeannerod M (2001) Neural Simulation of action: a unifying mechanism for motor cognition. *Neuroimage* 14:103–109
8. Sirigu A, Duhamel JR, Cohen L, Pillon B, Dubois B, Agid Y (1996) The mental representation of hand movements after parietal cortex damage. *Science* 273:1564–1568
9. Sirigu A, Daprati E, Ciancia S, Giroux P, Nighoghossian N, Posada A, Haggard P (2004) Altered awareness of voluntary action after damage to the parietal cortex. *Nat Neurosci* 7:80–84
10. Gallagher II (2000) Philosophical conceptions of the self: implications for cognitive science. *Trends Cogn Sci* 4:14–21

Action Tremor

Definition

Also called kinetic tremor is a tremor that occurs during voluntary movement.

►Essential Tremor

Activation

►Ion Channels from Development to Disease

Activation Gating

Definition

Specialized molecular regions of the ion channel protein, which undergo sequential conformational changes leading to channel activation (open-conductive configuration). For a voltage-gated channel the activation gate is controlled by a number of charged amino acids (gating charges), which move under the action of the electric field acting across the membrane and opens the channel.

Active Avoidance Learning

Definition

Active avoidance is a term applied to a class of tasks in which animals are required to actively exhibit certain experimenter-defined responses in order to avoid punishment. Behaviors that are more compatible with natural defensive responses to aversive stimuli (see SSDR in glossary) are more easily learned.

- ▶ Aversive Learning
- ▶ Passive Avoidance Learning

Activation Studies

Definition

Studies based on the fact that alteration in neuronal activity in a region correlates with alteration of local cerebral blood flow in the same region during a task performance. Alteration (activation) of a region indicates that it is involved in the maintenance of the task activity.

- ▶ Positron Emission Tomography

Active Electrolocation

Definition

The process by which weakly electric fish can sense their surroundings by detecting distortions in their own electric field.

- ▶ Reafferent Control in Electric Communication
- ▶ Temporal Coding in Electoreception

Activational Hormonal Effects

Definition

Acute changes in structure and/or function of particular anatomic systems; often resulting from natural hormonal fluctuations (e.g. menstrual cycle) or laboratory manipulation (e.g. gonadectomy) of adult organisms.

Activators

- ▶ Stimulants

Active Touch

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Definition

Active touch refers to the act of touching, and implies voluntary, self-generated movements. With active touch, the environment is explored using specialized touch organs (the hand or forepaw, whiskers in rodents) in order to gather information about the properties of surfaces (texture, hardness, temperature) and/or objects (size, shape, weight, location) located in the nearby peripersonal space. In contrast, passive touch, or the act of being touched, implies that the sensory input is generated by an external agent; this type of touch is not generally exploratory in nature (although there can be exceptions in the laboratory situation). For both modes of touch, the

sensory input can be dynamic, implying movement between the skin and the object, or static (no movement). For example, a hand-held object can be identified using a combination of active exploratory movements, turning the object over to examine all of its surfaces (dynamic active touch), combined with periods of static holds (static active touch). A special type of dynamic passive touch, often used in experimental situations, is to displace surfaces, mounted on a drum or a moveable platform, over a single region of skin.

Characteristics

Quantitative Description

Active touch is a complex, goal-oriented behavior. A wide range of relatively stereotyped movements accompany tactile exploration, and these are optimized to seek specific sensory information.

Description of the Process

In humans and other primates, the hand is generally used for active tactile exploration of the surround. Early in development, human infants preferentially use the mouth and perioral region for active tactile exploration; these regions continue to play an important role throughout the life span, but with more restricted roles (appetitive and sexual). Other species use different body parts for active tactile exploration, an important experimental model being the rodent vibrissa system, along with the associated whisking behavior. In all cases, the body regions used for active tactile exploration are characterized by having a high density of peripheral sensory receptors, a correspondingly large cortical representation (both sensory and motor), and high sensory acuity.

One important difference between primates and most other mammals is, however, the fact that the hand is not only a touch organ, but also has highly developed effector functions as witnessed by their ability to make independent finger movements. Indeed, humans are distinguished from other primates because the manipulative functions of the human hand are combined with our unique ability to build and use complex tools. This essay concentrates mainly, but not exclusively, on studies of active touch in humans and non human primates.

Sources of Feedback During Active Touch

Depending on the exploratory strategy used (see below), active touch can generate both cutaneous and proprioceptive feedback. The specialized skin mechanoreceptors innervated by large fiber myelinated afferents are considered to play a key role in discriminative touch (texture, local shape and pattern recognition). Proprioceptive signals, related to joint movement (**►kinaesthetic signals**) and position, arise from muscle (muscle spindle,

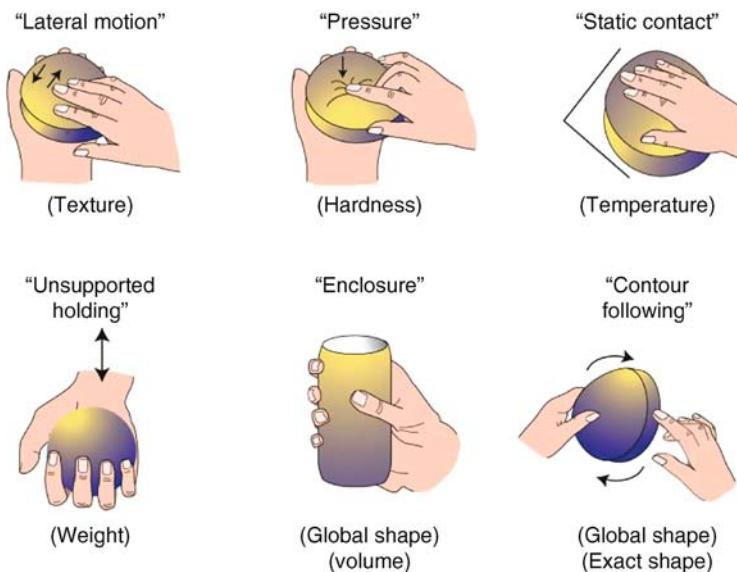
Golgi tendon organs), joint, and skin mechanoreceptors. Simultaneous cutaneous and proprioceptive feedback is often elicited when actively exploring the shape of an object, and this combined input is called haptic feedback [1]. The term haptic comes from the Greek term *haptesthai*, meaning “able to come into contact with” (OED online, <http://www.oed.com/>). In addition to the sensory feedback generated during active touch, subjects also have knowledge of the motor commands that guide the exploratory movements. Indeed, the ►primary somatosensory cortex (S1) is the only *primary* sensory receiving area to have direct, reciprocal connections with primary motor cortex, the region involved in the execution of active exploratory movements. Thus, S1 is well-placed to provide on-line sensory information critical for controlling the exploratory processes. Additional somatosensory inputs to motor cortex come from other parietal regions (area 5 and the ►secondary somatosensory cortex, S2), and also from the cerebellum via the motor thalamus (ventral lateral posterior nucleus).

The Exploratory Process

The movements used during active touch have the overriding goal of generating high quality sensory feedback. While tactile information can be gathered through a simple static contact, it is generally acknowledged that tactile perception is better with dynamic stimuli as compared to static stimuli. For example, roughness discrimination thresholds are approximately halved when using dynamic touch as compared to static touch [2]. The superiority of dynamic touch over static touch can be explained by several factors. Dynamic touch recruits rapidly adapting cutaneous mechanoreceptors [RA (**►RA afferents**) and ►PC afferents or Pacinian afferents] as well as slowly adapting cutaneous mechanoreceptors [SA types I and II (**►SAI and SAII afferents**)], while static touch only activates SA receptors. Also, the discharge rates for SA afferents are higher for dynamic stimuli than for static stimuli, increasing the signal-to-noise ratio. Finally, S1 neurones show a bias for dynamic as opposed to static stimuli, so that the population of neurones contributing to the processing of the tactile input is potentially larger for dynamic inputs.

During active tactile exploration, the types of movements made are critically dependent on the information sought. In fact, humans use a series of stereotyped movement patterns (also called exploratory procedures) in order to seek specific sensory information (Fig. 1) [3].

Static contact alone can provide information about the temperature, volume and global shape of an object, particularly for smaller or local geometric features (corresponding to what can be sensed with the fingertip) as well as providing some information about surface texture. The *pressure* exploratory procedure, essentially poking an object with the finger, gives information about its softness/hardness, along with other surface



Active Touch. Figure 1 During active tactile exploration of objects and surfaces, different exploratory procedures are used depending on the property, or properties, sought (in parentheses). (After [3], with permission of the authors and Elsevier Ltd.).

properties (temperature, texture). *Lateral motion*, or rubbing the fingers back and forth over a surface, is important for texture appreciation. The other exploratory procedures are used for extracting information about global object properties. These include *unsupported holding* (object is held in the hand and often hefted; this movement is important for weight estimation), *enclosure* (provides a general appreciation of both the material properties and global shape of objects by enveloping the object closely in the hand; static hold alternates with movements to shift the position of the object in the hand), and *contour following* (trace out the exact shape of objects). The exploratory procedures that are specialized for seeking information about surface properties (texture, temperature, local geometric features) are characterized by the fact that exploration is performed using the most sensitive skin surface of the hand, the fingertips.

Active touch generally employs relatively slow movements. For example, when an otherwise smooth surface is explored to find a small raised square (0.28 mm in height), then average exploration speed is 85 mm/s (range 55–110 mm/s) [4]. To put this into context, fair to good Braille readers scan text at 60–125 mm/s, while excellent Braille readers use faster scans of up to about 190 mm/s. The optimal scanning speed may, however, vary as a function of the task. For example, when subjects evaluate surface texture within the context of a forced-choice texture discrimination task, then higher average speeds are used, 160 mm/s (sinusoidal movements corresponding to the lateral motion exploratory procedure) [2]. The importance of optimizing speed during tactile exploration is

emphasized by observations that perceived roughness shows a modest decline when subjects are asked to adopt very rapid scanning speeds of ~200 mm/s; this latter falls outside the very wide range of speeds that subjects voluntarily choose when scaling roughness (~10–150 mm/s). With rapid movements, the stimulus likely becomes less effective, as there is less time for mechanical deformation of the skin as it passes over the textured surface. Finally, movements may slow considerably when the finger encounters a salient feature, presumably to optimize the quality of the sensory feedback elicited during the exploration. Thus, finger movement is very slow (3–4 mm/s) when subjects feel an object in order to estimate its softness or compliance.

The contact forces applied during active exploration with the fingertip are relatively light [4]. For example, average normal forces of ~0.5 N are used during tactile search for a small raised element. Most importantly, subjects adopt a strategy of keeping normal force relatively constant for a given tactile exploration task, but this is adapted depending on the goal. If subjects seek a small recessed, rather than an elevated, target, then normal force is slightly increased to ~0.65 N presumably to maximize the amount of skin penetrating the recessed square and so to improve detection.

Lower Level Processes

The mechanisms involved in generating the active movements essential for active touch have been described in another essay. The sensory receptors found in the skin and various deep tissues (muscle, joints),

and that are activated during active touch, have also been described elsewhere.

Higher Level Processes

Is Perception Equivalent With Active and Passive touch?

Intuitively, it seems obvious that active touch, in which case the salient sensory inputs are self-generated, should show an advantage over passive touch because the exploration is controlled and optimized by the subject. Indeed, Gibson [1] argued strongly that passive touch, in which the parameters of stimulation are controlled by an external agent, is an unnatural experience. He argued that active touch should be considered an entirely different order of sensory experience since the sensory impressions are directly projected to the environment. For example, during manual exploration of an object like a pencil or a paper clip, it is the object that is perceived and not the areas of skin contacted or the finger movements.

A number of studies have compared perceptual performance using active and passive touch, but these have concentrated almost exclusively on tasks dependent on cutaneous feedback. Their results show that perceptual performance with active and passive touch is similar when exploratory conditions are suitably matched [5]. Equivalence for active and passive touch has been shown for a variety of cutaneous tasks, including the detection of minute surface irregularities, texture discrimination, scaling the roughness of various surfaces, and recognition of raised tactile patterns (letters, Braille characters). Occasionally, investigators have shown an advantage for active touch over passive touch, e.g. recognition of Braille characters, but the findings have not been confirmed in other studies using similar types of pattern recognition tasks.

Few studies have looked at abilities dependent on haptic feedback within the context of the active-passive debate. This is a difficult problem, one that cannot be easily addressed, because the presence of the motor command itself modifies the sensitivity of muscle and joint proprioceptors to limb movements. Coactivation of the gamma motoneurones along with the alpha motoneurones directly modifies muscle spindle sensitivity to stretch; activation of muscles inserting into the joint capsule also modifies joint receptor sensitivity to movement. Thus, the sensory feedback during passive movements is likely substantially different from that associated with active movement (see also below). Despite these reservations, there have been a few attempts to compare active and passive touch, e.g. comparing performance during active and passive tactal exploration of raised line drawings of the type used in reading aids for the blind [5]. This task combined tactile feedback from the exploring index finger along with kinaesthetic feedback from the arm as the image is explored. When exploration time was limited (5 s), then active touch was better than passive;

this advantage disappeared when more time was allowed for passive touch (30 s). These observations suggest that active touch is more efficient than passive touch, but it is not clear whether the task used was truly haptic in nature, since performance depended most critically on the arm trajectory and so kinaesthetic feedback. With technological advances, it is now possible to use a robot arm with added force feedback to generate virtual shapes, and explore these by moving around a manipulandum (kinaesthetic feedback); force feedback is sensed both through the hand grip (cutaneous feedback), and the sense of effort required to perform the exploration. Although not directly tested yet, it appears that discrimination abilities may be similar for active and passive explorations of virtual shapes [6]. This is quite surprising given that the sensory feedback during passive movements is likely different from that during active movement (including no force feedback during the passive testing). If anything, the results argue in favour of considerable redundancy in encoding haptic shape.

To summarize, current evidence indicates that there is perceptual equivalence for active and passive touch in a range of tasks, mostly dependent only on cutaneous inputs. Active touch, on the other hand, likely enjoys an advantage over passive touch in being more efficient: the relevant sensory information is collected, and analyzed, more rapidly. More fundamentally, active, but not passive, touch is used for exploration.

Neuronal Mechanisms of Active and Passive Touch

As much of the evidence points in favor of similar perceptual abilities with active and passive touch, there has been a tendency to consider that the underlying neuronal mechanisms must be the same. One school of thought believes that sensory inputs are processed in the same fashion, regardless of the mode of touch; another school of thought (above) believes that active touch is more than the sum of its parts (cutaneous and proprioceptive inputs), including as it does a voluntary, intentional component.

During active touch, recordings of neuronal activity in S1 cortex show that the pattern of discharge reflects the expected discharge of the various peripheral mechanoreceptors (cutaneous and proprioceptive) activated during tactile exploration [7], with active touch being inherently noisier than passive touch because of associated discharge related to joint movements. In addition, small numbers of cells are active well in advance of movement onset, possibly reflecting the motor command itself, given the existence of reciprocal connections between motor cortex and S1. A variety of discharge patterns are found during active touch: the discharge frequency of some cells varies with both the stimulus (e.g. surface texture) and the movement parameters (speed, contact force); others show invariant responses to tactile

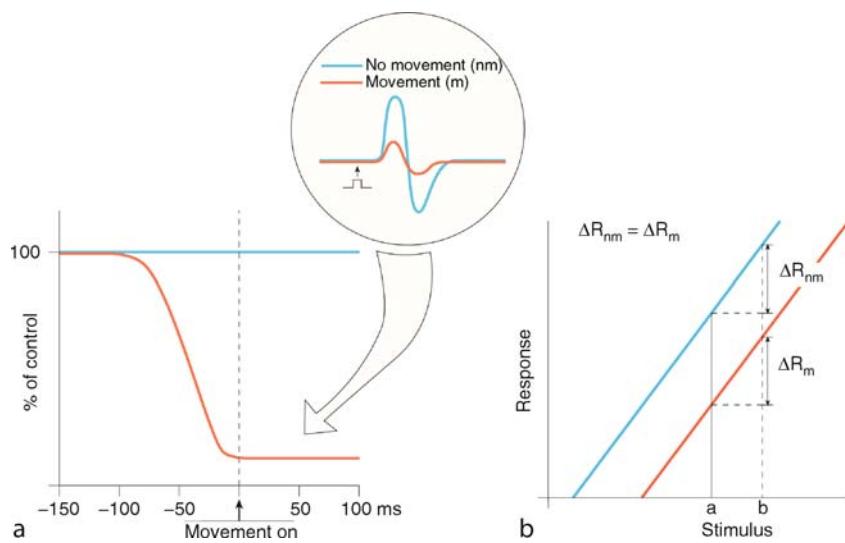
features, independent of the motor kinematics or kinetics; yet others signal information about the movement parameters alone. In contrast, S1 neuronal responses during passive touch are more focused, reflecting the details of the applied stimulus. As with active touch, a proportion of S1 cells show invariant responses to tactile features during passive touch, independent of the parameters of stimulation, e.g. the speed at which textures are displaced under the finger tips.

The movements that accompany active touch bring an added complication to the central processing of somatic sensory signals since the act of movement modulates the transmission of tactile inputs to S1 cortex. This phenomenon is widely referred to as movement-related gating of sensory transmission [5]. Both the motor command (efference copy) and sensory feedback from the moving limb (movement reafference) contribute. Sensory inputs are most frequently diminished during movement, but there is also evidence that some inputs can be selectively enhanced during active exploration. Much of the evidence showing gating during active movement comes from studies in which externally generated test stimuli (e.g. air puff or electrical stimuli) are applied to the body surface, so corresponding to passive touch [5]. These studies have shown that sensory inputs from the moving limb are diminished prior to, and during, movement (Fig. 2a).

Parallel changes in tactile detection and magnitude estimates are seen. In contrast, the relative differences

between suprathreshold stimuli are preserved (Fig. 2b). This latter observation is particularly important for the active-passive touch debate, because the majority of studies showing similar perceptual abilities for active and passive touch used tactile discrimination tasks, dependent on judgments of the relative differences between suprathreshold inputs, and not the absolute amplitude of the signals. Since relative differences are preserved during movement, performance is similar. This observation helps to explain the paradoxical observation of perceptual equivalence for active and passive touch, in the face of movement-related suppression in the transmission of tactile stimuli to S1 cortex.

Recordings from single S1 cortical neurons, in both monkeys and rats, indicate that even behaviorally relevant inputs during active touch show evidence for the existence of movement-related suppression of their responses: many neuronal evoked responses during active touch are smaller than those evoked during passive touch, consistent with a gating out of tactile inputs during movement [5,8]. Although it is difficult to ensure that stimulation is identical during both modes of touch, some S1 cells signal somatic stimuli equally well during active and passive touch, consistent with relative sparing from movement-related suppressive influences. In addition, the population of cells encoding behaviorally relevant inputs is actually smaller during active touch than passive touch, possibly reflecting some pruning of the inputs so that only cells directly involved



Active Touch. Figure 2 (a) During movement, there is a decrease in the amplitude of somatosensory evoked potentials (SEPs) recorded from the dorsal column-medial lemniscal pathway that conveys cutaneous and proprioceptive feedback from the periphery to primary somatosensory cortex (S1) (inset). The time-course of gating is identical for both perception (detection of near-threshold tactile stimuli) and SEPs, with the decrease preceding the onset of movement. (b) Psychophysical results suggest that gating is associated with a downward shift of the stimulus-response curve: the perceived magnitude of suprathreshold stimuli is decreased during movement (red curve) while relative differences, ΔR , and so the discrimination threshold, are preserved.

in the behavioral task are activated. The functional role of this suppressive mechanism is most likely to reduce the flow of afferent information that can be predicted from the motor command so that the detection of unexpected or novel stimuli is enhanced. Finally, there is evidence that inputs can be selectively gated in during active touch: neurones in monkey area 2 (S1) that lack an obvious peripheral receptive field, discharge in relation to specific shapes actively grasped in the hand [9]. Similarly, no-receptive field neurones in S2 encode surface texture during active touch.

To summarize, there has been a long-standing debate about the perceptual equivalence of active touch and passive touch. The underlying neuronal mechanisms differ, in part, because only active touch involves active voluntary movements. Moreover, apart from laboratory studies, passive touch is not used for exploration. It thus seems unwise to generalize from results obtained using one form of touch to the other. For example, it is conceivable that the motor commands associated with active touch may trigger central mechanisms (e.g. attention) that contribute to enhance neuronal responses to salient inputs during active touch. Finally, active touch enjoys a number of advantages over passive touch: digits can be oriented so that the most sensitive skin areas contact the object and; movement speed can decline at critical times during exploration, so minimizing suppressive gating influences (themselves speed-dependent).

Function

Active touch allows one to identify salient objects or surfaces in the immediate peri-personal space using the cutaneous and proprioceptive feedback generated during the exploration. One can then act on this information, either to control or interact with the surrounding environment. A typical example might be to search for a key in one's pocket; the key can then be used to unlock a door. This example highlights the use of the hand both as a touch organ and an effector (wielding a tool).

Pathology

Lesions of the anterior part of the parietal lobe (S1) produce profound deficits in somaesthesia, including both simple (light touch, two-point discrimination, position sense, vibration sense) and complex abilities (e.g. tactile object recognition, visuotactile matching). In contrast, patients with lesions of the posterior parietal cortex (posterior S1 and areas 5 and 7) are particularly impaired on complex tasks. Some of these patients also show difficulties in generating exploratory and manipulative finger movements within the context of active touch, although they can imitate the appropriate finger movements [10]. Such observations suggest that posterior parietal cortex plays an important role in generating and executing exploratory movements

within the context of using sensory feedback to choose and execute the appropriate exploratory procedure. This dissociation has been most clearly described in a case report of a patient with a deficit in tactile object recognition using active touch, but not passive touch. The patient had a large infarct that spared S1 but encompassed regions of the infero-posterior part of the parietal lobe (possibly including S2), as well as the temporal lobe and the frontal operculum. Thus, deficits in active touch do not necessarily follow directly from the problems in processing somatosensory information.

Active touch is also critically dependent on the integrity of the somatomotor system, and so lesions of, for example, the hand representation within the primary motor cortex (area 4 of the frontal lobe) result in profound deficits in active hand/digit movements, and so active touch. Even lesions restricted to more proximal parts of the arm representation (elbow, shoulder) can cause difficulties in active tactile exploration because the whole arm is frequently employed (for example, as one searches for a light switch in the dark).

Thus, active touch is critically dependent on the integrity of both the somatosensory cortical regions in the parietal lobe, as well as the various precentral motor cortical regions involved in planning and executing exploratory movements.

► Haptics

References

1. Gibson JJ (1962) Observations on active touch. *Psychol Rev* 69:477–491
2. Morley JW, Goodwin AW, Darian-Smith I (1983) Tactile discrimination of gratings. *Exp Brain Res* 49:291–299
3. Lederman SJ, Klatzky RL (1987) Hand movements: a window into haptic object recognition. *Cogn Psychol* 19:342–368
4. Smith AM, Gosselin G, Houde B (2002) Deployment of fingertip forces in tactile exploration. *Exp Brain Res* 147:209–218
5. Chapman CE (1994) Active versus passive touch: factors influencing the transmission of somatosensory signals to primary somatosensory cortex. *Can J Physiol Pharmacol* 72:558–570
6. Soechting JF, Poizner H (2005) The use of motion cues in the haptic sense of circularity. *Exp Brain Res* 165:413–421
7. Chapman CE, Tremblay F, Ageranioti-Bélanger SA (1996) Role of primary somatosensory cortex in active and passive touch. In: Wing A, Flanagan R, Haggard P (eds) *Hand and brain: neurophysiology and psychology of hand movement*. Academic Press, San Diego, CA, pp 329–347
8. Hentschke H, Haiss F, Schwarz C (2006) Central signals rapidly switch tactile processing in rat barrel cortex during whisker movements. *Cereb Cortex* 16:1142–1156

9. Iwamura Y, Tanaka M (1978) Postcentral neurons in hand region of area 2: their possible role in the form discrimination of tactile objects. *Brain Res* 150:662–666
10. Freund HJ (2003) Somatosensory and motor disturbances in patients with parietal lobe lesions. *Adv Neurol* 93:179–193

Active Vision

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Definition

The eyes are not static recorders of the visual surroundings. They scan the scene for new information by making fast eye movements (**saccades**) up to 4 times a second. Active vision is the study of the relations of these patterns of fixations to the control of ongoing behavior [1].

Characteristics

Why Move the Eyes?

The human **fovea**, the region of maximum acuity, has a maximum angular diameter of 2° , which means that it covers an area equivalent to a thumb nail at arm's length. Acquiring detailed information from different places thus requires the eyes to move. A second requirement of vision is that, having moved, gaze must remain still until the next eye movement. This is because the **photoreceptors** are slow to respond, and image motion results in blurring at speeds of more than a few degrees per second. As a result our usual method of viewing the world is with a saccade-and-fixate strategy in which we take in information during "snapshots" that typically last about 300 ms. Our eyes are then in rapid motion for about 30 ms, during which we are effectively blind. A major question in active vision is how the sequences of fixations that we make are adapted to the needs of the current task.

Patterns of Gaze During Different Activities

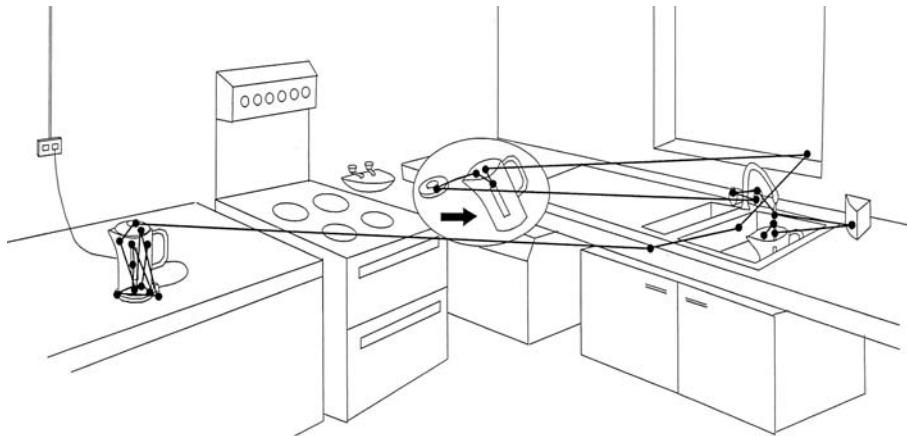
The task we are engaged in determines the pattern of fixations that we make. In reading Western languages the eyes move saccadically from left to right taking in about seven characters per fixation [2]. Interestingly this number is almost independent of the size of the type, indicating that the brain can scale saccade size to fit the letter spacing. In sight-reading piano music gaze alternates between the upper and lower staves, reading approximately 3 notes per fixation. In both reading aloud and sight-reading the time between seeing a

note or letter and speaking or playing it is about 1 s. Typing is similar. All three activities operate like conveyor belts. The content of each fixation passes through a processor to produce an appropriate motor act and leaves nothing behind, except meaning in the case of reading. Sight-reading is particularly interesting because the two staves are read serially, but combined in the processor to be emitted simultaneously by the fingers.

In **locomotory** activities such as walking vision is only used to guide the feet if the terrain is rough or there is a need to avoid obstacles. In those cases the point of gaze is about two steps ahead of the next footfall, though not usually exactly on the point of the footfall itself [3]. About twice as many saccades are made as there are footfalls, and the time interval between gaze position and footfall is again about 1 s. When driving the way gaze is deployed on the road varies with the type of road and traffic conditions. On winding country roads where continuous monitoring of curvature is essential many studies have found that drivers' gaze tracks the tangent point on the inside of the bend [4]. This is the moving point on the outward convexity of the road edge (or center line) where the line of sight is tangential to the lane marker. Provided the driver maintains a constant lateral position in the lane, the direction of this point relative to the driver's present direction of travel provides a direct measure of the curvature of the bend ahead, and hence can act as a direct feed-forward control signal for steering. In practice there is a very high correlation between observed tangent point direction and steering wheel angle, after a delay of about 0.8 s. The delay here is necessary because the vehicle has not yet reached the point where the curvature was measured. Town driving is very different. The main problem there is to find a route through parked vehicles, oncoming traffic and other obstacles. Gaze typically alternates between the various hazards, checking their moving locations at a rate of several fixations per second.

In ball games such as cricket gaze does not always follow the ball, but often anticipates its future position. Thus in cricket a batsman watches the bowler's delivery, and from the apparent speed of descent of the ball estimates the location of its bounce point. A gaze saccade is made to this point, reaching it about 100 ms before the ball [5]. In this way the location, time of arrival and behavior of the ball when it bounces can be observed, and from these the time and position of contact with the bat can be obtained. Much the same happens in table tennis, and no doubt lawn tennis as well, although that game is too fast to allow currently available head-mounted eye trackers to be used.

Some of the most interesting patterns of **eye-hand coordination** are seen in such ordinary domestic activities as food preparation [6]. These activities consist of a series of actions based around objects such as kettles, mugs, knives etc. (Fig. 1).



Active Vision. Figure 1 Eye fixations during the first 10 s of a tea-making video in which the participant inspects the kettle, picks it up, moves it to the sink while removing the lid, positions it under the faucet and turns on the tap. The 26 fixations are almost entirely on the objects involved in the action (the sink tidy on the right is the sole exception). They supply the information required for the task at the time it is needed. From [6].

There are three motor components to these object-related actions. First, if needed, there is a movement of the whole trunk towards the next object; this is followed about half a second later by the first fixation of the eyes on the object, and about half a second after that the hands start to move to perform one or more manipulations on the object. Interestingly, gaze moves on to the next object in the sequence about half a second before manipulation of the present object is complete, implying the existence of a buffer holding whatever information is required to complete the last action. The functions of the different fixations that are made during such actions can be classified into four categories. “Locating” (or “look-ahead”) fixations establish the locations or attributes of objects to be dealt with in the future, with no action occurring at the time. “Directing” fixations accompany actions where an object is fixated prior to a hand movement towards it or gaze moves to position where an object is to be set down. Typically only a single fixation is involved, and gaze usually leaves the object or set-down point before the hand reaches it, so that the act is completed without visual feedback. “Guiding” fixations are concerned with manipulations involving more than one object, for example a kettle and its lid, where both objects have to be guided relative to each other under visual feedback so that they dock in an appropriate way. Most tool use is of this kind (e.g. hammer and nail, spanner and nut). “Checking” fixations determine when some condition is met, for example the kettle is filled, the water boils, or the lid is off the bottle. Such fixations, which may be unusually long if there is a delay before the condition to be met, usually terminate actions and trigger the next one. Interestingly the hands themselves are rarely if ever fixated, nor are objects once they have been

acquired by the hands. It seems that vision is a scarce resource and is only employed when ►proprioceptive and ►haptic information is unavailable.

General Rules for the Use of Vision During Action

As the preceding paragraphs indicate, gaze is used to obtain the information needed by the action system, and each kind of action has a unique (though not exactly replicable) pattern of fixations associated with it. In other words the fixation sequences are highly task-specific. Early in the study of the subject Ballard [7] and his colleagues suggested two rules that seem to hold for most patterns of eye-hand coordination. The first is the “do it where I’m looking” strategy, which states that the point of fixation is usually very close to the point where action is taking place. Actions are not performed in peripheral vision, nor are they performed from memory when vision is available. The second is the “just in time” rule: actions are usually initiated within a second of the fixation that provides the information for that action. Both rules imply that memory is used frugally. Apart from look-ahead saccades, which do contribute to future action planning, there is little evidence that actions are set up in detail in advance of their execution.

What Drives Fixation Sequences?

A key question in the study of eye movements is: “What determines where the next saccade will land?” A popular model for the specification of saccade targets involves “►salience” [8]. Certain image features – contrast, color, high spatial frequency content, motion – are said to be salient, and it is argued that saccades are directed to those parts of the visual field where the appropriately weighted sum of such features is greatest. Whilst this may hold when vision is otherwise uncommitted, it certainly

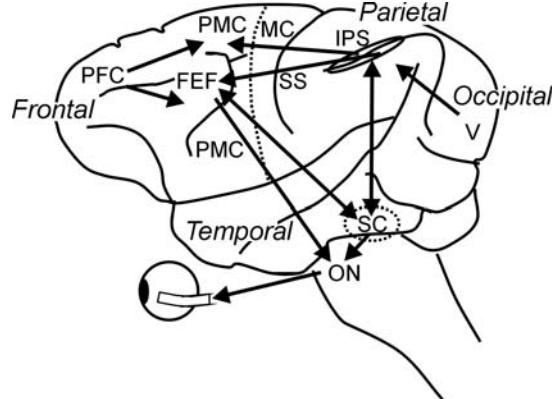
does not hold during active vision. Yarbus [9] demonstrated over 40 years ago that when subjects are asked to look at a picture the pattern of eye movements they make depends crucially on what the experimenter has asked them to look for. Thus there is a very strong “►top down” control over fixation sequences, as opposed to “bottom up” control by image features. The same is true during visually guided actions. In food preparation, for example, it is very rare to see fixations directed to objects that are not relevant to the action sequence, even though there are distracting objects around which, on a salience basis, should attract gaze more strongly.

What then does determine fixation sequences during active vision? Electrode recordings from monkeys and ►fMRI scans in humans have provided some information about their neural basis. For complex routines such as tea making it is necessary to assume that it is the overall plan, or script, of the activity which determines what is targeted, and in approximately what sequence. These plans originate in the ►prefrontal cortex (PFC) in primates and man. They specify to the eye movement system what is the next object to be fixated, and with that provide information about its likely location and appearance. Remarkably, objects are often fixated with a single saccade even when they are in the far periphery, indicating the efficiency of this process. The script must also inform the motor system what action to perform, and the eye movement system what to monitor as the action progresses. Many parts of the brain are involved (Fig. 2).

Output to the ►brainstem nuclei of the oculomotor system (oculomotor nuclei, ON) which move the eyes comes from the ►frontal eye fields (FEF) and ►superior colliculi (SC), with the ►parietal cortex involved in the coordination of reaching and grasping [10]. The limb motor system also has an input from the parietal lobe and from the ►somatosensory cortex (SS) and generates its output to the ►spinal cord via the ►premotor cortex (PMC) and ►primary motor cortex (MC). Visual input to both systems comes ultimately from the occipital lobe, and the temporal lobe is also likely to be involved in establishing the identity of objects. The coordination of apparently simple actions is a complex neural operation.

Conclusions

Although we can direct our gaze direction by an act of will, this rarely happens; for most of the time fixation patterns are automatic and are not available to conscious scrutiny. We are even unaware that we look around the room in a series of discontinuous jerks, rather than a smooth scan. The principal function of the eye movement system in man is to direct gaze to locations where the eyes can provide the executive systems of the brain with the information they need for perception and action. To do this the eye movement system has its own knowledge base – of where to look on a winding road, for example, or



Active Vision. Figure 2 Drawing of the left-hand side of a macaque brain showing some of the regions and pathways involved in the neural control of reach-and-grasp movements. Details in the text. The names of the four lobes of the cortex are shown. Abbreviations: FEF frontal eye fields; IPS intraparietal sulcus; MC primary motor cortex; ON oculomotor nuclei of the brain stem; PFC prefrontal cortex; PMC premotor cortex; SS somatosensory cortex; SC superior colliculus of the mid brain; V primary and secondary visual areas of the occipital lobe. The cortical output to the limbs originates in the motor cortex (MC) and runs to the spinal cord via the brainstem.

how to read a double stave of music – which we cannot access by introspection. Objective eye-movement recording is the only way to study this hidden information.

References

- Findlay JM, Gilchrist ID (2003) Active vision. Oxford, Oxford University Press
- Rayner K (1998) Eye movements in reading and information processing: 20 years of research. *Psychol Bull* 124:372–422
- Patla AE, Vickers JN (2003) How far ahead do we look when required to step on specific locations in the travel path during locomotion. *Exp Brain Res* 148:133–138
- Land MF, Lee DN (1994) Where we look when we steer. *Nature* 369:742–744
- Land MF, McLeod P (2000) From eye movements to actions: how batsmen hit the ball. *Nat Neurosci* 3:1340–1345
- Land MF, Hayhoe M (2001) In what ways do eye movements contribute to everyday activities. *Vision Res* 41:3559–3565
- Ballard DH, Hayhoe MM, Pelz JB (1995) Memory representations in natural tasks. *J Cogn Neurosci* 7:66–80
- Itti L, Koch C (2000) A saliency-based search mechanism for overt and covert shifts of visual attention. *Vision Res* 40:1489–1506
- Yarbus A (1967) Eye movements and vision. Plenum Press, New York
- Jeannerod M (1997) The cognitive neuroscience of action. Blackwell, Oxford

Active Zone

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Synonyms

Site of regulated neurotransmitter release

Definition

Physiologically, the active zone is defined as the restricted area of the presynaptic plasma membrane, at which ►synaptic vesicles can fuse and regulate neurotransmitter release can occur. The active zone, as defined here, consists of two major parts, the active zone plasma membrane and the associated cytoskeletal matrix, which is called presynaptic dense projection, presynaptic grid, presynaptic particle web or ►CAZ (cytomatrix assembled at the active zone) [1,2].

The general description given here refers to conventional chemical synapses of the central nervous system. It should be noted that different types of chemical synapses display differential adaptations of their active zones and the associated cytomatrices to their specific function. Of these specializations, we will briefly consider here the active zone of vertebrate ►neuromuscular junctions and of so-called ►ribbon synapses, i.e. specialized excitatory high-throughput synapses occurring, for example, in ►photoreceptor cells or bipolar cells in the retina or in ►inner ear hair cells.

Characteristics

Quantitative Description

Typically, the active zone has a diameter of several hundred nanometers. For representative conventional synapses in mouse hippocampus and piriform cortex, average surface areas of $\sim 0.04 \mu\text{m}^2$ (square microns) and $\sim 0.095 \mu\text{m}^2$ have been determined, respectively [3]. Active zones rarely exceed an area of $0.4 \mu\text{m}^2$, and large synaptic boutons would rather form multiple active zones than exceed this upper “limit.” On average, these active zones accommodate one docking site for synaptic vesicles per $3800\text{--}6200 \text{ nm}^2$ [3].

Specialized synapses have active zones of different sizes and shapes adapted to their particular function. At the vertebrate neuromuscular synapse, for example the frog’s ►neuromuscular junction, the active zone is frequently $1\text{--}2 \mu\text{m}$ (microns) long and $\sim 75 \text{ nm}$ wide [4].

Higher Level Structures

The active zone is a component of the neurotransmission apparatus of chemical synapses. It is part of the

plasma membrane of presynaptic boutons [1]. The active zone faces the synaptic cleft and is surrounded by (and tightly linked to) an endocytic zone, where synaptic vesicles that have fused with the active zone membrane are retrieved by clathrin-mediated endocytosis [5,6]. The active zone is precisely aligned with the region of postsynaptic membrane that harbors the neurotransmitter reception apparatus, and is defined by the ►postsynaptic density (PSD). The PSD is particularly prominent in excitatory brain synapses.

Lower Level Components

Ultra-Structure of the Active Zone

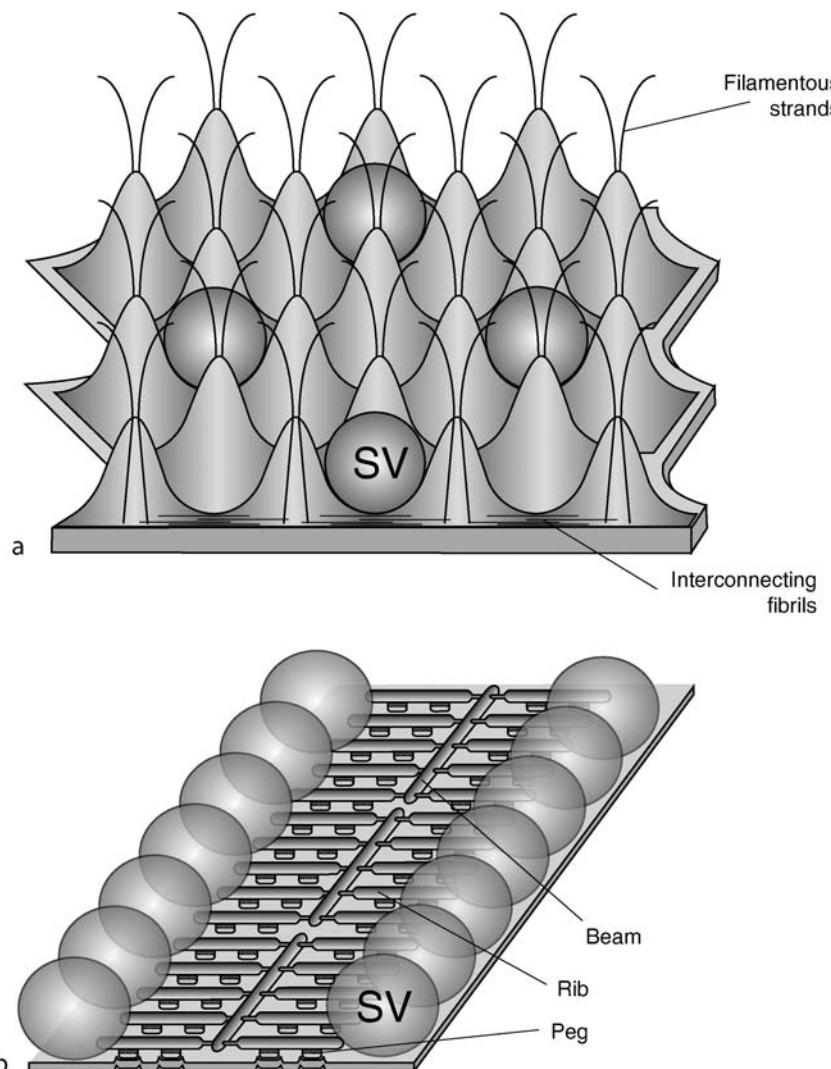
In the electron microscope, the CAZ or presynaptic grid appears as a more or less regular array of electron-dense cone-shaped particles, which extend $\sim 50 \text{ nm}$ into the cytoplasm. A meshwork of cytoskeletal filaments connects the 50 nm particles [2]. Additionally, filamentous strands extend 100 nm and more from the active zone plasma membrane into the presynaptic bouton (Fig. 1a).

At the frog neuromuscular junction, active zone material extends $50\text{--}75 \text{ nm}$ into the cytoplasm of the terminal and has a regularly arranged ultra-structure consisting of “pegs,” “ribs” and “beams” as revealed by electron microscope tomography [4]. The molecular composition of these structures is currently unknown (Fig. 1b).

►Synaptic ribbons in nerve terminals of ►retinal photoreceptors are horseshoe-shaped specializations of the CAZ, which extend $300\text{--}500 \text{ nm}$ into the presynaptic cytoplasm and tether ►synaptic vesicles. They are connected to the active zone plasma membrane via a specialized structure called arciform density [7].

Proteins of the Active Zone Plasma Membrane

Plasma membrane proteins present in the active zone primarily include ion channels and receptor proteins that are required for synaptic function, and cell adhesion molecules (CAMs) involved in adhesion and alignment of pre- and postsynaptic membranes as well as in trans-synaptic regulation of plasticity [8]. Most importantly, voltage-gated Ca^{2+} channels (N-type [$\text{Ca}_{v}2.2$], P/Q-type [$\text{Ca}_{v}2.1$]) mediate the influx of Ca^{2+} upon arrival of a depolarizing ►action potential, the trigger for synaptic vesicle exocytosis. Basically, all super-families of CAMs, including immunoglobulin superfamily members, integrins and cadherins, are represented at synaptic junctions and are involved in synaptic function and plasticity. Alpha- and beta-neurexins seem to be specific CAMs of the active zone membrane. Beta-neurexins make asymmetric contacts with postsynaptic neuroligins, while alpha-neurexins couple Ca^{2+} channels to synaptic vesicle exocytosis in a manner that is not yet understood. Active zone and opposite PSD are surrounded by a belt



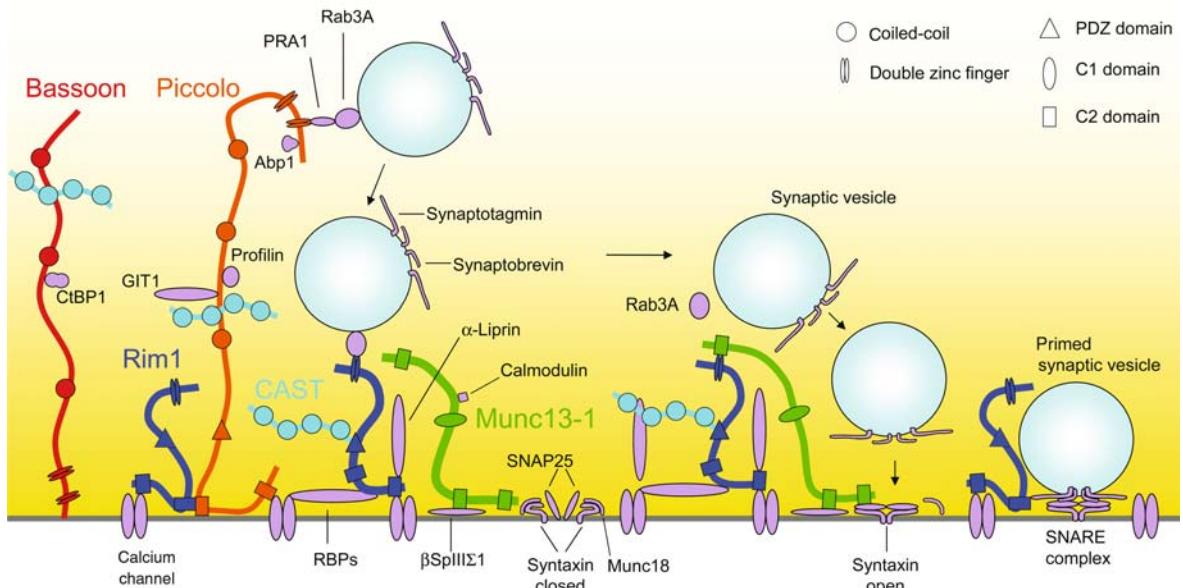
Active Zone. Figure 1 Ultra-structure of the cytomatrix assembled at the active zone. (a) Schematic depiction of the presynaptic grid at conventional brain synapses. A more or less regular array of 50-nm cone-shaped particles is thought to define docking sites for synaptic vesicles (SV). Cones appear to be interconnected by fibrils. In addition, filamentous strands extend 100 nm and more from the active zone plasma membrane into the presynaptic bouton [3]. (b) Cartoon of the active zone at the frog neuromuscular junction as revealed by electron microscope tomography [5].

of cadherin/beta-catenin complexes. Additional cell membrane proteins thought to reside within the active zone include ephrin ligand-receptor systems and receptor tyrosine phosphatases, as well as a variety of metabotropic receptors.

Molecular Organization of the CAZ

Only few CAZ-specific proteins have been identified to date [9]. These include the Munc13 synaptic vesicle priming factors; the ►RIM (Rab3-interacting molecules), multi-domain proteins that can interact with multiple other active zone proteins; ►Bassoon and Piccolo (►Piccolo/Aczonin), two very large CAZ scaffolding proteins; as well as ►CAST/ERC (CAZ-Associated

Structural Protein Or Elks/Rab6-Interacting Protein/ CAST), another family of CAZ-specific structural proteins. In addition, SH3 domain-bearing RIM-binding proteins (RIM-BPs) and alpha-liprins, which also bind RIMs and the receptor tyrosine phosphatase LAR, have been described as bona fide or potential CAZ components. These molecules are thought to form the scaffold of the CAZ, which links proteins of the active zone plasma membrane to the actin/spectrin-based cortical cytoskeleton and components of the synaptic vesicle cycle. Scaffolding molecules of the CAZ can physically integrate additional effector proteins that are involved in the organization and regulation of the synaptic vesicle cycle as listed in 1 and illustrated in (Fig. 2).



Active Zone. Figure 2 Molecular organization of the CAZ. The CAZ-specific multi-domain proteins RIMs, Bassoon and Piccolo and the CAST/ERC proteins are thought to act as major scaffolding proteins of the presynaptic cytomatrix. They can recruit a variety of effector proteins to the CAZ and thereby organize presynaptic processes functionally and topologically. The CAZ-specific protein Munc13 serves as a priming factor for synaptic vesicles (for further details and the definition of abbreviations see Table 1). The figure was adapted from Dresbach, Altrock and Gundelfinger (2003), Neuroforum 3.03, pp 79–86.

Moreover structural components of the CAZ, such as Piccolo, may serve as a physical link between the exocytic and endocytic machineries that have to cooperate precisely in presynaptic boutons [5]. In addition, a trimeric complex consisting of the membrane-associated guanylate kinase homolog CASK and the adaptor proteins Veli/Lin7 and Mint (Munc18/Sec1-interactor), which interacts with active zone membrane proteins such as beta-neurexins and voltage-gated Ca^{2+} channels, has been reported to occur at the active zone [9].

Specialization of the CAZ – Synaptic Ribbons

The photoreceptor ribbon synapse is a unique type of chemical synapse, structurally and functionally specialized for the tonic release of neurotransmitter in the dark. Basically, all scaffolding proteins present in the CAZ of conventional synapses can be found in synaptic ribbons. In addition, a ribbon-specific protein, RIBEYE, has been identified as a major component of synaptic ribbons [7]. Interestingly, CAZ proteins fall into two groups: those that are associated with the actual ribbon (RIBEYE, Piccolo, Rim1 and the Kinesin KIF3A), and those that associate with the active zone membrane and/or the arciform density (Munc13-1, Rim2, CAST1/ERC2). Bassoon seems to be involved in anchoring the ribbon to the arciform density [7]. Major constituents of photoreceptor ribbons including

RIBEYE, Piccolo and Bassoon are also present at inner hair cell ribbons.

Higher Level Processes

The active zone is integrated into the process of synaptic transmission. In this context, it serves an essential function in regulated neurotransmitter release and the organization of the underlying membrane trafficking cycle (synaptic vesicle cycle).

Lower Level Processes

At the active zone, processes of regulated exocytosis of neurotransmitter from synaptic vesicles, as well as refilling of synaptic vesicles (“kiss-and stay”) or their local recycling (“kiss-and-run” mode), takes place [5,6]. Components of the active zone plasma membrane and the associated CAZ are involved in the performance and regulation of these processes. Processes localized at the active zone include docking and priming of synaptic vesicles, entry and sensing of Ca^{2+} ions, control of membrane fusion and retrieval as well as regulation of efficiency and fidelity of stimulus-secretion coupling.

Process Regulation

Presynaptic Plasticity

At the active zone, arriving action potentials trigger exocytosis. Incoming signals can be modulated as

Active Zone. Table 1 Proposed protein–protein Interactions of CAZ proteins

Protein (Synonyms)	Domains/Motifs	Interaction partners (Literature)	Proposed function for the interaction
Rab3 interacting molecules (RIMs: primarily RIM1 α ; RIM2 α)	Zn finger	Rab3 ¹	SV tethering?, Regulation of SV exocytosis?
	PDZ	Munc13–1 ²	SV priming
	C2A	ubMunc13–2 ²	SV priming
	Proline-rich sequence (PRS)	CAST1/ERC2 ^{3,4}	Scaffolding
	C2B	Piccolo ⁵	Scaffolding
		N-type voltage-dependent Ca ²⁺ channel ⁶	Channel anchoring
		Synaptotagmin, SNAP-25 ⁶	Ca ²⁺ sensing
		RIM-BPs ⁷	Scaffolding
		α -Liprin ⁸	Scaffolding
		N-type voltage-dependent Ca ²⁺ channel ⁶	Channel anchoring
		Synaptotagmin, SNAP-25 ⁶	Ca ²⁺ sensing
Munc13s	N-term region of Munc13–1 and ubMunc13–2	RIM1 α ²	Scaffolding, Rab3 effector
	Conserved R region of Munc13s	Calmodulin ⁹	Ca-dependent plasticity
	C-term region of Munc13–1	DOC2 α (double C2 domain protein) ¹⁰	Unknown
		Spectrin β -spIII Σ ¹¹	Cytoskeleton anchoring
		msec7–1 ARF-GEF ¹²	Cytoskeleton regulation
		Syntaxin ¹³	SV fusion, SNARE complex regulation
Bassoon	Zn fingers	CtBP1/BARS-50 (Lysophosphatidic acid acyl transferase, LPAAT) ¹⁴	Membrane trafficking? Regulation of membrane curvature?
	N-terminal of CC2	Ribeye/CtBP2 (LPAAT) ¹⁴	Membrane trafficking?, Scaffolding
	CC3	CAST/ERC ¹⁵	Scaffolding
Piccolo (Aczonin)	Q domain	Actin-binding protein Abp1 ¹⁶	Actin binding, link to endocytosis
	Zn fingers	PRA1 ¹⁷	Unknown
	PRS	GIT (ARF-GAP) ¹⁸	GTPase regulation, membrane trafficking
	PRS	Profilin (actin binding protein) ¹⁹	Actin regulation
	CC3	CAST/ERC ¹⁵	Scaffolding
	PDZ	cAMP-GEFII ⁵	GTPase regulation
	C2A	RIM2 ⁵	Scaffolding, Rab3 effector
	C2B	Piccolo ⁵	Scaffolding
		L-type voltage-dependent Ca ²⁺ channel ⁵	Channel anchoring
CAZ-associated structural proteins (CASTs, ERCs)	Coiled-coil regions	Bassoon, Piccolo ¹⁵	Scaffolding
	C-term PDZ binding motif	α -Liprin ²⁰	Scaffolding, Transport?
		RIMs ³	Scaffolding

Active Zone. Table 1 Proposed protein–protein Interactions of CAZ proteins (Continued)

Protein (Synonyms)	Domains/Motifs	Interaction partners (Literature)	Proposed function for the interaction
RIM binding proteins (RIM-BPs)	SH3 domains (one of 3)	RIMs ⁷	Scaffolding
	SH3 domains (one of 3)	Ca ²⁺ channels Ca _v 2.2 (N-type), Ca _v 1.3 (L-type) ²¹	Channel anchoring
α-Liprins (SYD-2)	N-term CC region	CAST/ERC ²⁰	Scaffolding, Transport?
	C-term SAM domains	KIF1A (kinesin motor) ²²	Transport
		LAR (receptor tyrosine phosphatase) ²³	Receptor anchoring
		GRIP ²⁴	Receptor clustering

¹Wang Y, Okamoto M, Schmitz F, Hofmann K, Sudhof TC (1997) Nature 388:593.²Betz A et al. (2001) Neuron 30:183.³Ohtsuka T et al. (2002) J Cell Biol 158:577.⁴Wang Y, Liu X, Biederer T, Sudhof TC (2002) Proc Natl Acad Sci USA 99:14464.⁵Shibasaki T, Sunaga Y, Fujimoto K, Kashima Y, Seino S (2003) J Biol Chem.⁶Coppola T et al. (2001) J Biol Chem 276:32756.⁷Wang Y, Sugita S, Sudhof TC (2000) J Biol Chem 275:20033.⁸Schoch S et al. (2002) Nature 415:321.⁹Junge HJ et al. (2004) Cell 118:389.¹⁰Orita S et al., J Biol Chem 272:16081.¹¹Sakaguchi G et al. (1998) Biochem Biophys Res Commun 248:846.¹²Neef A, Koch H, Schurmann A, Brose N (1999) Eur J Cell Biol 78:533.¹³Betz A, Okamoto M, Benseler F, Brose N (1997) J Biol Chem 272:2520.¹⁴Tom Dieck S et al. (2005) J Cell Biol 168:825.¹⁵Takao-Rikitsu E et al. (2004) J Cell Biol 164:301.¹⁶Fenster SD et al. (2003) J Biol Chem 278:20268.¹⁷Fenster SD et al. (2000) Neuron 25:203.¹⁸Kim S et al. (2003) J Biol Chem 278:6291.¹⁹Wang X et al. (1999) J Cell Biol 147:151.²⁰Ko J, Na M, Kim S, Lee JR, Kim E (2003) J Biol Chem 278:42377.²¹Hibino H et al. (2002) Neuron 34:411.²²Shin H et al. (2003) J Biol Chem 278:11393.²³Pulido R, Serra-Pages C, Tang M, Streuli M, Proc Natl Acad Sci USA 92:11686.²⁴Wyszynski M et al. (2002) Neuron 34:39.

a function of the history of previous presynaptic activation (presynaptic plasticity). The major signal mediator, both for neurotransmitter release and its modulation is the bivalent Ca²⁺ ion. Two parameters are thought to determine presynaptic plasticity, i.e. the conversion of an action potential to a Ca²⁺ current and the conversion of a Ca²⁺ signal to exocytosis [6]. Components of the active zone essentially govern processes of presynaptic plasticity. Recently, two CAZ proteins, RIM and Munc13, have been implicated in the regulation of presynaptic plasticity [6,10]. Regulation of the synaptic vesicle priming factor Munc13 by the ubiquitous calcium sensor calmodulin may be a long-searched for molecular mechanism for Ca²⁺-dependent presynaptic plasticity. In addition, Munc13's function is regulated by the second messenger diacylglycerol [10]. RIM1alpha knock-out mice display deficits both in short-term plasticity of conventional synapses and in long-term potentiation of mossy fiber

boutons of the hippocampal CA3 region [6,9]. As RIM1a and Munc13s can physically interact, it is conceivable that they fulfill their modulatory effect on presynaptic function in a concerted manner.

Developmental Assembly of the Active Zone

During brain development, the active zone is assembled from distinct pre-formed packages in a quantal manner [8]. Assembly of the major components of the active zone including membrane proteins, such as N-type Ca²⁺ channels, cadherins and the target SNARE protein syntaxin, as well as bona fide CAZ components, like Bassoon, Piccolo, RIMs and Munc13, occurs inside the neurons, probably at the trans-Golgi complex. According to the “active zone transport vesicle” hypothesis these pre-assembled complexes bud off the Golgi membrane, are transported into the axon along microtubules, and fuse with the presynaptic membrane in response to a yet unknown signal. Dense-core active

zone transport vesicles have a diameter of ~80 nm, and are found in axonal growth cones and along axons before synaptogenesis. This mode of assembly may explain the speed and efficiency with which new synapses can be formed during development.

Function

The active zone, including the associated cytoskeletal matrix, is a specialized region of the presynaptic plasma membrane that serves the regulated release of neurotransmitter. Here, incoming action potentials are translated into chemical signals, which can then be detected by the postsynaptic cell. As both basic mechanisms of regulated exocytosis and processes of synaptic plasticity are triggered by calcium [6] (see above), the appropriate placement of voltage-dependent Ca^{2+} channels and of Ca^{2+} -sensing and -modulating systems is of key importance. Various active zone proteins including Munc13s, RIMs and Piccolo as well as Synaptotagmins, which are thought to act as principal Ca^{2+} sensors on synaptic vesicles, harbor multiple C2 domains as phospholipid-dependent Ca^{2+} -binding sites.

Proteins assembled at the active zone serve the local restriction as well as the structural and functional organization of the synaptic vesicle cycle [6,9]. They are involved in

- anchoring and clustering active zone membrane proteins, e.g. Ca^{2+} channels and CAMs,
- recruiting effector molecules to the active zone,
- docking, priming, fusion and retrieval of synaptic vesicles,
- the local integration and regulation of the actin/spectrin-based cortical cytoskeleton
- linkage to the endocytic apparatus.

Proposed functions for individual CAZ components and their interaction partners are summarized in Table 1.

Pathology

Mutations in CAZ genes may result in altered presynaptic plasticity, epilepsy and impaired vision and hearing. For example, RIM1alpha knock-out mice display a decreased probability of neurotransmitter release and impaired short-term and long-term synaptic plasticity [9]. Mice mutant for Bassoon suffer from rapidly generalizing epileptic seizures [9]. Moreover, in these mice, anchoring of synaptic ribbons to the active zone is impaired in retinal photoreceptors and cochlear inner hair cells [7] resulting in dramatic deficiencies in vision and hearing. To date, no corresponding genetic defects have been reported for humans. On the other hand, mutations in presynaptic calcium channels can result in episodic or spinocerebellar ataxia, familial hemiplegic migraine or idiopathic generalized epilepsy.

References

1. Dresbach T et al. (2001) The presynaptic cytomatrix of brain synapses. *Cell Mol Life Sci* 58(1):94–116
2. Phillips GR et al. (2001) The presynaptic particle web: ultrastructure, composition, dissolution, and reconstitution. *Neuron* 32(1):63–77
3. Schikorski T, Stevens CF (1999) Quantitative fine-structural analysis of olfactory cortical synapses. *Proc Natl Acad Sci USA* 96(7):4107–4112
4. Harlow ML et al. (2001) The architecture of active zone material at the frog's neuromuscular junction. *Nature* 409(6819):479–484
5. Gundelfinger ED, Kessels MM, Qualmann B (2003) Temporal and spatial coordination of exocytosis and endocytosis. *Nat Rev Mol Cell Biol* 4(2):127–139
6. Sudhof TC (2004) The synaptic vesicle cycle. *Annu Rev Neurosci* 27:509–547
7. Tom Dieck S, Brandstatter JH (2006) Ribbon synapses of the retina. *Cell Tissue Res* 362(2):339–346
8. Ziv NE, Garner CC (2004) Cellular and molecular mechanisms of presynaptic assembly. *Nat Rev Neurosci* 5(5):385–399
9. Schoch S, Gundelfinger ED (2006) Molecular organization of the presynaptic active zone. *Cell Tissue Res* 362(2):379–399
10. Rosenmund C, Rettig J, Brose N (2003) Molecular mechanisms of active zone function. *Curr Opin Neurobiol* 13(5):509–519

Activity Phase

Definition

Portion of the behavioral circadian cycle where the organism is active. In diurnal organism, the activity phase occurs during the daytime, in nocturnal organisms, during the nighttime.

- Arrhythmicity/Rhythmicity
- Circadian Cycle

Activity-dependent Synaptic Competition

Definition

A refinement process of neural circuitry to select stronger synaptic inputs among multiple inputs converging on the same target while the other weaker inputs are eliminated. This process is referred to as

“competition” because the relative strength of each synaptic input is evaluated.

- ▶ Activity-dependent Synaptic Plasticity
- ▶ Synaptic Elimination

Activity-dependent Synaptic Modification

Definition

Synaptic depression or facilitation induced by special patterns of activation of the synapse. Higher-frequency activation often causes synaptic facilitation, and lower-frequency activation gives rise to synaptic depression.

- ▶ Associative Long-Term Potentiation (LTP)
- ▶ Memory, Molecular Mechanisms

Acquired Immunodeficiency Syndrome (AIDS)

Definition

Illness and associated conditions caused by infection with the ▶ human immunodeficiency virus (HIV), a retrovirus. The syndrome may include neurological symptoms resulting from the combined degeneration (vacuolar ▶ myelopathy) of the ▶ corticospinal tract and the ▶ dorsal columns.

- ▶ Human Immunodeficiency Virus (HIV)

Activity-Dependent Synaptic Plasticity

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Synonyms

Neuronal plasticity

Definition

The ability of the connections between neurons (the synapses) to change in strength in response to activity.

Characteristics

Introduction

Central to the function of the nervous system is its ability to change dynamically in response to sensory input. The process of learning and the formation of memories allow the individual to adapt to and function in its environment. In order to accomplish this, the connectivity between the neurons must be able to change. Rather than occurring randomly, these changes must be guided by the information that flows through the neuronal network. Thus, activity dependent synaptic plasticity is an essential mechanism by which the cognitive function of the central nervous system is achieved. There are two tiers to the alteration of synaptic connectivity: changes that take place very rapidly, which allow immediate response to dynamic input; and more long-term changes that can consolidate memories for up to the life of the organism. As one would expect a mechanistic commonality between these two tiers exists, and short-term changes, if emphasized and repeated, will eventually become permanent.

Foundations

At the end of the nineteenth century the Spanish neuroanatomist Santiago Ramón y Cajal suggested that since no new neurons are created in the brain during the life of an individual, memories might be formed by improving the strength of the connections between them [1]. In the middle of the twentieth century Donald Hebb suggested a mechanism by which this strengthening could occur, postulating that through repeated and persistent stimulation of a neuron there is an increase in its efficacy of communication, arising from either a metabolic change in the cell or the activation of the growth process [2]. It is now generally accepted that the connectivity between neurons determines how information will be processed by the brain, and the ability to modify these connections in response to activity underlies learning and memory. The brain can change its information processing pathways in response to input by two basic mechanisms: by forming new connections or by strengthening the existing ones. Memory can be generally classified as being either short-term or long-term. While some forms of altered synaptic strength can last for extended periods of time (up to days or weeks), it is generally thought that short-term memory is associated with changes in synaptic efficacy, whereas long-term memory involves a structural change in the connectivity between neurons. These long-term changes can be expected to last for years. Of key importance to the function of the nervous system is that these changes in the strength of neuronal

connections arise in response to activity. This reflects an important aspect of how the brain functions, in that there is selective strengthening of circuits that are being used. In addition to activity-driven synaptic plasticity, subsequent regulatory plasticity can also occur. This is a slower process which modulates the changes in connectivity themselves, necessary to avoid a loss of stability in the neuronal network.

Mechanism of Altered Synaptic Efficacy: Long-Term Potentiation (LTP)

Long-term potentiation is an experimentally-induced phenomenon by which high frequency activity at a synapse results in an enhancement, or potentiation, of subsequent synaptic transmission. Although demonstration of an identical phenomenon occurring in the intact brain is limited, it is widely accepted as a basic mechanism for learning and memory. LTP was first described by Terje Lømo in 1966, when he observed that stimulation of the perforant pathway into the rabbit hippocampus caused an enhancement of the excitatory postsynaptic potentials induced in the cells of the dentate gyrus [3]. Many types and stages of LTP exist. Two of the most studied are often defined by their dependence on either the NMDA or on the AMPA glutamate receptors. Moreover, multiple durations and phases of LTP rely on different biochemical mechanisms, all of which have been extensively investigated [4]. It is generally believed that LTP is a fundamental mechanism by which short-term changes in synaptic efficacy can be achieved.

Long-Term Depression (LTD)

The counterpart to LTP, long-term depression, is a weakening of synaptic strength which results (in the hippocampus) from either persistent low-frequency stimulation or from an extremely strong synaptic stimulation such as occurs in the cerebellum. From a functional point of view, the presence of long-term depression of synaptic strength is essential. To develop a neural processing system based solely on enhancement of synaptic strengths would result in a general increase in activity in the brain during the life of the individual. The ability to reduce synaptic strength or prune out unwanted synapses is essential for the overall balance. Mechanistically LTD has not been as rigorously studied as LTP, however it is clear that many of the mechanisms are in common between the two, especially calcium influx [5].

Spike Timing Dependent Plasticity (STDP)

Spike timing dependent plasticity illustrates the fine balance between LTP and LTD. A single dendrite of a neuron receives many inputs from multiple axons. The synapses at these junctions most often fire independently,

each following its own rules and dynamics. Consequently, as excitatory postsynaptic potentials are induced and are traveling down a dendrite it is likely that other synaptic input will also be depolarizing the dendrites, causing the two signals to either summate or interfere with each other. Additionally, when a neuron fires there is a back propagating depolarization that arises from the action potential. This back propagating action potential can affect new incoming EPSPs. If neurotransmitter release occurs after a back propagating action potential arrives at the postsynaptic site, LTD can be induced and synaptic strength decreased. Conversely if the back propagating action potential arrives at the synapse after the EPSP, the potential is reinforced, and, LTP can be induced. Thus, the timing of the arrival of depolarizing potentials at the synapse can either strengthen or weaken it. The dependence of such changes in synaptic efficacy on the coincident timing of activity illustrate the ability of the nervous system to respond with a high degree of temporal specificity, and react in a finely tuned manner by changing the strength of the individual synaptic connections [6].

Mechanism of Structural Plasticity: Synapse Number

Perhaps the most direct mechanism of synaptic plasticity is structural change. The strength of the connections between two neurons can be directly altered by either adding or removing synapses. In the 1980s Bailey and Chen demonstrated that the process of habituation in an invertebrate system can alter the number of connections between neurons [7]. This has also been demonstrated in mammalian systems, and researchers hypothesize that by making physical changes such as these in connectivity, permanent changes in the functioning of a neuronal system that last the lifetime of an individual can be achieved. The mechanism of such changes is often assumed to be related to the initial process of synaptogenesis that occurs during embryonic development, which is subsequently reinitiated by activity. If one views the changes in synaptic efficacy as a precursor to more permanent structural change, one would expect common signaling pathways between the two processes. The most studied candidate for this signal is the calcium influx that occurs during synaptic transmission. It can not only play a determinate role in altering synaptic efficacy through mechanisms such as LTP and LTD, but can also induce cytoskeletal changes through mobilization of actin, a requisite for morphological change. Additionally, the nature of the direct change in synaptic connectivity can be related to the information carried by the activity, for example high frequency stimulation will cause an increase in the number of connections, where as low frequencies result in a loss of connectivity. This change in synapse density has been eloquently demonstrated *in vivo*, using high-resolution imaging of neurons from

trained versus untrained animals [8]. Synaptic remodeling has also been observed under more controlled conditions using dissociated hippocampal neuronal cultures [9]. Thus, during learning and memory formation, the brain can encode new information in its structure by directly altering the number of connections between neurons.

Spine Morphology

In addition to changing the number of presynaptic contacts, the shape and size of the postsynaptic structure can also be altered to modulate synaptic transmission. This can occur by both changing the size of the active zone, as well as by altering the diameter of the spine shaft. Changing the morphology of the postsynaptic spine will modulate the way an incoming depolarization propagates before actually entering the dendrite and proceeding to the cell body. Spine dynamics are also integral to the process of new synapse formation, acting as targets for synaptogenesis [10].

Summary

Activity-dependent synaptic plasticity describes the change in neuronal connectivity that occurs as a direct result of synaptic transmission. This plasticity can be manifested as either altered synaptic efficacy or as direct physical synaptic change. The process is assumed to provide a mechanism of altering information flow through the neuronal system in a manner which reflects the incoming activity patterns that initiated the change, providing a system for learning and memory.

References

1. Ramón y Cajal, Santiago (1894) The croonian lecture: la fine structure des centres nerveux. Proc R Soc Lond 55:444–468
2. Hebb DO (1949) Organization of behavior: a neuropsychological theory. Wiley, New York, ISBN 0-471-36727-3
3. Bliss T, Lømo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232(2):331–356
4. Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44(1):5–21
5. Dudek SM, Bear MF (1993) Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. J Neurosci 1993 13(7): 2910–2918
6. Lisman J, Spruston N (2005) Postsynaptic depolarization requirements for LTP and LTD: a critique of spike timing-dependent plasticity. Nat Neurosci 2005 8(7): 839–841
7. Bailey CH, Chen M (1988) Long-term memory in Aplysia modulates the total number of varicosities of single identified sensory neurons. Proc Natl Acad Sci USA 85(7):2373–2377
8. Zito K, Svoboda K (2002) Activity-dependent synaptogenesis in the adult Mammalian cortex. Neuron 35(6): 1015–1017
9. Colicos MA, Collins BE, Sailor MJ, Goda Y (2001) Remodeling of synaptic actin induced by photoconductive stimulation. Cell 107(5):605–616
10. Matus A (2000) Actin-based plasticity in dendritic spines. Science 290(5492):754–758

Activity-dependent Synaptic Rearrangement

Definition

A refinement process of neural circuitry regulated by the strength of neural activity in the pre- and postsynaptic cells.

► Synaptic Elimination

Actogram

Definition

An actogram depicts activity patterns of organisms.

Usually, activity on a time base of 24 h is plotted on horizontal lines below each other for consecutive days.

However, also other time bases can be chosen (modulo plots). Activity can be depicted quantitatively or as a state variable. Aligning the same actogram twice so that two consecutive time episodes are plotted one after the other and the second episode is repeated just below the first episode on the successive line is called a double plotted actogram, facilitating the identification of rhythms which cross the time base.

► Circadian Rhythm
► Circannual Rhythms

Actualism

Definition

The view that everything which exists actually exists; this implies that possible worlds, if they exist at all, have to exist as part of the actual world.

► Possible World

Actuator

Definition

An actuator is a device with the capability of transforming one type of energy into another. Actuator differs from sensor in the way it is used. The actuator is used to transform commands of a control algorithm into actions applied to the physical system to affect its behaviour (state).

► Control

Acutance

► Contrast Enhancement

Acute and Chronic Ataxic Neuropathy

► Large-Fiber Sensory Neuropathy

Acute Brain Slice

► Slice Preparation

Acute Disseminated Encephalomyelitis

Definition

ADEM belongs to the group of ► idiopathic inflammatory demyelinating diseases (IIDDs) and is an autoimmune disease with multifocal lesions throughout the brain and spinal cord, usually following a febrile viral infection or vaccination, with the highest incidence

during childhood. ADEM is characterized by ► encephalopathy and ► pyramidal, ► cerebellar, and ► brainstem signs, bilateral ► optic neuritis, transverse ► myelitis, and altered consciousness. ► Seizures are rare. The pathogenesis is unknown and may be triggered by a T-cell mediated autoimmune response to ► myelin basic protein. Treatment includes methylprednisolone, immunoglobulins, plasmapheresis, or cytotoxic drugs.

► Idiopathic Inflammatory Demyelinating Diseases (IIDDs)

Acute Pain

► Incisional/Postoperative Pain

Acute Sensory Neuronopathy Syndrome

Definition

Acute loss of large myelinated sensory nerves subserving touch and proprioception (see Section on Large-Fiber Sensory neuropathy).

► Proprioception: Effect of Neurological Disease

Adaptation of Saccadic Eye Movement

Definition

The saccadic eye movement or saccade is a rapid eye movement to capture an object in the visual field. When the target is displaced during the saccadic eye movement, it changes so that the target can be captured.

The forward or backward target displacement causes a gradual increase or decrease in the saccade amplitude, respectively. Such a phenomenon is called adaptation of saccade.

► Saccade, Saccadic Eye Movement

► Sensory Motor Learning/Memory and Cerebellum

Adaptation of Sensory Receptors

Definition

Adaptation is the decline of the electric responses of a receptor neuron over time in spite of the continued presence of an appropriated stimulus of constant strength. This change is apparent as a gradual decrease in the frequency of spikes generated within the receptor neuron. Phasic receptors adapt rapidly and inform, therefore, about the rate of change of a stimulus. Tonic receptors adapt slowly and inform about the presence and strength of a stimulus. Many sensory neurons may unify both response properties and are called phasic-tonic receptors. They usually show a phasic response at stimulus onset, followed by a long-lasting, but lower tonic response.

- Sensory Systems

first stares at (adapts to) a tilted grating for some time (say 60 s) and then looks at the isolated test grating again.

- Visual Illusions

Adaptive Behavior

Definition

The ability to adjust behavior to changes in the environment.

- Cognitive Elements in Animal Behavior

Adaptive Control

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Definition

An “adaptive controller” is a special form of control law (see separate article on “control”). Adaptive controllers have the distinguishing feature that they incorporate some form of inbuilt mechanism for adjusting their characteristics, based on perceived changes in the characteristics of the system or the environment in which the system operates.

One helpful way of thinking about adaptive control is via the concept of internal models (see separate articles on “internal model” and “control”). It can be argued (see article on “control”) that all controllers explicitly or implicitly contain internal models for both the system and the environment in which the system operates. A non-adaptive controller will typically utilize fixed internal models, whereas an adaptive controller will have some mechanism for changing the internal model, based on observations made regarding how the system responds to stimuli provided to the system through the actuators (see separate article on “control”).

There is a helpful example given in the article on internal models regarding lifting a box. Quoting from that article:

When you get ready to pick up a box that you believe to be heavy, you prepare your posture for

Adaptation of Vestibulo-Ocular Reflex

Definition

The vestibulo-ocular reflex is the eye movement driven by the head motion detected by inner ears. The eyeball turns in the opposite direction of head turn so that the image motion on the retina (retinal slip) is suppressed.

The amplitude of this reflex changes when there is a mismatch between the head and the eye movements.

The change works to reduce the retinal slip, thus it is regarded as adaptive.

- Retinal Slip
- Sensory Motor Learning/Memory and Cerebellum
- Vestibulo-ocular Reflexes

Adaptation of Visual Perception

Definition

Adaptation refers to the tendency of a sensory system to change its operating characteristics as a result of prolonged or repeated exposure to a specific type of stimulus. For example, a striped surface (a grating) that appears vertical when presented in isolation (test stimulus) can be made to look tilted if the observer

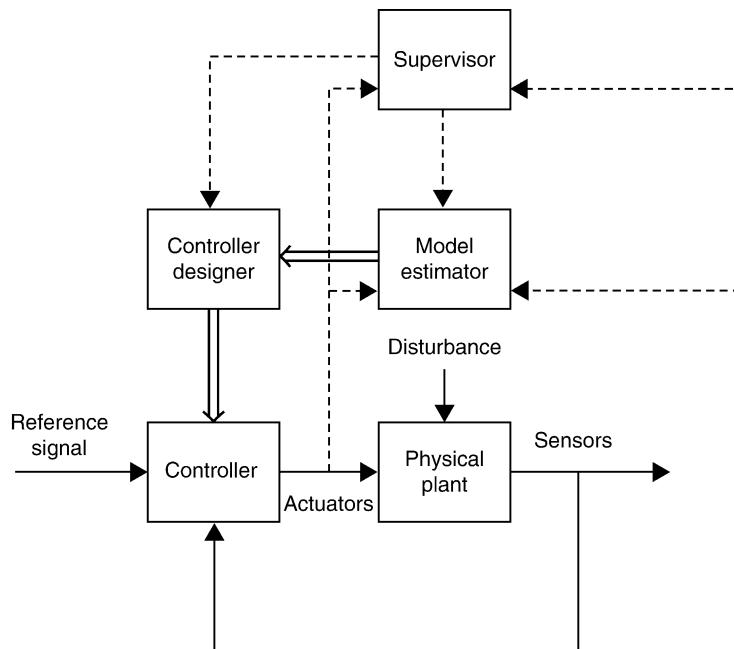
generating a large lift force long before you begin lifting. If the box turns out to be empty, it will move unexpectedly fast. One may say that your internal estimate of the dynamics of the object was inaccurate, or that you had the wrong internal model of its properties. Because you used an incorrect internal model of the box to guide your actions, you generated unnecessarily large forces in trying to pick it up.

Continuing this example, if you are asked to pick up the same box a second time, then you will almost certainly use a different posture and apply forces that are more appropriate. In other words, you will have adjusted (or adapted) the internal model for the true system and this will, in turn, have changed (or adapted) your control law.

Based on the above heuristic description, we can see that adaptive control is an interesting and potentially very useful concept. Clearly, there seems to be substantial merit in having control algorithms that are capable of initially designing themselves based on only partial knowledge of the process to be controlled.

Of even greater interest would be control algorithms that were capable of redesigning themselves in the face of significant process variations. The study of adaptive controllers takes on different forms in different areas. In the life sciences, researchers have postulated and studied the presence of adaptive mechanisms in biological control systems. In engineering, researchers

have endeavored to capture the essence of adaptive control to design control laws for use in man-made systems. In both cases, the question arises as to what form of adaptive mechanism results in the overall system behaving in the required fashion. Indeed, it is a non-trivial exercise to specify the adaptive rules so that the resulting controller has desirable properties. Understanding the general rules that lead to stable (or convergent) adaptive behavior has proven to be surprisingly difficult. Indeed, this question has captured the interest of engineers and mathematicians for the past five decades. Many insights have been obtained but the general question remains largely open. In the sequel, we will attempt to give some insights into adaptive controllers from an engineering perspective. We will not attempt to give a precise definition of adaptive control. However, in Fig. 1 we provide a possible conceptual view of an adaptive control system. At the heart of it is a typical feedback control (solid lines in Fig. 1 indicate signal flow in this part of the system), which consists of the controlled physical plant and a controller with a feedback loop. The typical starting point for traditional feedback control design is the availability of a ►mathematical model for the physical plant to be controlled (see companion article on “control”). The model typically consists of structure and parameters and similarly, the design process is aimed at determining the controller structure and parameters. There are many control design methodologies [1]. However,



Adaptive Control. Figure 1 A general adaptive control system.

irrespective of how the control law is designed, in a traditional setting, once the controller has been designed and implemented it stays “fixed.” On the other hand, an adaptive controller has the capacity of changing the control law by adjusting its internal models.

Specifically, an adaptive controller is aimed at providing:

- Capability to estimate the model of the process applicable at the current time – the ►Model Estimator in Fig. 1
- Capability to redesign the controller (using some underlying design methodology) – the Controller Designer in Fig. 1
- Capability to make decisions as to when to re-initiate the processes of model estimation and controller redesign – the Supervisor in Fig. 1

Over the past 50 years, the idea of adaptive control has sparked the imagination of many researchers as well as control engineers. This resulted in thousands of papers and tens of books on the subject (see, e.g., [2,3,4,5] and many more). The adaptive controllers reported in the engineering literature (both in theory and in practice) differ in the way each capability is implemented. This will be further discussed below. Ideally, one would like to have an algorithm that was capable of changing the model and controller structure as well as their parameters. The reality, however, is that most adaptive controls in common engineering use, are limited to parameter adaptation only, while the structures of both model and controller are predetermined. As a result, the model estimation used in most contemporary adaptive controllers consists of parameter estimation and the redesign is limited to determination of controller parameters. Hence, a close connection has emerged between the area of system identification [6,7] (which studies how one can estimate model parameters from observations of input–output data) and adaptive control. Basically, one could attempt to combine any identification algorithm with any control design methodology to get an adaptive control scheme.

Description of the Theory

Direct and Indirect Adaptive Control

As shown in Fig. 1, estimated parameters are fed to the controller design block, which typically treats them as if they were true system parameters when designing the controller. This idea is called “►Certainty Equivalence” [5]. More sophisticated procedures may also try to give a measure of local accuracy of the current model and this can also be used in the control system design procedure.

There are also several ways that one can utilize the updated model information. For example, one could use the current model until one has a high level of confidence

that on-line parameter estimation has led to a better model. In other schemes, every time new estimates reach the design block, the controller is redesigned. Unfortunately, the resulting systems typically turn out to be highly nonlinear and time varying, hence, very difficult to analyze. A stumbling block is often the Controller Design block, which introduces much of the nonlinear relationships. In very special types of simple control law design, it is possible to avoid the need for a control design block. In those cases, the system model is manipulated into a form where it is expressed directly in terms of the control law parameters. Namely, the system parameters and the controller parameters are identical. In this case, the control law design phase becomes trivial. These cases have been referred to in the literature as direct adaptive control while the other cases where one needs to translate system parameters into control law parameters have been called indirect adaptive control. ►Model reference adaptive control [5] and the self-tuning regulator [2] are prime examples of direct adaptive controllers.

Analysis of behavior

An adaptive controller can thus be seen as a special form of nonlinear control law, which incorporates on-line adjustments to a feedback law. Not surprisingly, it is very difficult to analyze the behavior of these algorithms. Initial attempts focused on proving closed loop stability under idealized assumptions.

For the direct adaptive controllers, proof exists of stability in the literature (see, e.g., [3,4]) under idealized assumptions. It is also possible to extend these ideas to indirect adaptive control at the expense of additional simplifying assumptions [5].

Following these initial results, stability proofs were generated when the system was affected by disturbances and noise. Again, very idealized assumptions were made, e.g., time invariant, linear dynamics, stationary stochastic disturbances, etc.

Ideally, it would be good to have a theory that allowed one to understand the behavior of adaptive controllers in practical scenarios, e.g., when there is noise, non-stationary behavior, non-linearities and unmodeled dynamics. While some preliminary ideas are available in the literature (see for example, [8]), a comprehensive theory of adaptive control has proven to be illusive.

Two Time Scale Adaptive Controllers

It is well known in the system identification literature, for the parameter estimators to work properly one needs to “shake up” the system to excite all its parts and exhibit its different behavioral patterns [6,7]. On the other hand, a controller typically tries to “calm” the system down. These two contradicting processes are at the core of the problem of adaptive control performance. One idea that has been shown to lead to

interesting properties is the use of two time scales (or, block invariance). The idea is to use different time scales, a fast one for the control law action and data collection for the purposes of identifying the model parameters, and a slow one for the controller redesign. Specifically, a ►sufficiently exciting signal [6,7] is inserted into the system while the controller parameters are kept constant. During this period the identifier improves its estimated parameters. At the end of this predetermined period, the redesign block is triggered, generating a new, improved, controller design. This process is repeated at predetermined fixed intervals. It has been argued (see [9]) that this idea can be applied to many combinations of identification algorithm and control design method leading to convergent behavior.

Supervised Adaptive Controllers: Switched Control

While, in two time scale adaptive controllers, the controller redesign is “switched on” at predetermined instances, one could readily imagine the incorporation of additional logic that gets all the available information from the system and, based on some mechanism, decides when to switch on the redesign. Currently available configurations for this type of idea in the engineering literature are relatively simple. One idea is to utilize a finite set of fixed, distinct controllers with a supervisor which switches on the “most appropriate” controller at different times (see, e.g., [10]). So far the results in the literature have been limited to establishing stability of the resulting control system with no performance claims.

Adaptive Controllers in Practice

A comprehensive theory of adaptive control is not yet available. This is perhaps not surprising, given the fact that these controllers are inherently nonlinear and exhibit complex behavior. Nonetheless, the idea of adaptive control is both persuasive and interesting.

Adaptive controllers have frequently been used in practical engineering applications [2]. Indeed, the authors of the current article have used a form of adaptive control in thickness control in rolling mills, where it has proven to be an effective design tool – allowing expensive sensors to be replaced by less expensive “virtual” sensors.

Physiological systems also frequently contain instances of control loops that appear to exhibit adaptive behavior. Indeed, it could be argued that the use of adaptive controllers by engineers is nothing more than a somewhat naïve attempt to mimic behavior which is intrinsic to all biological systems. In summary, adaptive control remains an exciting concept that will undoubtedly continue to attract interest from many fields including engineering and the life sciences.

References

1. Goodwin GC, Graebe SF, Salgado ME (2001) Control system design. Prentice Hall, New Jersey
2. Astrom KJ, Wittenmark B (1995) Adaptive control, 2nd edn. Addison-Wesley, Reading, MA
3. Feuer F, Morse AS (1978) Adaptive control of single-input, single-output linear systems. IEEE Trans Automat Contr 23(4):557–569
4. Goodwin GC, Ramadge PJ, Caines PE (1980) Discrete-time multivariable adaptive control. IEEE Trans Automat Contr 25(3):449–456
5. Goodwin GC, Sin KS (1984) Adaptive filtering, prediction and control. Prentice Hall Information and Systems Sciences Series. Prentice Hall, Englewood Cliffs, NJ
6. Goodwin GC, Payne RL (1977) Dynamic system identification: experiment design and data analysis. Academic, New York
7. Ljung L (1987) Identification: theory for the user. Prentice Hall, Englewood Cliffs
8. Morse AS (1990) Towards a unified theory of parameter adaptive control: tunability. IEEE Trans Automat Contr 35(9):1002–1012
9. Shimkin N, Feuer A (1988) On the necessity of “block-invariance” for the convergence of adaptive pole-placement with persistently exciting input. IEEE Trans Automat Contr 33:775–780
10. Morse AS, Anderson BDO, Bitmead TS, de Bruyne F, Hespanha JP, Liberzon D (2000) Multiple model adaptive control. Int J Robust Nonlinear Contr 10:909–929

Adaptive Controller

Definition

An Adaptive Controller consists of a controller with changeable parameters combined with an adaptive scheme that changes control parameters based on plant measurements.

►Adaptive Control

Adaptive Immune Responses

Definition

Also known as acquired immunity that has four characteristic attributes: (i) antigen specificity; (ii) diversity; (iii) immunological memory; and (iv) self/nonself recognition. Adaptive immunity is capable of specifically recognizing and selectively eliminating

foreign micro-organisms and molecules via activated T and B lymphocytes and the factors they release.

Activation of adaptive immunity is directed by the cellular responses in the innate immune response and can be activated faster and more effectively upon re-encounter with the same antigen, known as a memory response. In the central nervous system (CNS), immunity conferred by T and B cells as a result of their specific recognition of certain antigens assists in the recruitment, activation, and regulation of innate immune cells for the purpose of tissue maintenance, repair, renewal, and recovery.

- Autologous Macrophages for Central Nervous System Repair
- Immune System and Pain

Adaptive Multi-Layer Systems

Definition

An architecture of neural networks composed of multiple layers of adaptive neurons. A network normally has one input layer and one output layer.

Other layers are called hidden layers. There may be both inter-layer connections and intra-layer connections between neurons. The networks which have only feed-forward inter-layer connections from input to output are called feed-forward networks. Signals on the input layer are transferred through inter-layer connections to the output layer. By modifying the weight of connections according to an adequate learning rule, desired input-output relations can be acquired.

- Competitive Learning Theory

Adaptor Protein

Definition

An accessory protein having a number of different protein-binding modules that facilitate specific protein-protein (or other molecular) interactions. It thus promotes the formation of protein complexes, and plays a role in regulating signal transduction pathways.

- Synaptic Proteins and Regulated Exocytosis

Addiction

Definition

Addiction is a neuropsychiatric disorder characterized by compulsive thoughts and actions directed toward obtaining and consumption of pharmacological and natural reward stimuli, with no regard for the potential injury to health, family or society. Casual use of substances such as heroin, cocaine, or methamphetamine does not constitute addictive behavior. Addiction is also characterized as a “chronic-relapsing disorder” which may be triggered by drug-associated cues and environments, or stress, even after long periods of abstinence from drug-seeking behavior. Addictive behaviors often entail “risk-taking” and harmful activity which may constitute a danger to public health.

Repeated exposure to drugs of abuse, excessive sexual activity, or gambling has been shown to activated specific brain systems, most notably dopaminergic and glutamatergic pathways converging on the nucleus accumbens and prefrontal cortex. Long-term changes in synaptic plasticity, in the form of long-term potentiation and long-term depression in these pathways are hypothesized to be the neural correlate of addictive behavior, hence the claim that addiction is a brain disease.

- Learning and Motivation
- Long-term Depression
- Long-term Potentiation

ADEM (Acute Demyelinating Encephalomyelitis)

Definition

ADEM has a monophasic course, occurs more often in children and may follow immunization or infection.

Onset is usually abrupt with rapid progression.

Pathologically, perivenous inflammation with macrophage infiltration and associated demyelination in a sleeve like distribution along the perivenous zones is seen. Magnetic resonance imaging (MRI) shows perivenular inflammation, extensive demyelination and gadolinium enhancement of white matter in the brain and spinal cord and often involve deeper layers of cortical or subcortical structures.

Treatment may be attempted with high-dose corticosteroids or plasma exchange.

Adenohypophysis

Definition

- Diencephalon
- Anterior Lobe of the Hypophysis

Adenosine

Definition

Adenosine is a purine nucleoside that forms adenosine triphosphate (ATP), adenosine diphosphate (ADP) and cyclic adenosine monophosphate (cAMP), which are all important in cell metabolism throughout tissues of the body.

During cellular activity (and formation of ATP from two ADP molecules), free adenosine is released and transported out of cells, including neurons. Extracellular adenosine levels increase with increasing activity or under pathological conditions. Adenosine acts upon different receptors, which are associated with inhibitory (A₁ and A₃) or excitatory (A_{2a} and A_{2b}) effects on target cells. In the heart, adenosine acts upon A₁ receptors to inhibit pacemaker cells and slow heart rate in a manner that is thought to be protective, particularly under conditions of ischemia or hypoxia. In the brain, concentrations of extracellular adenosine increase during prolonged periods of waking and associated neural activity. Acting upon A₁ receptors, adenosine can inhibit neurons of the arousal system to promote sleep. Caffeine, well known as one of the major stimulants, acts by blocking A₁ receptors.

Adenylate Cyclase

Definition

Enzyme that generates cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP).

Adenylate cyclase activity is either inhibited or stimulated by signaling through G-protein coupled receptors. There are nine mammalian adenylate cyclases.

Adequate Stimulus

Definition

Adequate stimulus denotes that physico-chemical stimulus, for whose reception a sensory receptor is specialized and responds to at the lowest possible intensity (energy). For example, under optimal conditions, rods in the mammalian retina respond very sensitively to low-intensity light, even single photons (adequate stimulus), while a strong blow to the eye may evoke flashes of light sensations (phosphemes), but at much higher intensity (inadequate stimulus).

- Sensory Systems

Adjuvant Analgesics

Definition

Adjuvant analgesics are drugs with analgesic properties that were initially developed to treat other health problems, such as anticonvulsants and antidepressants.

These drugs have become a cornerstone of pain control for children with chronic pain, especially when pain has a neuropathic component.

- Pain in Children

Adolescent Pain

- Pain in Children

Adrenal Insufficiency (Addison's Disease)

Definition

Addison's disease is a condition in which patients excrete copious amounts of dilute urine and drink comparable volumes of water in compensation. The patient may suffer from adrenal tumor or atrophy.

Adrenaline or Epinephrine

Definition

Adrenaline is a catecholamine, which is released as a neurotransmitter from neurons in the central nervous system and as a hormone from chromaffin cells in the adrenal gland. Adrenaline is required for increased metabolic and cardiovascular demands during stress. Its cellular actions are mediated via plasma membrane bound G protein-coupled receptors.

Adrenergic Fiber

Definition

An adrenergic fiber is an axon of a postganglionic sympathetic neuron that synthesizes noradrenaline (or adrenaline in some amphibians and fish). These fibers are more commonly referred to as noradrenergic fibers when noradrenaline is the neurotransmitter. Adrenergic/noradrenergic fibers travel from sympathetic ganglia to target tissues within bundles, usually mixed with other autonomic and sensory nerve fibers, before they branch extensively and become varicose. Most adrenergic/noradrenergic fibers also contain co-transmitters like ATP or neuropeptide Y.

- Adrenaline
- Postganglionic Neurotransmitter
- Sympathetic Pathways

Adrenoceptors

Definition

Adrenoceptors are receptors of the sympathetic nervous system activated by the postganglionic transmitter noradrenaline or by adrenaline. They occur in the main subtypes of α_1 , α_2 , β_1 , β_2 and β_3 and may occur as auto- or heteroreceptors modulating transmitter release.

- Postganglionic Neurotransmitter
- Sympathetic Nervous System
- Sympathetic Pathways

Adroitness

- Coordination

Adult Neurogenesis

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Synonyms

Neuron production in the adult brain; Secondary neurogenesis; Ongoing neurogenesis

Definition

Neurogenesis is the process by which new neurons are generated. It encompasses the entire series of events from ► precursor cell division to survival and functional integration of the neural progeny into the neural network.

Characteristics

For many years, the idea that the brains of almost all mammals retained a constant structure throughout life and could not generate new neurons prevailed in the field of neuroscience. Reports contradicting this long-standing dogma first emerged in the early 1960s, but it was another 40 years before the notion of the adult brain as a static organ was finally overturned. With the advent of new methods for labeling dividing cells and improvements in imaging techniques, investigators have confirmed that neurogenesis takes place in discrete areas of the central nervous system (CNS) throughout life (reviewed in [1]). Ongoing neurogenesis is now thought to be an important mechanism underlying ► brain plasticity, enabling organisms to adapt to environmental changes and influencing learning and memory in adulthood.

Adult Neurogenesis in Mammals

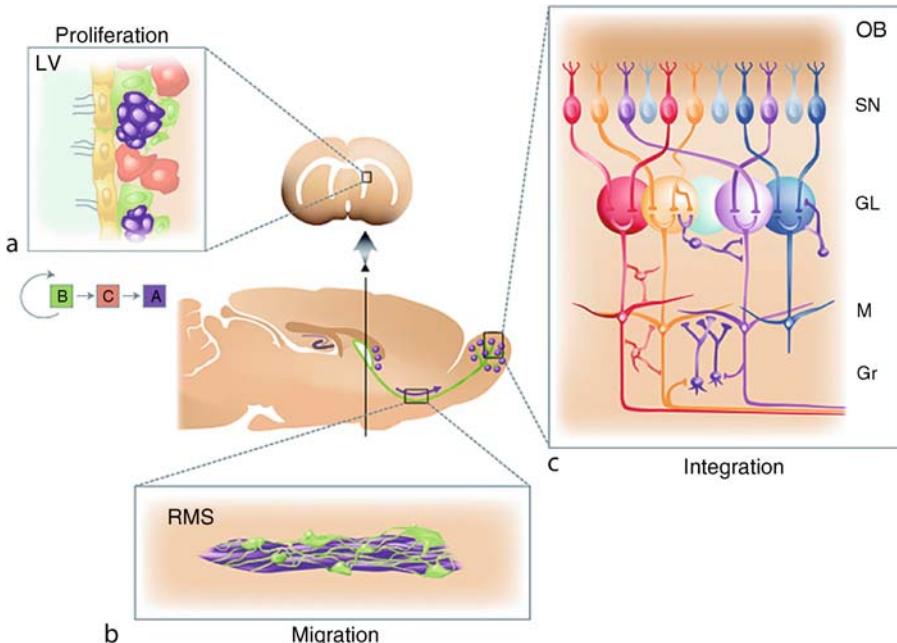
In mammals (including humans), new neurons are added to two main areas of the adult brain: the hippocampus [2] (which is involved in certain types of learning and memory) and the olfactory bulb (OB) [3] (which is involved in the sense of smell).

In the hippocampus, neurons are generated by neural precursor cells located in the dentate gyrus (DG), in a region known as the subgranular zone (SGZ). Neuroblasts generated in the SGZ migrate into the adjacent

granular layer, where they mature into granular neurons. In contrast, new olfactory neurons arise from neural precursors located outside of the olfactory system, in a region lining the border between the striatum and the lateral ventricle, the subventricular zone (SVZ). In this case, neuroblasts cover long distances as they migrate towards the OB along a path known as the rostral migratory stream (RMS). They migrate tangentially in chains, through tubular structures formed by astrocytes. After detaching from these chains and migrating radially from the RMS to the OB, the new neurons mature into olfactory inhibitory interneurons of two main types: granule cells and periglomerular cells. Both cell types make only local contacts in the bulb, directly or indirectly modulating the processing of sensory information by the OB's projection neurons: the mitral and tufted neurons (Fig. 1). Outside these two germinal regions, little or no neurogenesis seems to occur. In both the SGZ and the SVZ, precursor or **►stem cells** reside in specialized niches, providing a local microenvironment that influences the behavior of precursors and their ability to

differentiate into neurons (reviewed in [4]). The transplantation of SVZ precursor cells into the hippocampus results in the generation of hippocampal neurons, whereas the transplantation of SGZ precursor cells into the RMS results in the generation of olfactory interneurons. Conversely, when implanted outside these neurogenic regions, these two types of precursor generate only glia. These observations indicate that neurogenesis depends on the presence of a permissive environment, rather than on regionally different properties of precursor cells [5].

The SVZ is the neurogenic region that generates by far the largest number of new neurons in the adult CNS. However, most of the cells generated in the SVZ die, with only a subset going on to achieve maturation and functional integration. OB neurogenesis appears to involve both neuronal turnover (neuronal replacement) and a net increase in the number of neurons (neuronal addition). The cell types and architecture of the SVZ have been characterized at the ultrastructural level, and four main cell types have been identified: astrocyte-like



Adult Neurogenesis. **Figure 1** *Neurogenesis in the adult olfactory bulb:* (a) Schematic representation of the SVZ showing the cell types present in this region and their organization. Multi-ciliated ependymal cells (yellow) line the wall between the lateral ventricle and the striatum. Neuroblasts (A, purple), appear forming clusters that are surrounded by astrocytes (B, green) and occasionally for rapidly dividing Type C cells (red). SVZ astrocytes can eventually extend a process to contact the lateral ventricle and exhibit a short single cilium. (b) New-born neuroblasts migrate tangentially along the rostral migratory stream to reach their final destination in the olfactory bulb. Migrating neuroblast group together in chains that are surrounded by tubular structures formed by the process of astrocytes. (c) After reaching the core of the olfactory bulb, neuroblasts detach from the chains and migrate radially to the overlaying layers, where they differentiate into two local interneuron subtypes: granule cells (located in the deeper layer of the olfactory bulb) and periglomerular neurons (located in the most superficial layer). LV: lateral ventricle; RMS: rostral migratory stream; OB: olfactory bulb; SN: sensory neurons; GL: Glomerular layer; M: Mitral layer; Gr: granular layer.

cells (GFAP-positive, with an astrocytic morphology, type B cells), intermediate amplifiers (type C cells), neuroblasts (type A cells), and ependymal cells lining the lateral ventricle (Fig. 1). B cells are thought to be multipotent neural precursors. They divide to generate the neuroblasts, via transit-amplifying C cells, which migrate through the RMS towards the OB. This region also contains a specialized basal lamina, which extends from blood vessels in the SVZ and terminates in small bulbs adjacent to the ependymal cells [4].

In contrast to neurons destined for the OB, which migrate over long distances, DG granule neurons are generated locally in the SGZ. Neurogenesis in the SGZ occurs in foci associated with blood vessels and containing primary precursors (astrocyte-like, type B cells), dividing immature (type D cells) cells that already express markers of neuronal differentiation, newly generated granule neurons and endothelial cells. D cells divide less frequently and are more differentiated than the type C cells of the SVZ [4].

Despite their astrocytic phenotype, not all the astrocytes in the germinal regions of the adult brain seem to act as stem cells. Only some of these cells proliferate slowly, giving rise to mature neurons in the OB or hippocampus. The other astrocytes may act as ►niche cells, possibly providing crucial signals to the diverse stem and progenitor cells in this lineage [6].

Regulation of Adult Neurogenesis

The molecular mechanisms involved in regulating adult neurogenesis remain unclear. It is currently thought that the process is orchestrated by an intricate, complex network of signals inducing or inhibiting the proliferation of ►precursors, influencing fate choice or favoring migration towards target areas. The transcription factors E2F or Notch 1, and molecules such as ephrins (Eph) and their tyrosine kinase receptors (EphB1–3 and EphA4) provide just a few examples of proteins involved in regulating the proliferative activity of stem cells [7]. The sonic hedgehog (SHH) pathway has also been implicated in ►progenitor cell maintenance during adulthood. A loss of hedgehog signaling results in abnormalities in the DG and OB, whereas stimulation of the pathway induces an increase in the rate of proliferation of adult progenitors. Finally, growth factors, such as brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), insulin growth factor 1 (IGF1) and vascular endothelial growth factor (VEGF) also enhance the proliferation of progenitors in the DG or SVZ, or both [7].

Bone morphogenic protein (BMP) has been shown to induce the differentiation of neural stem cells into glial cells, whereas the local presence of BMP antagonists is associated with the generation of new neurons. Ependymal cells in the SVZ secrete Noggin and astrocytes in the SGZ secrete neurogigin-1, both of which are

BMP antagonists. The Wnt signaling pathway may also guide cells toward a neuronal fate, and it has been shown that the WNT inhibitors sFRP2 and 3 (secreted frizzled-related proteins 2 and 3) partially block astrogli cell-induced neurogenesis in the DG [8]. The transcription factors paired box 6 (Pax6) and oligodendrocyte transcription factor 2 (Olig2) are involved in the mechanisms determining the fate of newborn cells and the timing of this specification along the SVZ-olfactory bulb pathway. Olig2 is produced in the SVZ, but only in transit-amplifying cells. The overproduction of this factor facilitates oligodendrocyte maturation, but represses neural development. By contrast, Pax6 is produced in only small amounts in the SVZ, but its repression is associated with a decrease in neuroblast formation. Pax6 is also produced in large amounts in the migrating neuroblasts along the RMS, providing further evidence of a role for Pax6 in promoting neuronal differentiation [8].

The process of migration is also highly regulated during neurogenesis. The tangential migration of neuroblasts from the SVZ to the OB is modulated by a cohort of factors, including PSA-NCAM, netrins and integrins. Reelin and tenascin-R play a role in radial migration, facilitating the detachment of neuroblasts from the chains. Neuroblasts also respond to ambient GABA levels by modulating their speed of migration [7].

Adult Neurogenesis Under Pathological Conditions

Neurogenesis is also stimulated in the mammalian brain in response to injury and disease. Experiments in rodents have demonstrated that new cells are generated in response to ischemia or brain trauma. Remarkably, newly generated neurons can migrate to the site of the injury in the cerebral cortex or striatum (where neurogenesis does not normally occur) and differentiate into mature neurons forming connections with neighboring cells [9]. Enhanced neurogenesis has also been reported in degenerative diseases, such as Huntington's chorea and Alzheimer's disease. Although this injury-induced neurogenesis does not lead to recovery, many scientists believe it represents the brain's attempt at self-repair [8]. Neurogenesis also increases in response to seizure activity, but the production of new neurons is not beneficial because these neurons develop, migrate and integrate inappropriately, and actually seems to contribute to recurrent seizures [8]. The functional significance of abnormal neurogenesis in these and other medical conditions is not yet understood, but this area is the focus of intensive research, which may one day yield new treatments for these disorders.

Functions of Adult Neurogenesis

The precise function of newly generated neurons in the adult brain remains unclear. It has been suggested that neurogenesis in the OB system may be a plastic response coupled to the high turnover of receptor neurons in the

olfactory epithelium. However, another potential role of bulbar granule neurons generated in adulthood has emerged in recent years. An odor-enriched environment enhances neurogenesis and improves olfactory memory, and the genetic disruption of olfactory neurogenesis has been shown to result in a loss of performance in odor discrimination tasks in mice. These observations indicate that newly generated neurons may contribute to perceptual and memory functions in the bulb [7,9]. The hippocampus has been shown to be involved in learning and memory, and it has been suggested that newly generated neurons within the hippocampus contribute to these processes. The conditions impairing adult neurogenesis, such as stress, have also been shown to impair learning. In contrast, conditions promoting the generation of new neurons, such as physical exercise, are often associated with improvements in memory and the learning of tasks dependent on the hippocampus [7,8]. Studies have also shown that learning promotes the survival of new neurons, and better learners seem to retain more new neurons, particularly when trained to perform difficult tasks [9]. Hippocampal neurogenesis may also play a role in various neurological disorders and diseases, including epilepsy and depression, as some of the treatments and drugs successfully used to treat individuals suffering from depression may increase the production of new hippocampal neurons [10]. Furthermore, the beneficial effects of some antidepressants are blocked by the inhibition of neurogenesis, suggesting that low levels of neurogenesis may be an underlying cause of depression.

References

- Gould E (2007) How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci* 8(6):481–488
- Gage FH (2000) Mammalian neural stem cells. *Science* 287:1433–1438
- Alvarez-Buylla A, Garcia-Verdugo JM (1999) Neurogenesis in adult subventricular zone. *J Neurosci* 22:629–634
- Doetsch F (2003) A niche for adult neural stem cells. *Curr Opin Genet Dev* 13(5):543–550
- Suhonen JO, Peterson DA, Ray J, Gage FH (1996) Differentiation of adult hippocampus-derived progenitors into olfactory neurons *in vivo*. *Nature* 383 (6601):624–627
- Ninkovic J, Gotz M (2007) Signaling in adult neurogenesis: from stem cell niche to neuronal networks. *Curr Opin Neurobiol* 17(3):338–344
- Lledo PM, Grubb M, Alonso M (2006) Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Neurosci Rev* 7:179–193
- Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci* 28:223–250
- Sohur US, Emsley JG, Mitchell BD, Macklis JD (2006) Adult neurogenesis and cellular brain repair with neural progenitors, precursors and stem cells. *Philos Trans R Soc Lond B Biol Sci* 361(1473):1477–1497
- Malberg JE (2004) Implications of adult hippocampal neurogenesis in antidepressant action. *J Psychiatry Neurosci* 29:196–205

Advanced Sleep Phase Syndrome (ASPS)

Definition

Advanced sleep phase syndrome (ASPS) is most common in the elderly. It is characterized by a difficulty in staying awake in the evening and by early morning awakening. Sleep maintenance insomnia is often related to ASPS. This disorder is treated by taking 0.5 mg of melatonin at each awakening during the night after 1 a.m. and a final dose of up to 0.5 mg at final awakening in the morning. Bright light (2,000–10,000 lux) scheduled between 7 and 9 p.m., ending no later than 1 h before desired bedtime is also helpful.

► Circadian Sleep Phase Syndromes

Aerotaxis

Definition

Motility in relation to a gradient of oxygen concentration such that the organism migrates to an optimal oxygen concentration in an oxygen gradient.

Aetiology

Definition

Causal explanation, the cause of a disease.

A-Fibers of Dorsal Root of the Spinal Nerve

Definition

C and A delta fibers innervate primarily nociceptors but also thermo- and some mechanoreceptors. Conversely,

A-beta and A-delta fibers innervate touch receptors of the skin. All these fiber types enter the spinal cord via the dorsal root.

► **Medulla Spinalis**

Affect

► Emotion

Affective Dimension

Definition

The way an individual feels or experiences emotion in response to a particular setting, process, characteristic, attitude, or sensation. A full description of a particular item would usually include the affective dimension of the item, along with its cognitive and behavioral dimensions (plus sometimes the sensory dimension).

Afferent

Definition

The term afferent (from Latin “ad” = towards and “ferre” = carry) refers to nerves that carry information towards the central nervous system. Somatic afferent nerves innervate muscles, joints or skin. Visceral afferent nerves innervate body organs and blood vessels.

► **Sensory Systems**

Afferent Innervation of the Heart

► **Visceral Afferents**

Afferent Input to Rhythm Generating Networks

► **Peripheral Feedback and Rhythm Generation**

Afferent Regulation of Locomotion

► **Locomotor Reflexes**

AFP

Definition

Anterior forebrain pathway.

► **Song Learning of Songbirds**

Afterdepolarization

Definition

Afterdepolarization (delayed depolarization) is the depolarization after the fast spike repolarization phase, either appearing as a slow phase of repolarization or as an intermittent depolarization between a fast afterhyperpolarization and a subsequent afterhyperpolarization.

► **Action Potential**

Aftereffect in Circadian Rhythm

Definition

A long-term change in the endogenous circadian period as a result of entrainment to a light-dark cycle. For example, if a mouse with an endogenous period of 23 h

was entrained to a 24.5 h light dark cycle for a period of six months and released into constant darkness, it might show a new endogenous period of 24 h for several weeks to months before eventually returning to a period of approximately 23 h.

► Masking (Positive/Negative)

Aftereffect Measurement

Definition

Generally, an aftereffect is measured as follows: An observer judges a test stimulus in isolation (called a pretest trial or baseline measure) and then judges it in isolation again, but this time after prolonged adaptation to an inducing stimulus (called a posttest trial). There is no difference between the stimulus displays in the pretest and posttest because the inducing is removed prior to the posttest. The aftereffect, that is, the effect of the inducing stimulus on the test stimulus, is defined as the algebraic difference between the posttest and pretest judgments. Because the posttest stimulus is judged after the inducer is removed, an aftereffect is a successive effect.

► Visual Illusions

Afterhyperpolarization (AHP)

Definition

Afterhyperpolarization (AHP) – hyperpolarization following an (action potential). In the squid axon, the afterhyperpolarization is generated by the slowly inactivating voltage-dependent K⁺ conductance activated during the action potential. In mammalian central neurons, AHPs may show different phases: fast, medium and slow, in some cases interrupted by afterdepolarizations. Second, the contributing K⁺ channels include BK and SK channels and Kv7 channels mediating the M-current. BK-channel-mediated AHPs are usually brief, while SK-channel-mediated ones can last up to seconds.

► Action Potential

Ageing

Definition

Ageing refers to growing old, maturing or exhibiting the effects of the passing of time.

Ageing of Autonomic/Enteric Function

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Synonyms

Vegetative nervous function; Visceral nervous function; Gastrointestinal function

Definition

The ►autonomic nervous system is part of the peripheral nervous system, which is instrumental in maintaining the internal environment of the body in a steady state and in returning the internal environment to a steady state following internal and external stimuli. In order to accomplish this, the autonomic nervous system maintains a controlling influence over the cardiovascular, digestive, thermoregulatory and urinogenital systems. This is achieved by both motor and sensory innervation of the major organ systems together with other structures such as sweat glands and intraocular muscles. Autonomic function is involuntary, and we are not usually conscious of ongoing autonomic activity except at times of increased emotions such as anger or fear, when autonomically induced increases in heart rate or in sweating occur.

The ►enteric nervous system is the intrinsic, local nervous system of the digestive system which controls the processes of digestion such as motility of the gut, secretion of chemicals for the breakdown of food and the absorption of the products of digestion. The enteric nervous system also regulates the flow of blood throughout the gastrointestinal tract. The enteric nervous system can also act autonomously but, like the autonomic nervous system, is under the control of the central nervous system. In old age, there is a tendency for the ability of autonomic and enteric function to be perturbed, such that it is not as capable of maintaining a homeostatic state as it is in the young adult. There is considerable variability in the extent to which different organ systems are affected by ►aging. As advanced health care in the developed world leads to increased longevity of the human population, the

incidence of ►autonomic and enteric dysfunction in the elderly will undoubtedly increase.

Characteristics

Quantitative Description

By virtue of the fact that autonomic nerves travel alongside the arteries of the body and within somatic peripheral nerves and their branches, the ►autonomic nervous system is present in all regions of the body. Likewise the ►enteric nervous system extends throughout the digestive system from the oral to the anal cavity.

Higher Level Structures

The autonomic nervous system is divided into parasympathetic and ►sympathetic divisions, which usually both innervate the same organ but have opposing functions. In general, parasympathetic function is anabolic whilst sympathetic function is catabolic in nature.

The anatomical organization of both the parasympathetic and sympathetic divisions is essentially similar. The efferent (motor) limb is a two neuron chain originating in the central nervous system in which the two neurons synapse in an ►autonomic ganglion in the periphery. The first of these neurons is termed the ►preganglionic neuron, and it has its cell bodies located in the brainstem or spinal cord. The second neuron is termed the ►postganglionic neuron, having its cell body in a ganglion sending its axon to innervate the target organ. The position of the ganglion varies and in consequence so does the length of the axons of preganglionic and postganglionic neurons. In the ►parasympathetic system, the ganglia are located close to, or even within, the innervated organ, with the consequence that the preganglionic axon is relatively long and the postganglionic axon relatively short. Sympathetic ganglia are located closer to the central nervous system and in consequence the preganglionic axon is relatively short and the postganglionic axon relatively long. All preganglionic neurons are under the control of the central nervous system by descending supraspinal pathways or by local interneurons. The afferent (sensory) limb of the autonomic reflex consists of receptor endings in the walls of the viscera, a peripheral process running either in an autonomic or a somatic peripheral nerve trunk, a cell body in a spinal or cranial ganglion and a central process entering the dorsal horn of the spinal cord or grey matter of the brainstem.

The enteric nervous system consists of two networks, or plexuses, of neurons that are located in the wall of the digestive tract. The myenteric plexus (of Auerbach) is located between the outer longitudinal and inner circular layers of the muscularis externa, and is principally concerned with the control of gut motility such that the contents are propelled in an oral to anal direction. The submucous plexus (of Meissner) is located within the submucosa. Its role is to regulate

gastrointestinal blood flow, control the functioning of the epithelial cell lining of the gut and in sensing the chemical composition of the contents of the gut lumen. The enteric nervous system has important connections with the sympathetic and parasympathetic divisions of the autonomic nervous system, and can therefore come under controlling influences of the central nervous system.

Lower Level Components

The chemical neuroanatomy of the autonomic nervous system is relatively simple and can be summarized as follows:

1. Preganglionic neurons are multipolar and receive glutameric, glycinergic, monoaminergic, cholinergic and peptidergic afferents.
2. All preganglionic neurons release acetylcholine at the ganglionic synapse.
3. All parasympathetic postganglionic neurons release acetylcholine at their targets but this is often accompanied by the release of vasoactive intestinal polypeptide (VIP), particularly at secretomotor terminals.
4. The majority of sympathetic postganglionic neurons release noradrenaline at their targets, often accompanied by the release of neuropeptide Y (NPY). The exception to this concerns sweat glands where acetylcholine acts as the neurotransmitter.
5. The occurrence of nitric oxide is widespread in both preganglionic and postganglionic autonomic neurons.

In addition to their extrinsic autonomic connections, ►enteric neurons secrete a wide range of neurotransmitters of which acetylcholine, nitric oxide, and many neuropeptides (principally substance P, VIP, NPY, galanin and somatostatin) which occur in different functional types of enteric neuron. The combinations of neurochemicals in enteric neurons have been used to code them and to define their functional characteristics [1,2]. In general terms, enteric neurons can be divided into the following categories:

1. Motor neurons controlling gastrointestinal motility by innervation of the muscularis and secretion from a variety of secretory cell types within the intestine.
2. Sensory neurons receiving information from terminals in the mucosa sensitive to chemical, osmotic thermal and mechanical changes and from terminals in the smooth muscle which are sensitive to stretch.
3. Interneurons responsible for the co-ordination of activity between individual ganglia of the plexuses and between the myenteric and submucous plexus. The co-ordination of descending (oral to anal) reflexes controlling peristaltic function is of special importance in promoting the passage of gut contents.

Structural Regulation

Neurons of autonomic and enteric ganglia originate in the neural crest and migrate to their final locations. Their axons then grow into their target organs. These neural migrations are guided by a variety of factors such as neurotrophins and glial derived neurotrophic factor as well as constituents of the extracellular matrix. Failure of the ontogenetic process resulting in neurons not migrating into their correct locations results in serious malfunctions: for example, mice whose cardiac neurons have failed to reach the heart die at birth [2], and congenital dysfunctions of the gastrointestinal system such as motility disorders, megacolon and gastric outlet obstruction result from the failure of neuronal migration during development.

Higher Level Processes

Cardiovascular System. Aging is associated with a reduced capability of the autonomic nervous system to maintain hemodynamic stability. A decline in the tonic influence of the parasympathetic system and an increase in sympathetic activity coupled with a change in the structure of the heart and major blood vessels from a supple nature to a more resistant, stiffer nature are characteristic of the elderly. This increased systemic vascular resistance leads to hypertension accompanied by increased systolic pressure and left ventricular hypertrophy. Decreases in cardiac output and stroke volume may be compensated for by reduced metabolic demand in the elderly. Changes with age occur in many cardiovascular reflexes including cardiopulmonary reflexes, respiratory sinus arrhythmia and in the baroreceptor reflex. Baroreceptors are stretch receptors in the carotid sinus and aortic arch, and the increased stiffening of the walls of these vessels with age results in a reduction in the ability of the receptors to respond to changes in blood pressure with a reduction in afferent input to autonomic regulatory centres in the brainstem. This is likely to be a factor in the increased occurrence of orthostatic hypotension in the elderly, a problem that is nowadays also associated with the administration of antihypertensive medication. Postprandial hypotension is also common in the elderly where there is inadequate cardiovascular compensation for the increased blood flow to the gastrointestinal system after a meal.

Urinogenital System. In old age, dysfunctions of urinary voiding are common and the frequency of micturition and the amount of urine voided are increased. Changes in the structure of the bladder wall and internal urethral sphincter, changes in the nerve supply of the bladder and changes in the central nervous system control of the micturition are implicated in the development of urinary incontinence. Normally, the smooth muscle of the bladder receives a dual innervation from the parasympathetic and sympathetic nervous systems. Sympathetic activity causes a relaxation of the bladder wall and a

constriction of the base of the bladder, including the internal urethral sphincter allowing the bladder to fill whilst maintaining continence. The parasympathetic effects are directly opposite, thereby inducing a voiding of urine. The sensory innervation of the bladder is a crucial part of the voiding reflex. It is considered that the age-associated changes in micturition are more likely to be due to the neural control of the bladder than to changes in the responsiveness of bladder smooth muscle to adrenergic and cholinergic agonists. The pelvic neurons innervating the lower urinary tract are, in common with those innervating the internal genital organs, sensitive to circulating androgens such as testosterone which also has potent effects on reproductive behaviour. Testosterone affects the ability of these neurons to maintain their morphology, synthesize neurotransmitters and express receptors. The age-associated reduction of plasma testosterone is likely to have serious consequences for the maintenance of pelvic neurons resulting in dysfunction of urinogenital function.

Enteric Function. In elderly human beings there is an increased incidence of problems associated with gastrointestinal motility. Dysphagia due to reduced oesophageal peristalsis and relaxation of the oesophago-gastric junction, increased transit time of gut contents with the danger of faecal stasis and also faecal incontinence are the most common ►enteric dysfunctions which may be attributed to the enteric innervation. Other age-associated dysfunctions include diminished ability to absorb certain constituents of the diet.

Lower Level Processes

Cardiovascular System. Well documented changes occur in the sympathetic innervation of the cardiovascular system with age. There is a reduction in the density of sympathetic innervation of the heart and in many, but not all, arteries and veins, stimulus-induced noradrenaline release increases, beta-adrenoceptor vasoconstrictive responsiveness declines, the re-uptake of noradrenaline by sympathetic nerve terminals declines and there is an increase in the concentration of plasma noradrenaline.

Urinogenital System. Investigations of the effects of age on the innervation of the lower urinary tract [3] have revealed that the sympathetic innervation is much more susceptible than is the parasympathetic innervation. This differential susceptibility affects both the preganglionic and postganglionic neurons supplying the bladder but also the descending supraspinal afferents to the preganglionic sympathetic neurons. The supraspinal pathways so far investigated contain glutamate, GABA, substance P and monoamines. Age-associated changes in the sensory innervation of the bladder wall have not been detected. There is some evidence that the neurodegeneration of postganglionic sympathetic pelvic neurons in old age may be

attributable to decreases in calcium binding proteins, leading to raised intracellular calcium concentrations [4].

Enteric Function. Neurodegeneration in the enteric nervous system with increasing age is now a well established phenomenon and affects both the myenteric and submucous plexuses [5]. Moreover, thanks to the neurochemical coding of enteric neurons [6], it is now possible to determine which functional types of enteric neuron are susceptible to age-associated neurodegeneration. In summary, there is a significant loss of cholinergic neurons from the myenteric plexus, which is likely to impair the propulsion of gut contents [7] and also of sensory neurons of the submucous plexus, possibly also contributing to reduced gut motility [5]. The postganglionic sympathetic innervation which has an inhibitory effect on the myenteric neurons is also much reduced in old age [8]. The mechanism for age-associated neurodegeneration in the gut may well be the excessive production of reactive oxygen species, as this can be almost totally prevented by caloric restriction [9,10].

Function

Autonomic and enteric functions are complex, vital processes in the maintenance of ►homeostasis of mammals. Perturbation of these processes during aging will be detrimental to the health of individuals and may eventually be life-threatening, thus influencing the longevity of an individual.

Pathology

Some of the age-associated effects of the ►ageing autonomic nervous system are similar to those seen in multiple systems atrophy (Shy–Drager syndrome), a progressive disease of the autonomic nervous system, in which there is a ►selective vulnerability of certain brainstem nuclei that control the preganglionic autonomic outflow. This selective vulnerability is also a feature of ageing in autonomic ganglia, in which certain target-specific groups of neurons are affected in old age whereas others are not [9]. This observation is reinforced by neuropathological evidence of neuronal degeneration in sympathetic ganglia of both man and rodents.

Therapy

Two factors which certain groups of autonomic and enteric neurons require for successful development and maintenance in adult life have been proposed as possible therapeutic agents in instances of autonomic and/or enteric change in old age: neurotrophic factors have possible wide-ranging application and androgens whose potential beneficial effects are restricted to the androgen-sensitive pelvic neurons.

References

1. Brookes SJH (2001) Classes of enteric nerve cells in the guinea-pig small intestine. *Anat Rec* 262:58–70
2. Young HM, Anderson RB, Anderson CR (2004) Guidance cues in the development of the peripheral autonomic nervous system. *Auton Neurosci* 112:1–14
3. Santer RM, Dering MA, Ranson RN, Waboso HN, Watson AHD (2002) Differential susceptibility to ageing of rat preganglionic neurons projecting to the major pelvic ganglion and of their afferent inputs. *Auton Neurosci* 96:73–81
4. Corns RA, Hidaka H, Santer RM (2001) Decreased neurocalcin immunoreactivity in sympathetic and parasympathetic neurons of the major pelvic ganglion in aged rats. *Neurosci Lett* 297:81–84
5. Wade PR, Cowen T (2004) Neurodegeneration: a key factor in the ageing gut. *Neurogastroenterol Motil* 16 (Suppl 1):19–23
6. Scheman M, Schaaf C, Mäder M (1995) Neurochemical coding of enteric neurons in the guinea-pig stomach. *J Comp Neurol* 353:161–178
7. Phillips RJ, Kieffer EJ, Powley TL (2003) Aging of the myenteric plexus: neuronal loss is specific to cholinergic neurons. *Auton Neurosci* 106:69–83
8. Santer RM, Baker DM (1993) Enteric System. In: Amenta F (ed) Aging of the Autonomic Nervous System. CRC, Boca Raton, pp 213–225
9. Cowen T (2002) Selective vulnerability in adult and ageing mammalian neurons. *Auton Neurosci* 96:20–24
10. Cowen T, Johnson RJR, Soubeyre V, Santer RM (2000) Restricted diet rescues rat enteric motor neurones from age related cell death. *Gut* 47:653–660

Agency

Definition

The property of being an agent. That is, the property of being an entity that acts. Typically, the term “agency” is applied only to agents capable of acting intentionally or purposively.

►Freedom of Will

Agent Causation

Definition

Agent causation is a relation supposed to hold between a substance, the agent, and its actions. The agent is construed as a prime mover. Agent causation contrasts

with event causation, a relation between events (including a person's motivational and representational states), and is taken by some theorists to be the key for understanding how free will is possible.

- Freedom of Will
- Information

Age-related Macular Degeneration

Definition

An age-related degeneration of the central retina (macular region). It causes irreversible loss of central vision (see Inherited Retinal Degenerations).

- Inherited Retinal Degenerations

Ageusia

Definition

Ageusia corresponds to the inability to detect and discriminate taste qualities. Most complaints of 'loss of taste' correspond in fact to hyposmia or anosmia, the loss of olfactory capability, since olfaction is essential for flavor perception. True aguesia is rare and hypogeusia, which refers to a diminished, rather than lost, sense of taste, is more common.

Direct damage of the tongue is one of the causes for taste disturbances. It could result from head and neck radiation therapy, inflammation of the tongue (glossitis) or other conditions. Tobacco use and dry mouth (xerostomia), such as that resulting from Sjögren's syndrome, may also have the same effects.

The chorda tympani nerve, a branch of the facial (VIIth) cranial nerve, contains primary sensory neurons that transmit chemosensory information from the anterior two-thirds tongue. The glossopharyngeal (IXth) cranial nerve contains the peripheral taste fibres from the posterior third of the tongue. Damage to any of these nerves, for example due to trauma or surgery (e.g., iatrogenic chorda tympani lesion during otologic surgery) may cause hypogeusia. Ageusia from peripheral neural lesion is unlikely since multiple anatomically distinct nerves would have to be damaged. Central lesions (e.g., trauma, tumor or ischemia of the parietal lobe) may also cause loss of taste in discrete areas of the

taste field. Non-traumatic peripheral or central neurological disorders, such as Bell's palsy or multiple sclerosis, may also affect taste function.

Systemic disturbances may also affect the sense of taste. Vitamin deficiency, endocrine disorders, cancer, renal or hepatic failure and multiple drugs, are known causes of ageusia. Aging is also typically accompanied by loss of taste sensitivity.

- Gustation

Aggression

Definition

Attack and threat; behavior directed to other organisms with the aim to intimidate, hurt or drive another animal away.

Aging of Tactile Sense

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Definition

Characteristics

None of the sensory systems is immune from the deficits in function that occur as a consequence of the natural process of aging. It is a slow process that advances throughout the life span, but does not become noticeable until the mid-40 and 50 decades of life. Most people become aware of this decline when the visual system makes it necessary to wear "reading" glasses in order to bring a printed page into proper focus. The tactile sense (touch) is not exempt from the effects of advancing age. However these effects go largely unnoticed by most people because interaction with the environment is much more salient in vision and hearing and there is no dramatic "end product" such as blindness and deafness. For this reason there has been a paucity of research funding and effort in tactile research as compared to that of vision and hearing. Although these effects have been studied for about 80 years, for the most part the early studies used poorly controlled stimulators such as cotton swabs, hairs and primitive electronic devices. Hardly quantifiable, the

results of these experiments are difficult to interpret. Controlled laboratory experiments using modern technologies for measurement have been used routinely only in the past 35 years.

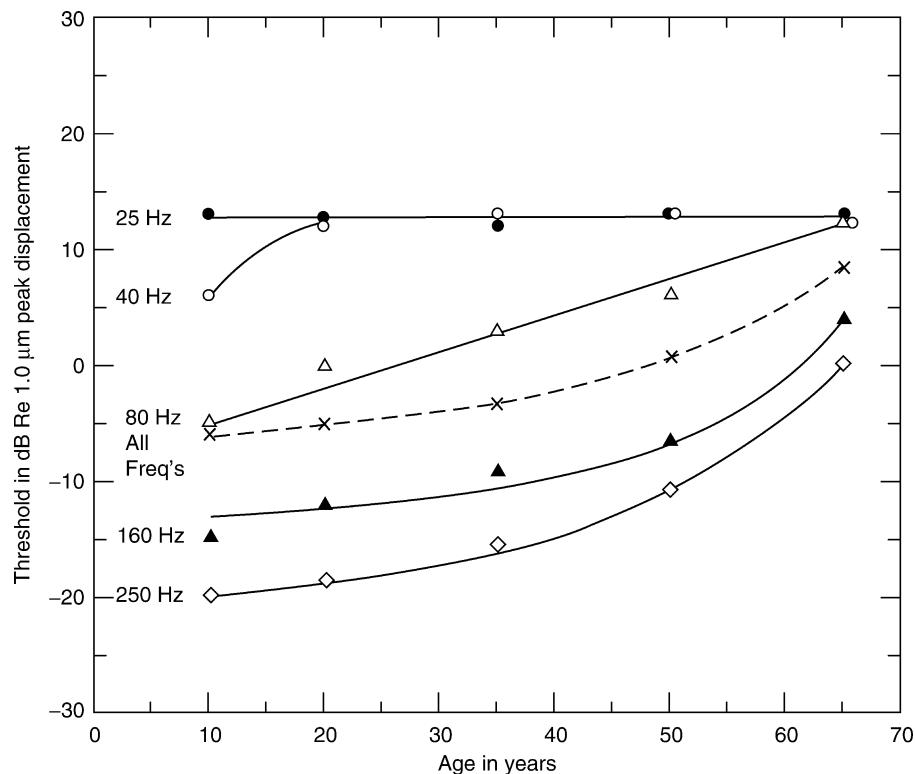
Studies of the tactile sense usually fall into two broad categories, namely measurements made at ►threshold and at ►suprathreshold levels of stimulation. Threshold experiments are performed to determine the minimal amount of energy that an observer is able to detect, in this case mechanical displacements (vibration). Suprathreshold experiments are performed in order to determine the observer's judgments and perceptions of energy levels well above the just-detectable level. Research on the effects of aging on the tactile sense has focused on measuring both threshold and suprathreshold responses.

Threshold

The onset of a loss of sensitivity in the tactile system is measurable at a relatively early age. Between the ages of 10–20 years youngsters show a loss of sensitivity especially at frequencies above 80 Hz [1,2]. Later Verrillo [3] tested a different group of subjects at the age

of 10 and the same subjects again at 23 years of age in a longitudinal study and found the same result. This confirmed that the results of the earlier study were not due to a bias in cross-sectional selection of subjects. All of the frequencies between 40 and 600 Hz were affected; only at 25 Hz was there no change in sensation. The span of ages was expanded further from 10 to 65 years in a series of experiments that determined that the loss of sensitivity was progressive throughout the life span, slow in the younger years but increasing more rapidly after about 55 years of age [4,5] which confirmed an earlier finding that covered approximately the same span of ages (20–70 years) [6]. Figure 1 shows the threshold values for vibrotaction in subjects ranging in age from 10 to 70 years. Increasing threshold values denote a loss of sensitivity.

The data also revealed an effect of gender; beyond 65 years of age in males suffered a greater loss of sensitivity than did females [5]. The loss of sensitivity in all of these studies occurred only at high frequencies from 80 to 250 Hz. At lower frequencies (25–40 Hz) the sensitivity to vibration remained constant through the life span. This suggests that in the ►vibrotactile



Aging of Tactile Sense. Figure 1 Detection thresholds of vibrotaction measured at five frequencies plotted as a function of age. The dashed line represents a composite of all frequencies combined. Decreasing sensitivity is indicated by increasing values along the vertical axis. From Verrillo [3].

neural channel subserved by the ►Pacinian-corpuscle receptors, which are activated optimally by high-frequency vibration, there are anatomical and physiological changes in structure and/or biochemical composition that do not occur in non-Pacinian channels. Non-Pacinian receptors respond primarily to low-frequency vibrations. Many explanations have been offered to account for the loss of sensitivity with advancing age including changes in receptor morphology, loss of receptors, decrease of spinal-root fibers, decreased peripheral circulation and dietary deficiency. Throughout the life span, and especially in adulthood, there is a progressive loss of nerve fibers that is steady and continuous. A decrease in the number of receptor end organs accompanies the loss of nerve fibers. The large Pacinian corpuscles decrease in number, change in size and become more complex in structure with advancing years, becoming convoluted in shape, which can affect their ability to respond to mechanical deformations. Once fully developed in infancy, all of the cutaneous nerves and receptor end organs undergo a steady decrease in number and in morphological change that continues throughout the span of life. The rate of change is constant throughout the age span at 80 Hz, at about 3 dB per decade of age. At higher frequencies the loss accelerates at greater age levels. Throughout the span of years tested below the age of 65 there was no difference between men and women in the sensitivity to vibration, but beyond 65 years of age males suffered a greater loss of sensitivity than did females [5]. The loss of sensitivity in all of these studies occurred only at high frequencies from 80 to 250 Hz. At low frequencies (25–40 Hz) the sensitivity to vibration remained constant through the life span. It is likely that no single factor can explain the loss of sensitivity but that a combination of several or many of these is probably responsible.

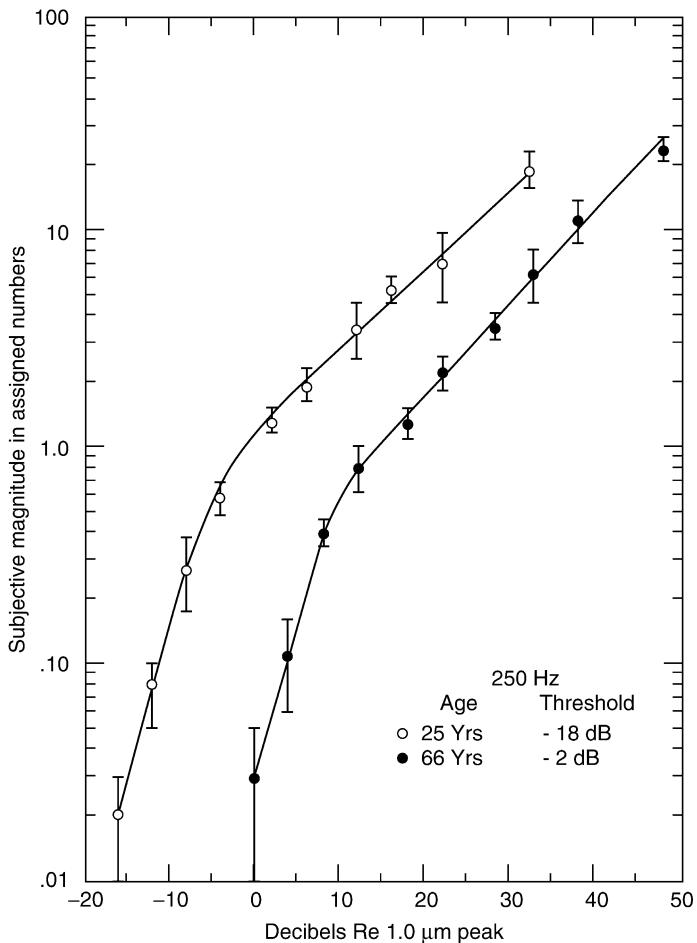
Suprathreshold

Because we live in an environment in which we are stimulated by and respond to stimuli that are, for the most part, above the threshold of detection, it is essential that the effects of these higher energy levels be considered. There are a number of psychophysical methods used to measure responses to suprathreshold stimulation, but the method of choice for measuring the relationship between the physical intensity of a stimulus and an observer's subjective impression of that intensity is a technique called Absolute Magnitude Estimation (AME). Subjects are asked to assign a number (greater or less than 1.0) whose magnitude is judged to be a match to that of the stimulation that is perceived. No standard, modulus or range of numbers is suggested by the investigator. The numbers assigned by the subjects are then plotted as a function of

the physical intensities of the stimulus. The subject is free to use any number, large or small that seems an appropriate fit to the perceived intensity of the stimulus. The resultant curve is typically a power function. This method has been used in a number of sensory modalities and along many dimensions of the stimulus. The slope of the curve (exponent) is different for each sense modality, but it is consistent within each modality.

Figure 2 shows the results obtained when a group of 25 year olds was compared to an older group with a mean age of 66 years [7]. They were both tested using the AME method at a frequency of 250 Hz. The shift in the curve of the older group to higher intensities by 16 dB indicates that for the same perceived intensity in assigned numbers, the older group required at least a 16 dB increase in the physical intensity of the vibration. This means that at both threshold (Fig. 1) and at above threshold levels of stimulation there is a loss of vibrotactile sensitivity associated with the process of growing older. The 16 dB difference in threshold values would predict this outcome. However, the slopes of the two curves are identical; both slopes are about 1.0 in the mid-to upper-levels of physical intensity. This suggests that although there is a loss of sensation with age, there is no difference in the rate at which suprathreshold stimuli grow in perceived magnitude. This would imply that in the vibrotactile system the effects of aging are manifested more as a result of changes at central levels of the nervous system (cortical) rather than changes at the periphery.

Judgment of the subjective magnitude of vibration is not the only suprathreshold performance that suffers a deficit with advancing age. From a practical viewpoint the sense of touch has been used as a surrogate channel for both vision and hearing as an aid to communication for the blind and the deaf. The blind have used ►Braille for many years and more recently electromechanical devices to read the printed word with their fingertips. In a parallel effort, for many years researchers have made the effort to develop a method of substituting the tactile sense for hearing as an aid to the profoundly deaf. As the blind and the deaf grow older or develop pathologies such as adult-onset diabetes mellitus, which degrades the sense of touch, their ability to access the world becomes severely limited. The sensory input from the fingertips is a vital link with the world that has become reduced or disrupted. Human speech is the most sophisticated and complex form of communication throughout the animal kingdom. All animals communicate with one another in various ways, but none approaches the subtlety and richness of expression as that of human speech. To render this into a system of tactile stimuli has been a formidable task indeed.



Aging of Tactile Sense. **Figure 2** Absolute magnitude estimation of vibrotaction plotted as a function of the displacement intensity of the vibration. Comparison of a younger group (mean age 25 years) and an older group (mean age 66 years) is shown. From Verrillo [7].

In order to develop tactile sensory aids for the deaf (►tactile vocoders) investigators have studied a large number of speech parameters so that these elements might be incorporated into the design of a practical tactile device. One of the elements essential in understanding speech is the ability to distinguish rapidly changing temporal sequences of stimuli. In one study a group of subjects 22 years of age was compared to a group of 66 year olds in the ability to distinguish two short bursts of vibration separated by ►interstimulus intervals of various durations [7]. The younger group was able to detect two bursts separated by as little as 25 ms whereas the older group was unable to make that distinction when the separation of the double burst was less than 150 ms. Older subjects would be at a severe disadvantage in understanding the spoken word by the use of a tactile vocoder unless the design of the device would contain a feature to compensate for this serious limitation.

Another measurement used to assess the ability to understand speech (in the hard-of-hearing) is the test of gap-detection, that is, the ability to detect a silent interval between two long bursts of sound. Similar measurements have been made using the sense of touch [8]. Tests made using subjects between the ages of 8 and 75 years using both bursts of sinusoids and bursts of noise showed that the ability to detect a silent interval was significantly worse in older than in younger subjects. Again this limitation must be compensated for by design features of the tactile aid.

In summary, in every comparison of young and elderly persons tested at suprathreshold levels of stimulation, the performance of the elderly is poorer than that of the young. It is imperative that the designer of a tactile aid for the communication of speech takes these findings into consideration so that the aid can be used successfully by young and old alike. The reader is

referred to Verrillo [10] for a discussion in greater depth of the topics considered here.

References

1. Verillo RT (1997) Comparison of child and adult vibrotactile thresholds. *Bull Psychonom Soc* 9:197–200
2. Frisina RD, Gescheider GA (1977) Comparison of child and adult vibrotactile thresholds as a function of frequency and duration. *Percep Psychophys* 22:100–103
3. Verrillo RT (1980) Age related changes in the sensitivity to vibration. *J Gerontol* 35:185–193
4. Verrillo RT (1980) Change in vibrotactile thresholds as a function of age. *Sens Proc* 3:49–59
5. Gescheider GA, Bowlanowski SJ, Hall KL, Hoffman KE, Verrillo RT (1994) Effects of aging on the information processing channels in the sense of touch. I. Absolute sensitivity. *Somatosens Mot Res* 11:345–357
6. Plumb CS, Meigs JW (1961) Human vibration perception. I. Vibration perception at different ages. *Arch Gen Psychiat* 4:611–614
7. Verrillo RT (1982) Effects of aging on the suprathreshold responses to vibration. *Percep Psychophys* 3:61–68
8. VanDoran CL, Gescheider GA, Verrillo RT (1990) Vibrotactile temporal gap detection as a function of age. *J Acoust Soc Am* 87:2201–2206
9. Gescheider GA, Edwards RR, Lackner EA, Bowlanowski SJ, Verrillo RT (1996) The effects of aging on the information-processing channels in the sense of touch. III. Differential sensitivity to changes in stimulus intensity. *Somatosens Mot Res* 13:73–80
10. Verrillo RT (1993) The effects of aging on the sense of touch. In: Verrillo RT (ed) *Sensory research: multimodal perspectives*. Lawrence Erlbaum, Hillsdale, NJ, pp 260–275

Agmatine or AGB

Definition

An organic cation that enters cells via cation channels. It is used to label cells secondary to excitatory drive or photoreceptors destined to degenerate.

- Inherited Retinal Degenerations

Agnathan(s)

Definition

Descriptor for all jawless fishes; the two extant groups, lampreys (petromyzontids) and hagfishes (myxinoids)

are not considered monophyletic here, since petromyzontids are more closely related to gnathostomes

- Evolution of the Brain: In Fishes
- Evolution of the Telencephalon: In Anamniotes
- The Phylogeny and Evolution of Amniotes

Agnosia

Definition

Inability to recognize visual objects. Agnosias come in various specific forms, for example, color agnosia (►achromatopsia), motion agnosia (►akinetopsia), ►agnosia for form or object, agnosia for faces (►prosopagnosia), agnosia for depth.

- Achromatopsia
- Akinetopsia
- Visual Neuropsychology

Agnosia of Form or Object

Definition

Characterized by the difficulty a brain-damaged patient has in identifying an object without being blind. This affliction is also called “psychic or mind blindness”. There are two types of object agnosia. Apperceptive agnosia denotes the problem of putting together pieces of visual information into a coherent percept of objects etc.; the world looks fragmented and chaotic. This syndrome often follows ►carbon monoxide poisoning causing many small, disseminated brain lesions in the ►occipital lobe. Associative agnosia is the difficulty of associating visual perceptual input with stored information of similar objects. Patients with this disorder can tell whether two objects are the same, but cannot identify them because this would require reference to memory. This syndrome is not uniform and may result from lesions of the ►temporal lobes or temporo-occipital areas.

Agonist (Pharmacological)

Definition

A ligand that binds to a specific cellular receptors and triggers a response in the cell.

Agouti-related Peptide

Definition

Hypothalamic neuropeptide that regulates hair color and bodyweight.

- Neuroendocrinology of Eating Disorders

Agraphia

Definition

Disorder of the ability to write.

Agrin

Definition

Agrin is a heparin proteoglycan expressed by motor neurons and muscle. The neuronal isoform is important for clustering acetylcholine receptors at synaptic sites.

- Neuromuscular Junction

AIDS

Definition

- Acquired Immunodeficiency Syndrome

Air Sickness

- Anti-Motion Sickness Drugs

Airways

- Visceral Afferents

Akinesia

Definition

An extension of bradykinesia that implies nearly absent voluntary movement (failure of willed movements to occur). There may be two reasons for akinesia: either the movement is too small to be seen or that the time to generate movement is extremely long, so that the movement never really occurs.

- Bradykinesia
- Parkinson's Disease

Akinetopsia

Definition

An incapacity to perceive moving visual stimuli, resulting from damage to cortical visual area V5.

- Visual Neuropsychology
- Visual Perception

Alar Plate

Definition

Dorsal portion of the developing neural tube separated from the ventral, basal plate by the sulcus limitans. In the spinal cord and rhombencephalon, it contains most of the sensory neurons.

- Neural Tube

Alcohol

- Central Nervous System Inflammation: Astroglia and Ethanol

Alcoholic Brain Damage

- Effects of Alcohol on the Brain

Alertness Level

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Synonyms

Arousal; Vigilance; Sleepiness (antonym)

Definition

The ability to direct and sustain attention. It reflects cortical activation and is modulated by sleep/wake regulatory mechanisms.

Characteristics

Neurophysiologic Regulation of Alertness Level

The regulation of alertness is closely tied to sleep/wake regulation, as is obvious from its antonym ►sleepiness. As such, alertness level may be expressed on a scale ranging from wide awake to struggling not to fall asleep. There are two primary neurophysiologic processes of sleep/wake regulation driving dynamic changes in the waking level of alertness across hours and days: a homeostatic process producing a ►homeostatic sleep drive, and a circadian process (►circadian cycle) producing an opponent circadian wake drive [1]. These two processes have been instantiated in conceptual and mathematical models of sleep/wake regulation and alertness.

The homeostatic sleep drive increases progressively from the time of awakening until the beginning of the next sleep period, and decreases progressively during sleep. The dissipation rate during sleep is greater than the build-up rate during wakefulness, such that the homeostatic sleep drive pattern is stable from day to day for the average person given a typical schedule of 16 h of wakefulness and 8 h of sleep. If wakefulness is extended and/or sleep duration is reduced, the dissipation of the homeostatic sleep drive is incomplete.

In contrast to the homeostatic sleep drive, the circadian wake drive waxes and wanes with time of day regardless of sleep and wake duration, such that wake drive is highest in the early evening and lowest in the early morning. For a normal schedule of daytime wakefulness and nighttime sleep, the result is a sustained high level of alertness through most of the waking period [2]. The reason for this is that while the homeostatic sleep drive increases with time awake, it is also increasingly counteracted by the growing circadian wake drive. As such, the alertness level remains stable from morning to evening, with only a minor mid-afternoon dip observable in some individuals [3].

In the early evening hours, the circadian wake drive is high, such that it would be difficult to fall asleep if

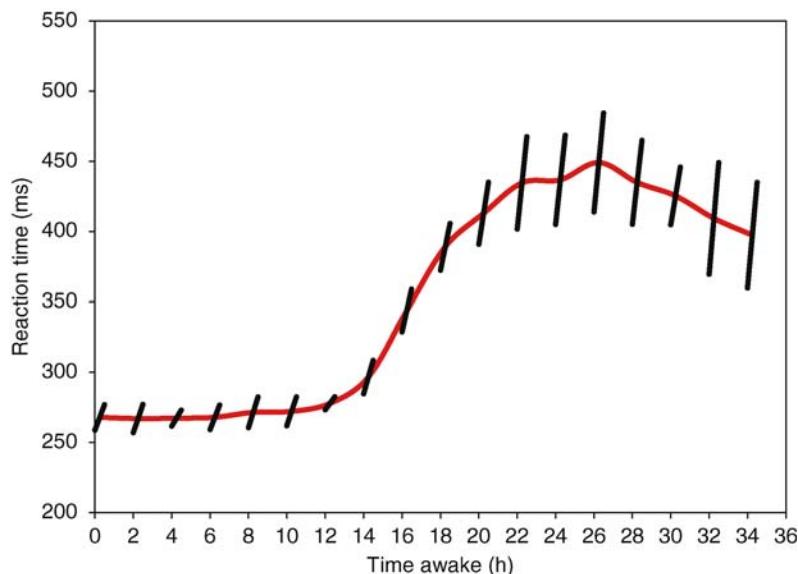
sleeping were attempted. This is known as the wake maintenance zone [2]. Later in the evening, however, the circadian wake drive falls and the homeostatic sleep drive becomes the dominant factor determining the alertness level. Thus, in late evening there is a rapid increase in sleepiness signaling that it is time to go to sleep. Assuming the sleep period is long enough to dissipate the homeostatic sleep drive, this pattern repeats itself the next day. Immediately after awakening there is a brief interval of residual sleepiness known as ►sleep inertia, but it quickly subsides to be followed by another daytime period of high, stable alertness.

If sleep is postponed and wakefulness continued into the night – as may occur in ►shift work settings – the further increasing of the homeostatic sleep drive and the further waning of the circadian wake drive produce a considerable deterioration of the alertness level. This continues until the next morning. At that time, the circadian wake drive begins to rise again, providing a partial rebound of alertness later in the afternoon and early evening. This is illustrated in Fig. 1.

Just as extending the waking period reduces the alertness level as modulated by the homeostatic process, so does altering the timing of the waking period reduce the alertness level through the action of the circadian process. This can be observed when traveling to another time zone, which results in a temporary misalignment of the circadian cycle with the new local day and night. This yields reduced daytime alertness and difficulty sleeping at night – a phenomenon known as ►jet lag. Depending on the number of time zones crossed, it may take several days for ►entrainment mechanisms to realign the circadian process with the local time.

In addition to the long-term action of the homeostatic and circadian processes, a variety of short-term neurobiological effects on the alertness level have been reported. For reasons not well understood, sustained attention to perform a task results in progressive declines of alertness while the task is ongoing [4]. This ►time-on-task effect is undone by a break from the task – see Fig. 1. The time-on-task effect is thought to be amplified by monotony or boredom, while it may be dampened in tasks that are inherently novel or interesting (although it is not clear what determines the latter). Reductions in alertness may be overcome by motivation (e.g., through incentives), but this effect is likely to be transient. Alertness is also affected by ►stress, where the nature of the stress determines whether alertness is increased or decreased. Posture plays a role as well, in that supine positions appear to enhance sleepiness while standing up enhances alertness.

The environment can influence the alertness level as well. Bright light (e.g., sunlight) is known to provide a short-lasting boost of alertness (in addition to its ►photoperiodic effect on the circadian cycle). Sound may enhance alertness, but chronic exposure to noise



Alertness Level. Figure 1 Pattern of alertness across 36 h of total sleep deprivation beginning at 10:00 (10 A.M.), as measured by mean reaction time on a 10-min psychomotor vigilance task [5] administered every 2 h in a laboratory (averages shown for ten healthy young adults). The red curve displays the combined effect of the homeostatic sleep drive, which increases progressively across time awake, and the circadian wake drive, which waxes and wanes across the 24 h of the day. The black lines show deterioration of performance (assessed with linear regression) during each 10-min test bout, which is known as the time-on-task effect. The steeper the rise of the line, the greater the time-on-task effect. The time-on-task effect is greatest when the overall alertness level is lowest, revealing an interaction between this effect and the homeostatic and circadian processes. Note also that the breaks between the test bouts provide recuperation from the time-on-task effect.

may have the opposite effect. The effects of tactile and olfactory stimulation on alertness have not been well documented. When measuring the endogenous (neurophysiologically driven) alertness level, it is important to take these environmental factors into account (e.g., by standardization in a controlled laboratory environment).

Neurobehavioral and Physiological Correlates

Changes in the alertness level can be observed in a variety of neurobehavioral and physiological variables. Individuals experiencing reduced alertness (e.g., due to sleep deprivation) report elevated feelings of sleepiness and fatigue, negative effects on mood, difficulty concentrating, and greater effort needed to stay awake. They show stereotypical behaviors such as yawning and muscle stretching. They exhibit **cognitive impairment**, ranging from increased **reaction times** and greater numbers of performance errors to **executive control** deficits and poor decision making. Indices of **attention** appear to be particularly affected, with tasks requiring sustained attention showing increased variability in responses. This latter effect has been hypothesized to reflect the episodic intrusion of sleep processes into wakefulness [5].

Indeed, reduced levels of alertness are associated with greater propensity to fall asleep, which translates into reduced sleep latencies – i.e., falling asleep faster – as determined through sleep physiological

recording (**polysomnogram**). This phenomenon, which is observed both when sleep is attempted and when it is to be resisted, provides a basis for physiological tests of sleepiness, including the **multiple sleep latency test** and the **maintenance of wakefulness test**. Physiological changes can also be seen before the occurrence of sleep, though. **Visual evoked potentials** and **auditory evoked potentials** show changes indicative of impaired signal processing under conditions of diminished waking alertness. The background waking **electroencephalogram** (EEG) also changes, reflecting enhanced synchronization [6] possibly associated with sleep initiation mechanisms in the brain (drowsiness).

Alertness changes are further reflected in ocular measures, including the appearance of slow-rolling eye movements, changes in blink rate, extended partial or complete eye closures, and variations in pupil diameter. Additionally, cardiovascular indices (heart rate, heart rate variability) have been reported to covary with alertness. These physiologic changes may be mediated by alterations in the tone of the **autonomic nervous system**.

There are considerable inter-individual differences in the effects of alertness-reducing interventions such as sleep deprivation on the various correlates of alertness described above [7]. The expression of these inter-individual differences is found to vary from one correlate of alertness to another. It might be concluded that there is not just a single overall level of alertness,

but that there are several alertness levels depending on which specific measure is considered. However, measures of alertness typically involve other neurophysiologic and neurocognitive systems as well, which contribute to the measurement outcomes in potentially non-trivial and/or person-specific ways. For instance, a cognitive performance measure of alertness is also affected by a person's aptitude for the performance task as well as any practice effects. Understanding such issues is important for the interpretation of alertness measurement data [3].

Neuroanatomical Structures and Neurotransmitters

Although the neuroanatomical and neurochemical mechanisms underlying the regulation of alertness have only partially been delineated, it is known that there is a strong modulation of the alertness level by the ►**ascending neuromodulatory projections**. Briefly, this system involves ►**arousal** of the ►**cortex** by monoaminergic and cholinergic nuclei in the ►**brainstem**, ►**hypothalamus** and ►**basal forebrain**. These nuclei and their ►**neurotransmitters** include the ►**locus coeruleus** (noradrenalin), the ►**tuberomammillary nucleus** (histamine), the ►**raphe** (►**serotonin**), and nuclei in the ►**tegmentum** (►**acetylcholine**). The ascending neuromodulatory projections can be blocked by activation of the ►**ventrolateral preoptic nucleus** (►**GABA**, galanin), which initiates sleep [8]. It is possible that the activity of this system represents, in part, the homeostatic sleep drive, but definitive evidence is lacking and other pathways, neurotransmitters/►**neuromodulators** (►**dopamine**, ►**adenosine**) and mechanisms are likely involved as well [9]. The source of the circadian wake drive is much better understood. It is driven by the ►**suprachiasmatic nuclei** (►**SCN**) in the hypothalamus [1], the functioning of which has been elucidated in considerable detail.

The neurotransmitter systems involved in sleep/wake and alertness regulation are targets of a wide variety of pharmacological substances affecting alertness. These include hypnotics such as benzodiazepine receptor agonists, which reduce alertness and promote sleep; and ►**stimulants** such as caffeine and amphetamine, which enhance alertness. Hypnotics are particularly useful to improve sleep quality and increase sleep duration as part of the treatment repertoire for clinical sleep disorders. Stimulants are administered to treat excessive sleepiness associated with certain sleep disorders (e.g., narcolepsy), and to maintain optimal (baseline) alertness levels in operational settings [10] (caffeine being the most widely used). With specific stimulants (e.g., amphetamine), it is possible to temporarily raise alertness and enhance performance beyond the baseline level, although this does not necessarily translate into better cognitive/behavioral outcomes and often involves undesirable side effects. The mechanisms of actions of most hypnotics and stimulants have only partially been determined.

References

1. Edgar DM, Dement WC, Fuller CA (1993) Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 13:1065–1079
2. Dijk DJ, Czeisler CA (1994) Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 166:63–68
3. Van Dongen HPA, Dinges DF (2005) Circadian rhythms in sleepiness, alertness, and performance. In: Kryger MH, Roth T, Dement WC (eds) *Principles and practice of sleep medicine*, 4th edn. Elsevier Saunders, Philadelphia, pp 435–443
4. Bills AG (1937) Fatigue in mental work. *Physiol Rev* 17:436–453
5. Doran SM, Van Dongen HPA, Dinges DF (2001) Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol* 139:253–267
6. Strijkstra AM, Beersma DGM, Drayer B, Halbesma N, Daan S (2003) Subjective sleepiness correlates negatively with global alpha (8–12 Hz) and positively with central frontal theta (4–8 Hz) frequencies in the human resting awake electroencephalogram. *Neurosci Lett* 340:17–20
7. Van Dongen HPA, Vitellaro KM, Dinges DF (2005) Individual differences in adult human sleep and wakefulness: leitmotif for a research agenda. *Sleep* 28:479–496
8. Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437:1257–1263
9. Krueger JM, Obál F, Kapás L, Fang J (1995) Brain organization and sleep function. *Behav Brain Res* 69:177–185
10. Penetar D, McCann U, Thorne D, Kamimori G, Galinski C, Sing H, Thomas M, Belenky G (1993) Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharmacology* 112:359–365

Alginic

Definition

Alginic is derived from brown seaweed. Alginic is a polysaccharide like glycosaminoglycan composed of two monosaccharides, β -D-mannuronic acid and α -Lguluronic acid.

Allele

Definition

Different forms or variants of a gene that occupy a given locus on a chromosome.

Allocentric Cues

Definition

Distal and local environmental cues used for navigation.

Distal cues are principally visual and provide information about the distance to landmarks and spatial arrangement among landmarks. Local cues, such as odors on the ground, are also allothetic. Typically contrasted with “idiothetic cues”.

- Spatial Learning/Memory

Allocentric Reference Frame

Definition

Framework centered outside of the body of the subject such as mountain, or individual object.

- Spatial Memory

Allocortex

Definition

“Other” cerebral cortex, referenced against six-layered isocortex.

Allocortex includes cerebral cortical areas, such as the hippocampus and olfactory cortex, which comprise fewer than six-layers.

- Hippocampus
- Isocortex
- Olfactory Cortex

Allodynia

Definition

Pain due to a stimulus which does not normally provoke pain (e.g., gentle static pressure, non-painful thermal stimuli).

- Hyperalgesia and Allodynia

Allodynia, Hyperalgesia

Definition

Hyperalgesia denotes increased pain generated by a stimulus which is normally painful and excites nociceptors. It has a peripheral (sensitization of nociceptors) and/or a central component (sensitization of central neurons, e.g. in the dorsal horn of the spinal cord). *Allodynia* is pain generated by stimuli which activate low-threshold mechanoreceptors (mechanical allodynia) or cold receptors (cold allodynia). The mechanism of allodynia is central (central sensitization generated by persistent excitation of nociceptors). *Secondary allodynia* is pain elicited by stimulation of low-threshold mechanoreceptors in an area of skin which surrounds a territory with sensitized nociceptors (e.g. generated by inflammation) *Causalgia*.

- Complex Regional Pain Syndromes: Pathophysiological Mechanisms

Allografting

Synonyms

Allotransplantation

Definition

Transplantation of tissues and organ pieces from one person to another, or from one animal to another of the same species.

Allometric

Definition

A scaling relationship, usually exponential, between the size of a part of the body, and the whole body. There is an allometric relationship between brain and body size in the primate order.

- Evolution of the Brain in Humans – Paleoneurology

Allometry

Definition

Measurement and correlation of biological size of organs or organ-systems.

- Evolution and Brain-Body Allometry

Allophone

Definition

Phonetic variant of a phoneme; substituting one allophone for another does not change the meaning of a word (e.g., [bath] does not differ in meaning to [bat]; [th] is an aspirated /t/ and [t] is an unaspirated /t/).

- Phoneme

Allosteric Enzyme

Definition

An enzyme that alters its three-dimensional conformation as a result of the binding of a smaller molecule (at a site different to its active site), often leading to inhibition or activation of its activity.

Allosteric Protein

Definition

A protein that can adopt several conformations. These conformations can be stabilized by different molecules, that bind at the same, or different sites.

Allotrophic Information

Definition

Stimuli providing information about the environment like visual, olfactory, sound, tactile inputs.

Alpha (Activity Phase) in Circadian Cycle

Definition

Alpha is the duration of the active portion of the daily rest-activity cycle.

- Circadian Cycle
- Rest-activity Cycle

Alpha Rhythm

Definition

A neocortical pattern of 8–13 Hz EEG activity characteristic of quiet wakefulness in humans.

- Brain Rhythms

Alpha Subunit of Gustducin

- Gustducin

Alpha-gustducin

- Gustducin

Alpha-internexin

Definition

A 66 kDa protein encoded on chromosome 10q24.33.

Alpha-motoneuron

Definition

A motoneuron that exclusively innervates the large extrafusal striated muscle fibers that make up the bulk of anatomical muscles and that generate output force.

► Motor Units

Alpha-synuclein: From Neurological Disorders to Molecular Pathways

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Definition

α -Synuclein is a small acidic protein of 140 amino acid residues and a member of a multi-gene synuclein family (Fig. 1a). The N-terminal part has seven imperfect repeats containing the consensus core sequence Lys-Thr-Lys-Glu-Gly-Val, whereas the C-terminal part (residues 96–140) has no recognized structural elements. The central portion of α -synuclein (residues 61–95) is known as the non-A β component of ►amyloid plaques in Alzheimer disease (Fig. 1b). It comprises the highly amyloidogenic part of the molecule that is necessary for α -synuclein (i) to undergo a conformational change from ►random coil to ►Beta Sheet structure, (ii) to form single cylindrical β -sheets, and (iii) to form protofibrils and fibrils. These features distinguish α -synuclein from its two close relatives β -synuclein and γ -synuclein that fail to form copolymers with α -synuclein [1]. α -Synuclein displays an extended unfolded structure and thus belongs to the group of natively unfolded proteins also comprising protein tau. α -Synuclein exists physiologically in both soluble and membrane-bound states, with an unstructured or alpha-helical conformation, respectively. The function of α -synuclein is poorly resolved, though it is attributed with wide-ranging roles such as molecular chaperone, axonal transport and turnover of synaptic vesicles [2].

Characteristics

Alpha-Synuclein and Neurological Disorders

Pathological accumulation of α -synuclein is associated with multiple neurodegenerative diseases that are collectively known as synucleinopathies (Fig. 2). The

most prominent of these is Parkinson's disease (PD), a progressive disorder that impairs movement in nearly 2% of individuals over 65 years. Other disorders include Dementia with ►Lewy bodies (DLB), the second major cause of dementia in the elderly after Alzheimer's disease (AD), the Lewy body variant of Alzheimer's disease, multiple system atrophy, neurodegeneration with brain iron accumulation type 1, familial forms of AD and Down syndrome. α -Synuclein-containing inclusions are also found in several more disparate neurodegenerative diseases that are not commonly referred to as synucleinopathies [3].

A causative role for α -synuclein in neurodegeneration was fortified by the identification of three mutations (A30P, A53T and E46K) in the α -synuclein gene, as well as multiplication of the normal gene that results in increased α -synuclein protein expression, in families with early-onset PD [4]. Affected family members present clinical and pathological features that are similar to sporadic PD that is clinically characterized by the three cardinal symptoms including muscle rigidity, bradykinesia and resting tremor [5]. These motor impairments are primarily due to degenerating dopaminergic neurons in the substantia nigra and the loss of their dopaminergic projections to the striatum and can be corrected by dopamine-replacement therapy. Moreover, histological analyses of PD brains reveal dense aggregations of insoluble material including α -synuclein in intracellular inclusions called Lewy bodies (LB).

Development of PD appears to be linked to processes that increase the rate at which α -synuclein forms aggregates. These processes include increased protein concentration (via either increased expression or reduced turnover), and altered forms of α -synuclein (such as truncations, missense mutations, or post-translational modifications [6]). Phosphorylated α -synuclein at Ser-129 has been observed in post-mortem analyses of patients with PD, multiple system atrophy, and neurodegeneration with brain iron accumulation type 1. Under normal physiological conditions, about 4% of α -synuclein is phosphorylated at Ser-129, but in LB, 89% of α -synuclein is phosphorylated at this residue. The effects of phosphorylation of Ser-129 on α -synuclein conformation are not known, but phosphorylation at Ser-129 caused a fourfold increase in insoluble α -synuclein and inhibited interaction of α -synuclein with phospholipids and phospholipase D2. Moreover, mutation of Ser-129 to alanine (to prevent phosphorylation) completely suppressed DA neuronal loss produced by expression of human α -synuclein, and substituting aspartate for Ser-129 (to mimic phosphorylation) significantly enhanced α -synuclein toxicity.

Role of Alpha-Synuclein

α -Synuclein is widely expressed in mammalian CNS, and particularly concentrated in presynaptic terminals,

a. Synuclein sequence homologies:

	1	11	21	31	41	51	Repeat
		Repeat 1	Repeat 2	Repeat 3	Repeat 4		
α -synuclein	mdvfmkglsk	akegvvaaae	tkqggvaeaa	gktkegvlvv	gsktkegvvh	gvatvaektk	
β -synuclein	mdvfmkglsm	akegvvaaae	tkqggvteaa	ektkiegvlvv	gsktrgevvq	gvasvaektk	
γ -synuclein	mdvfkkfgsi	akegvvgave	tkqggvteaa	ektkiegvmyv	gaktkenvvq	svtsvaektk	
				p	k	t	
	61	71	81	91	101	111	
	5		Repeat 6				
α -synuclein	eqvtvnggav	vtgtavak	tvegagsiaa	atgfvkkdql	gkneegapqe	giledmpvdp	
β -synuclein	eqashlggav	fsgagniaaa	tglvkreefp	tdlkpeevaq	eaeepliep	lmepegesye	
γ -synuclein	eqanavseav	vssvntvatk	tveeaeniam	tsgvvrkedl	rpsapqgegv	askekeevae	
	121	131					
α -synuclein	dneayempse	egyqdyapea					
β -synuclein	dppqeeyqey	epea					
γ -synuclein	Eaqsggd						

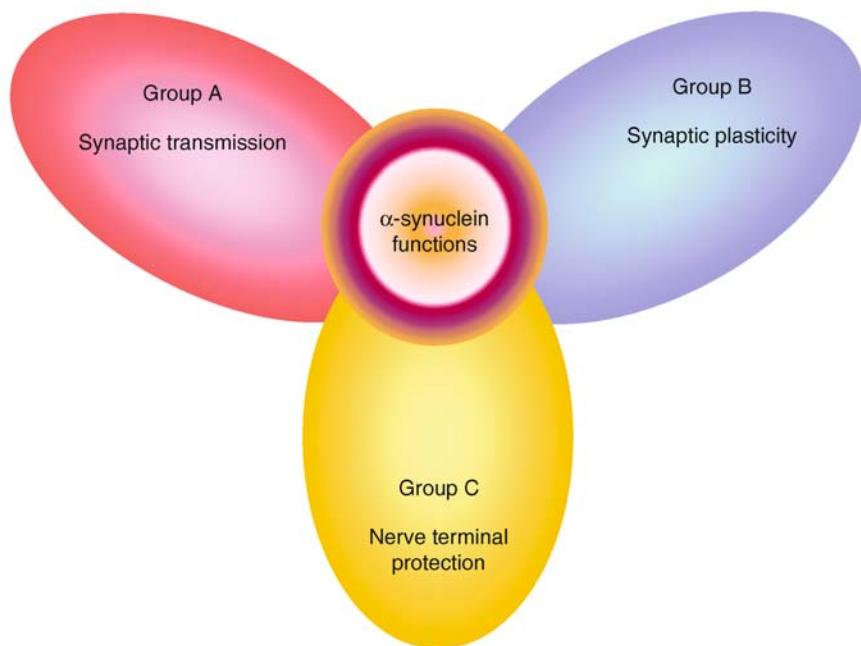
Keys:**Residues** - Familial PD associated mutations**Residues** - conserved sequence between α -, β - and γ -synuclein**Residue** - Serine 129**Residues** - ktkegvg imperfect repeats**b. α -synuclein Structure:** α -helicoidal domain
(Residues 1–67)Hydrophobic region
(Residues 61–95)Acidic Rich region
(Residues 96–140)

Alpha-synuclein: From Neurological Disorders to Molecular Pathways. **Figure 1** α -Synuclein homologies and structure. (a) The synuclein family consists of three members: α -synuclein, β -synuclein and γ -synuclein that range from 127 to 140 amino acids in length and are 55–62% identical in sequence, with a similar domain organization. (b) α -synuclein structure is divided in three regions: (i) N-terminal domain (residues 1–67) contains two α -helical regions separated by a short break; (ii) hydrophobic domain (residues 61–95) and (iii) C-terminal domain acidic rich region.

where it is associated with synaptic vesicles and freely-diffusible in the cytoplasm. While the exact functions of normal α -synuclein remain to be fully elucidated, several studies suggested it may play a role in synaptic plasticity; regulate dopamine (DA) neurotransmission via effects on vesicular DA storage and protecting neurons from neurodegeneration induced by the loss of ►cysteine string protein (Fig. 2; [7]). More recently, it has been suggested that α -synuclein may be involved in the trafficking of cargo within the endoplasmic reticulum/Golgi network since one of the most profound initial consequences of artificially expressing α -synuclein in yeast appears to be a disruption of ER-Golgi trafficking [8].

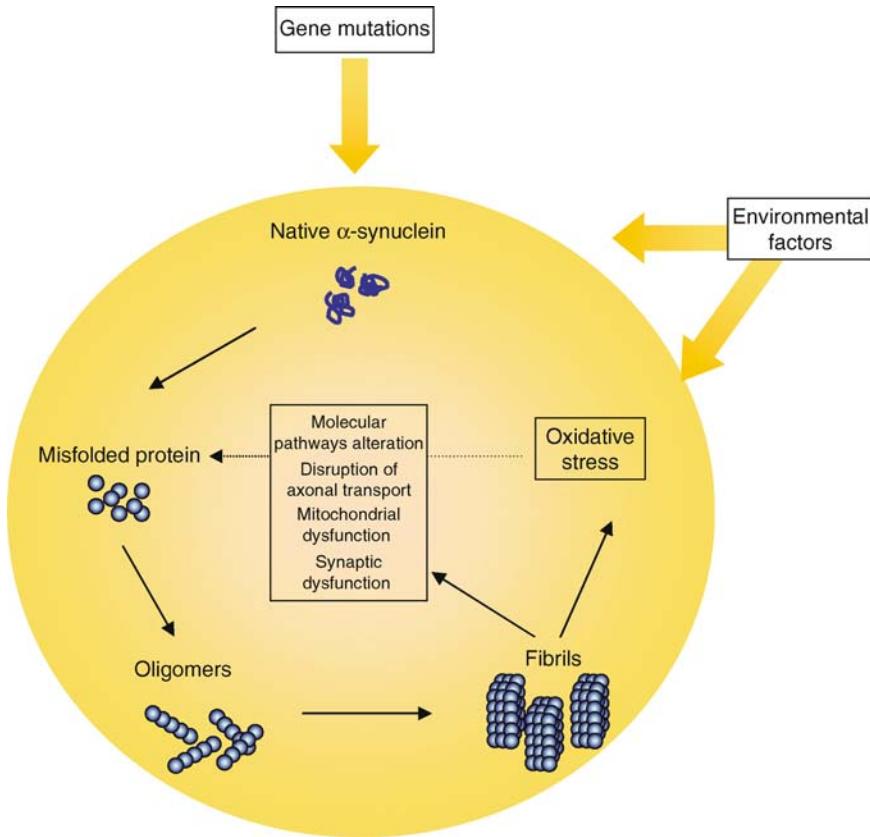
So far, the exact role of α -synuclein in healthy brain as well as in pathological conditions still remain unclear. However, several protein interactions with α -synuclein suggest a function in specific molecular pathways. Figure 3 summarizes potential functions associated with

α -synuclein. However, it is unclear if the α -synuclein binding proteins compete for overlapping binding sites, interact differentially depending on α -synuclein conformation, or bind in a competitive/allosteric manner. It also remains to be determined if these interacting proteins bind to α -synuclein in distinct subcellular compartments. Conformational changes in α -synuclein due to temperature, pH and/or posttranslational modification could alter the protein and ligand binding properties of α -synuclein as well as its aggregation properties. In addition to lipids, various reports suggest that α -synuclein is capable of interacting with a variety of proteins including PLD2, UCH-L1, parkin, synphilin, 14-3-3, different PKC isozymes, BAD, Rab3A, Rab5A, Rabphillin, the ELK-1/ERK-2 complex, ERK-1/2, p38MAPK, and SAPK/JNK mitogen activated kinases, A β , MAP1B, heterodimeric but not microtubule Tubulin, tau, TBP-1, the DAT, the mitochondrial complex IV enzyme cytochrome oxidase, and TH, and calmodulin [1] (Reviewed by Dalfo et al.,



Interacting protein	Role	References
Calmodulin M	Major calcium-binding protein in the brain.	Martinez et al., 2003
TBP-1	Recognized as a component of a 19S regulatory subunit of the 26S proteasome which degrades ubiquitinated proteins	Nakamura et al., 1998
Rab	Small GTPases of the Rab family control timing of vesicle fusion.	Jordens et al. 2005
TH	Enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to dihydroxyphenylalanine (DOPA)	Sung et al., 2001
HSP90	Important roles in cellular regulation, primarily as a chaperone for a number of key intracellular proteins. Also involved in cell migration.	Sidera et al., 2004
Parkin	E3 ubiquitin ligase and, which ubiquitinates proteins such as CDC rel-1, synphilin-1, the O-glycosylated form of α -synuclein, and parkin-associated endothelin receptor-like receptor to facilitate their proteasomal degradation.	Mukhida et al., 2004
14-3-3	14-3-3 proteins modulate the action of proteins that are involved in cell cycle and transcriptional control, signal transduction, intracellular trafficking and regulation of ion channels.	Berg et al., 2003
MAP1B	Major component of the neuronal cytoskeleton which play a crucial role in neuronal morphogenesis and neurite extension	Takei et al., 1997
Synphilin	The physiological function of the protein is currently unknown, although several protein domains have been defined and are known to be present in a variety of proteins mediating protein-protein interactions	Kruger, 2004
ERK, MAPk, JNK	A large kinase network in which upstream kinases activate downstream kinases that, in response to phosphorylation, translocate to the nucleus and activate transcription factors.	Adams et al., 2000
PKC	C kinases (PKCs) are a family of enzymes essential for the transduction of signals	Kuo et al., 1997
BAD	BAD represents a bridging molecule which interconnects signal transduction pathways from extracellular survival factors with the Bcl-2 intracellular checkpoint upon cell death.	Hong et Wu, 2002
TAU	Tau has a variety of functions, most prominently in microtubule stabilization or neurite outgrowth	Garcia et Cleveland, 2001

Alpha-synuclein: From Neurological Disorders to Molecular Pathways. Figure 2 Summary of the potential role of α -synuclein. The exact role of α -synuclein still needs to be defined, however, it seems that this protein is involved in synaptic transmission as well as protection and plasticity and is reported to interact with different proteins.



Alpha-synuclein: From Neurological Disorders to Molecular Pathways. Figure 3 Hypothetical routes for α -synuclein to induce neurodegeneration. α -synuclein gene mutations as well as environmental factors may induce the α -synuclein fibrilization which may lead to changes in cell activity, dysfunction, and cell death. However, it is still unclear if those factors act first on the fibril formation which then induces dysfunction or if the fibrilization is a consequence of the functional dysregulation.

2005). Interaction has been shown also with divalent cations include Fe^{2+} , Al^{3+} , Zn^{2+} , Cu^{2+} , and Ca^{2+} [1]. For most of these interactions, their relevance to cell physiology and pathophysiology remains to be clarified. Moreover, it is interesting to note that only some of the α -synuclein interacting proteins are found in LB.

6. Shults CW, Barrett JM, Fontaine D (2006) *Neurosci Lett* 405:223–225
7. Chandra S, Gallardo G, Fernandez-Chacon R, Schluter OM, Sudhof TC (2005) *Cell* 123:383–396
8. Lee VM, Trojanowski JQ (2006) *Neuron* 52:33–38
9. Dalfo E, Ferrer I (2005) *Neuroscience Letter* 380:170–175

References

1. Dev KK, Hofele K, Barbieri S, Buchman VL, van der PH (2003) *Neuropharmacology* 45:14–44
2. Bennett MC (2005) *Pharmacol Ther* 105:311–331
3. Galpern WR, Lang AE (2006) *Ann Neurol* 59:449–458
4. Jain S, Wood NW, Healy DG (2005) *Clin Sci (Lond)* 109:355–364
5. Goedert M (2001) *Nat Rev Neurosci* 2:492–501

ALS

Definition

- Amyotrophic Lateral Sclerosis

Alternative Splicing

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Definition

Alternative splicing refers to the post-transcriptional modification process in which coding regions (exons) of a primary transcript are joined in different combinations through the removal or retention of non-coding intervening sequences (introns) to produce distinct mature messenger RNA (mRNA) transcripts.

Characteristics

Mechanisms of Alternative Splicing

One surprising finding stemming from genome analyses is that proteomic diversity of an organism does not correlate with the number of protein-coding genes observed. It was later revealed that alternative splicing provides the major mechanism for increasing transcriptome and proteome complexity. An analogy to explain this idea would be to liken alternative splicing to a glass prism which can disperse white light into a spectrum of colors (Fig. 1).

Through alternative splicing, a single pre-mRNA can generate a diverse array of mRNA splice variants which will be translated into protein isoforms with varying structure and/or function.

Recent genome analyses have estimated that 60–80% of human genes are subjected to alternative splicing and this biological phenomenon is emerging to be of central importance in the nervous system [1,2]. Furthermore, sequence- and microarray-based

analyses have suggested that transcripts from genes expressed in functionally complex tissues, such as that of the brain, undergo alternative splicing at a higher frequency [1].

There are several types of alternative splicing events leading to the generation of distinct transcripts: cassette exon, alternative 5' splice site, alternative 3' splice site, mutually exclusive exons, intron retention, alternative promoter, and alternative polyadenylation site (Fig. 2).

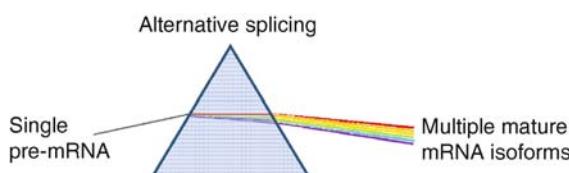
In general, these events occur in a combinatorial manner to produce multiple alternatively spliced isoforms or splice variants. The *Drosophila melanogaster* Down syndrome cell adhesion molecule (*Dscam*) gene is one of the best examples to illustrate this process. The *Dscam* gene, which contains four clusters of exons alternatively spliced in a mutually exclusive fashion (12, 48, 33, and 2 exons respectively), can theoretically give rise to as many as 38,016 different mRNAs by virtue of combinatorial alternative splicing [3]. Remarkably, this number is even greater than the predicted number of genes in the *Drosophila* genome.

Protein variations generated by alternative splicing can range from subtle to drastic [3]. While alternative splicing in the untranslated regions does not alter the protein sequence, it can affect mRNA stability and localization, which in turn influence the expression pattern and subcellular localization of the protein [3]. On the other hand, alternative splicing in the coding region can lead to the addition or removal of a functional motif or domain, or in some cases, bring about frameshifts that introduce premature termination codons that result in truncated, non-functional proteins [3].

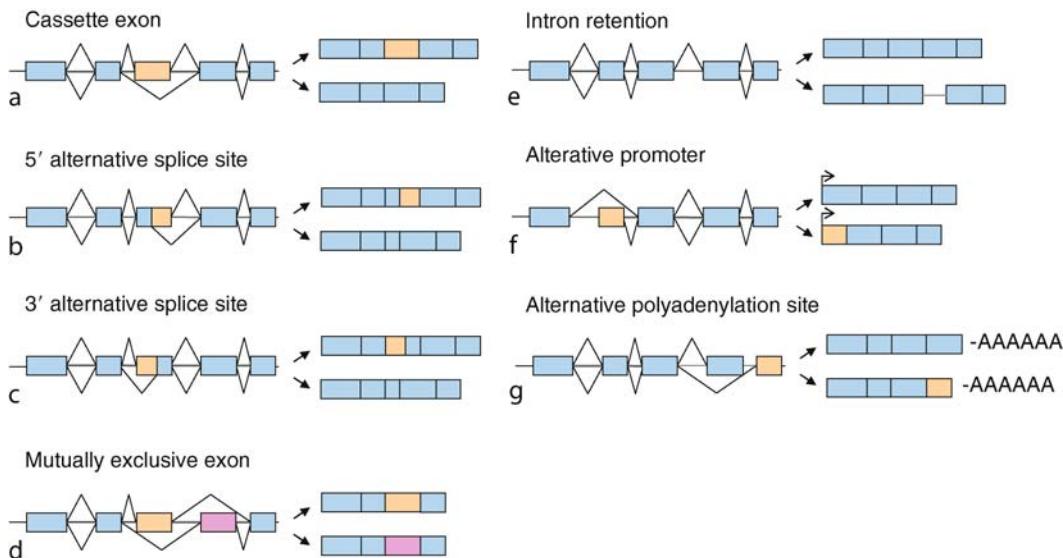
Regulation of Alternative Splicing

Pre-mRNA splicing reaction takes place on a cellular machinery known as the spliceosome, a large complex composed of five small nuclear ribonucleoproteins (snRNPs) (U1, U2, U4, U5, and U6) and many additional proteins. The spliceosome assembles onto the pre-mRNA in a stepwise fashion and catalyzes the removal of introns and ligation of exons. Four conserved sequence elements at both ends of the intron, namely the 5' splice site, the branchpoint, the polypyrimidine tract, and the 3' splice site, act as splicing signals that define the intron-exon boundary. However, additional *cis*-acting elements are required to ensure that the splicing process proceeds with high fidelity and accuracy.

Exonic and intronic splicing enhancers (ESEs and ISEs) and silencers (ESSs and ISSs) are splicing regulatory sequences in the pre-mRNA that facilitate correct splice site recognition [1]. ESEs and ISEs usually enhance the use of weak splice sites and thereby promote inclusion of an alternatively spliced exon; whereas ESSs and ISSs generally inhibit the use of splice sites and in doing so, promote skipping of an



Alternative Splicing. Figure 1 Analogous to the dispersion of white light into the color spectrum by a glass prism, a single pre-mRNA can generate a diverse array of mature mRNA transcripts through alternative splicing.



Alternative Splicing. **Figure 2** Schematic illustrations of alternative splicing events. Exons are represented by boxes, while introns are depicted as thick grey lines. Alternative splicing can lead to (a) either the inclusion or exclusion of an exon, (b and c) the use of alternative splice sites, (d) the use of mutually exclusive exons, (e) the retention of an intron, (f) the use of an alternative site for translation initiation, or (g) the use of alternative site for translation termination.

alternatively spliced exon [1]. These sequences are bound by splicing factors, such as members of the serine/arginine-repeat (SR) and heterogeneous nuclear ribonucleoprotein (hnRNP) families of proteins which define the splicing pattern in many cases by either facilitating or blocking spliceosome assembly [1]. Expanding on the simplistic view that SR proteins mostly bind to ESEs and activate splicing, while hnRNP proteins mostly bind to ISSs and repress splicing, a recent global analysis of splicing regulators in *Drosophila* demonstrates that these two families can have both positive and negative effects on splice site choice [2].

Central to the regulation of alternative splicing is the combinatorial interplay of the *cis*-acting sequences with the *trans*-acting splicing factors [1]. A major mechanism used in the regulation of alternative splicing is the differential expression of splicing factors [2]. More specifically, unique alternative splicing patterns across different cell types can be achieved by the tissue-specific expression of splicing factors in one cell type but not others [2]. In addition, expression levels of splicing factors have also been found to vary across different developmental stages [2]. Further regulatory potential is derived from post-translational modifications of the splicing factors [2]. Such modifications can modulate functions of splicing factors by regulating their ability to bind to RNA or interact with other

proteins [2]. For instance, phosphorylation is critical for the protein activity of SR proteins [2]. Recent studies have explored the regulation of alternative splicing events by cellular signaling pathways, and looked into alternative splicing events resulting from genetic polymorphisms and such events are characterized by the production of allele-specific transcript isoforms [2].

In the following sections, the role of alternative splicing in the nervous system will be illustrated with several examples. To truly understand the physiological significance of the utilization of an alternatively spliced exon in a specific excitable cell in the nervous system, however, will require multi-pronged studies. One approach is to determine the cellular or sub-cellular localization of an alternatively spliced exon to provide more defined clues as to its functional importance in the native cells. Another approach is to evaluate the functional diversifications via alternative splicing of cognate protein to provide important predictions of selective requirements for the splice variants in physiology or disease. A third approach is to examine the expression profiles of the alternatively spliced exons in response to physiological or pathophysiological signals to provide evidence for their dynamic roles in adaptation or response to changing cellular conditions or inputs. Finally, it will be of immense interest to genetically delete an alternatively spliced exon from the genome and to assess the physiological significance of its total

exclusion from the cognate protein in a transgenic mouse model.

Alternative Splicing as a Determinant of Subcellular Localization and Tissue Distribution

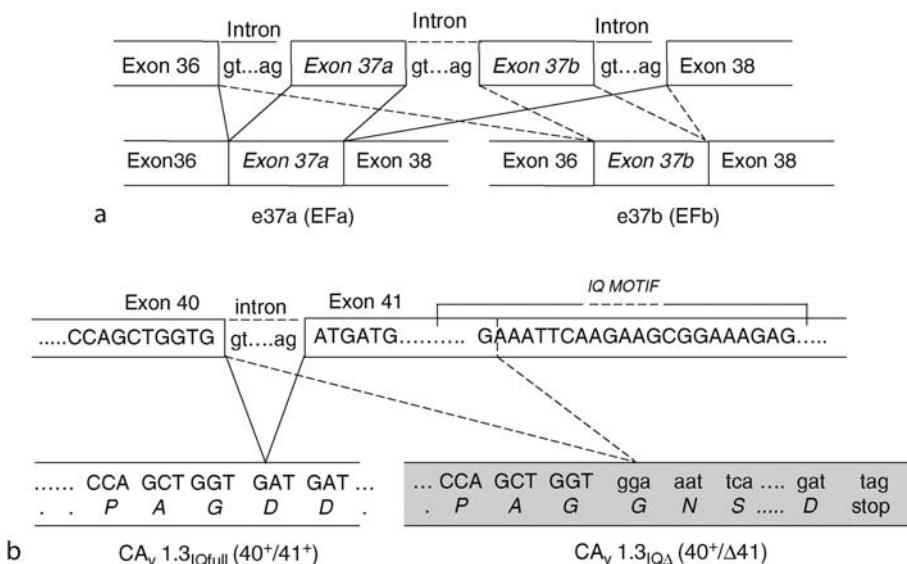
Alternative splicing of the calcitonin/calcitonin gene-related peptide (CT/CGRP) is one of the earliest examples of diversification of protein properties and localizations by alternative splicing. In the peptide-hormone system, the inclusion or exclusion of an exon in the final mRNA can alter the biological behavior of a molecule and change the peptide-ligand binding properties. In thyroidal C cells, the majority of the CT/CGRP pre-mRNA is processed to include exon 4 which leads to production of calcitonin peptide [4]. However, in neuronal cells, 99% of the CT/CGRP pre-mRNA is processed to exclude exon 4 and this leads to the production of CGRP peptide [4]. Clearly, through alternative RNA processing, two peptide hormones having completely different structures and functions are generated.

Recent studies indicate that alternative splicing is similarly important for controlling the function of voltage-gated calcium channels (Ca_v) in neurons. For instance, the mutually exclusive exons e37a and e37b in the Ca_v2 subfamily exhibit selective cellular or sub-cellular distribution in neurons (Fig. 3).

The Ca_v2 calcium channels are integrally involved in neurotransmission and pain processing. The N-type $\text{Ca}_v2.2$ calcium channels show specific expression of e37b in the neurons of the brain, while e37a is preferentially expressed in the nociceptive neurons of

the dorsal root ganglia [5]. On the other hand, the pair of e37a/b exons of the P/Q-type $\text{Ca}_v2.1$ calcium channels show differences in subcellular localizations, where e37a is expressed preferentially in the soma, while e37b is found predominantly in the dendrites of the cerebellar Purkinje neurons [6]. Additionally, the e37a/b exons of the $\text{Ca}_v2.1$ calcium channels are developmentally regulated, with a switch in expression from e37b in the fetal brain towards more e37a in the adult brain. In the adult brain, the expression patterns also vary across different regions, where, for example, e37b is expressed at higher levels in the amygdala, and e37a in the thalamus.

Other proteins of the nervous system show similar selective expression patterns. Another example is the K_v3 subfamily of voltage-gated potassium (K_v) channels. The K_v3 subunits play an important role in driving fast repolarization of action potentials to enable neurons to fire repetitively at high frequencies. It has been proposed that alternative splicing of the K_v3 subunits mediates differential subcellular targeting and modulation. In neurons of the mouse brain, the $\text{K}_v3.1a$ isoform is localized exclusively on the axons and presynaptic terminals while $\text{K}_v3.1b$ channels are prominently expressed on somatic and proximal dendritic membrane [7]. Interestingly, $\text{K}_v3.1$ channels are co-expressed with $\text{K}_v3.4a$ channels that are found mainly in the globus pallidus neurons, CA1 hippocampal interneurons and subthalamic nucleus neurons that are all fast-spiking. $\text{K}_v3.4a$ channels are, however, absent in the regular-spiking hippocampal, striatal and basal forebrain neurons.



Alternative Splicing. Figure 3 Postulated mechanism underlying splice variation of both α_1 subunits of $\text{Ca}_v2.1$ and $\text{Ca}_v1.3$ calcium channels. The nucleotide sequences of the relevant exon-intron boundaries are displayed in the top, while the bottom shows the resultant transcript and encoded amino acids of each variant.

Alternative Splicing as a Molecular Switch for Protein Function

Alternative splicing often results in isoforms with different functional properties. For instance, the e37a- but not the e37b-containing $\text{Ca}_v2.2$ channels allow large currents to flow and are regulated by G-proteins in a voltage-independent manner. Importantly, alternatively spliced exons located at other loci of the $\text{Ca}_v2.2$ channels modify other channel properties or control the trafficking of the channels.

Interestingly, the e37a/b exons of the $\text{Ca}_v2.1$ calcium channels act as an exquisite molecular switch to determine channel function. The e37a-containing $\text{Ca}_v2.1$ calcium channels respond to Ca^{2+} -dependent regulation by promoting the opening of the channels in a process called Ca^{2+} -dependent facilitation (CDF). This process may be important in short term plasticity as the increase in Ca^{2+} influx will result in much greater neurotransmitter release at the CNS synapse [6]. This property is missing from the e37b-containing channels. Similar to $\text{Ca}_v2.2$ calcium channels, the other alternative splicing loci of the $\text{Ca}_v2.1$ calcium channels act to modify channel electrophysiological and pharmacological properties [5,6]. Interestingly, the paralogous pairs of e37a/b exons of the $\text{Ca}_v2.1$ and $\text{Ca}_v2.2$ channels instill dissimilar properties on the channels.

Clearly, alternative splicing can diversify protein functions providing a spectrum of protein isoforms customized to support the complex operations within the central nervous system where information has to be processed rapidly. In this regard, the discovery of the entire suite of alternative splicing loci in a gene, and their coordinated assembly, will provide a compendium essential for reference and for understanding of physiological relevance. Nonetheless, the identification of novel splice variation at single splice locus has been useful to explain discrepancies between observed activity of a protein and the cloned cDNA assayed in a heterologous system. One such example is the observed lack of Ca^{2+} -dependent inactivation (CDI) of native hair cell Ca^{2+} currents as compared to robust CDI exhibited by the cloned L-type $\text{Ca}_v1.3$ calcium channel. Recent work showed that a splice variant ($\text{Ca}_v1.3_{\text{IQ}\Delta}$) missing the IQ-motif that is important for CDI is expressed in the outer hair cells of the cochlea (Fig. 3b) [8]. The $\text{Ca}_v1.3_{\text{IQ}\Delta}$ channels expressed in HEK 293 cells showed total lack of CDI that in part explains the behavior of the native Ca^{2+} currents in the cochlear hair cells.

Alternative Splicing as a Molecular Switch for Physiological Responses

It is important to understand how cells alter their splicing patterns in response to extracellular stimuli and signaling pathways. Ion channels and neurotransmitter-receptor pre-mRNAs undergo extensive alternative splicing to

generate multiple isoforms. An example is the vertebrate *Slo* (also known as *slowpoke* or *BK*) gene, which encodes a voltage-gated Ca^{2+} and K^+ channel expressed widely in the nervous system. *Slo* splice variants containing the STREX exon exhibit slow deactivation and enhanced channel activation. Changes in the concentration of stress hormones can modulate STREX (stress axis-regulated exon) exon inclusion in the *Slo* pre-mRNA and evidence suggests that STREX splicing is repressed by depolarization of GH3 pituitary cells and signaling through Ca^{2+} /calmodulin-dependent protein kinase (CaMK) IV [9].

A good example of how alternative splicing regulates neuronal function is the pattern of expression of the *cSlo* (chicken *Slo* gene) splice variants that correlates well with the tonotopic frequency map along the cochlear basilar membrane [9]. In addition, alternative splicing could remodel synaptic proteins, ion channels or receptors to modify neuronal excitability, synaptic plasticity, and efficacy of synaptic transmission in order to adapt to the myriad of neuronal activities and inputs. For instance, with NDMA receptors neuronal activity influences the choice for the inclusion or exclusion of alternatively spliced exon C2 or C2' possibly to facilitate homeostatic regulation of synaptic plasticity [10].

Alternative Splicing in Disease and Disorder

Alternative splicing generates phenotypic variations of proteins that impacts the diversity of their biological function. As such, it is not surprising that dysfunction or dysregulation of the splicing machinery can contribute to human diseases. Aberrant splicing of a gene can alter the abundance, spatial and/or temporal expression of a splice variant. Mutations in the tau gene can give rise to frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), by increasing the levels of proteins with the inclusion of exon 10 [9,10]. This tau isoform, which comprises four microtubule binding motifs, enhances the formation of filamentous tau aggregates in the brain [9,10]. In contrast, a translationally silent C to T nucleotide substitution in the survival of motor neuron protein 2 (*SMN2*) gene of spinal muscular atrophy (SMA) patients results in the skipping of exon 7 and the formation of a non-functional protein [10].

Alternative splicing can also play a role in modifying disease severity as evidenced in Timothy's syndrome, a disorder where patients suffer multi-organ dysfunction that includes lethal arrhythmias, cognitive abnormalities and autism. The severity of the cardiac arrhythmias depends on which mutually exclusive exon, e8 or e8a, carries the G406R mutation on the L-type $\text{Ca}_v1.2$ calcium channel, *CACNA1C*, gene. There is a correlation between the severity of cardiac arrhythmias and the level of expression of the cardiac-selective exon e8a in

the heart. Especially for genes critical for the survival of an organism, hereditary neurological disorders could arise because the genetic mutations were found on alternatively spliced exons or in regions that modulate splicing efficacy.

Conclusions

Alternative splicing is an exquisite mechanism to customize and diversify protein function to cater and respond to the complexity and immense plasticity of the nervous system. The dynamic regulation of alternative splicing will allow the neurons to respond appropriately to changing conditions in physiology or disease. As such, it is important to evaluate the altered activities of a mutant protein, arising from single genetic mutations, in the backbone of the predominant combinatorial splicing code for that gene. However, answers to fundamental questions as to what directs the specific utilization of an alternatively spliced exon, what is the physiological role of a specific alternatively spliced exon, and how it behaves in the context of different combinatorial arrangements of other alternatively spliced exons will require a wide array of ideas and multidisciplinary approaches.

References

- Blencowe BJ (2006) Alternative splicing: new insights from global analyses. *Cell* 126:37–47
- Soller M (2006) Pre-messenger RNA processing and its regulation: a genomic perspective. *Cell Mol Life Sci* 63:796–819
- Lee CJ, Irizarry K (2003) Alternative splicing in the nervous system: an emerging source of diversity and regulation. *Biol Psychiat* 54:771–776
- Lou H, Gagel RF (2001) Alternative ribonucleic acid processing in endocrine systems. *Endocr Rev* 22:205–225
- Gray AC, Raingo J, Lipscombe D (2007) Neuronal calcium channels: splicing for optimal performance. *Cell Calcium*
- Chaudhuri D, Alseikhan BA, Chang SY, Soong TW, Yue DT (2005) Developmental activation of calmodulin-dependent facilitation of cerebellar P-type Ca^{2+} current. *J Neurosci* 25:8282–8294
- Ozaita A, Martone ME, Ellisman MH, Rudy B (2002) Differential subcellular localization of the two alternatively spliced isoforms of the Kv3.1 potassium channel subunit in brain. *J Neurophysiol* 88:394–408
- Shen Y, Yu D, Hiel H, Liao P, Yue DT, Fuchs PA, Soong TW (2006) Alternative splicing of the Ca(v)1.3 channel IQ domain, a molecular switch for Ca^{2+} -dependent inactivation within auditory hair cells. *J Neurosci* 26(42):10690–10699
- Grabowski PJ, Black DL (2001) Alternative RNA splicing in the nervous system. *Prog Neurobiol* 65:289–308
- Licalatosi DD, Darnell RB (2006) Splicing regulation in neurologic disease. *Neuron* 52:93–101

Alternative Splicing and Glial Maturation

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Definition

The number of protein-coding genes in an organism does not always correlate with its overall cellular complexity. Genes may be relatively simple, containing only a single or a small number of exons; some genes, however, may be incredibly complex and can give rise to literally thousands of different protein isoforms. One way to generate a huge variety of different protein variants from a gene with only moderately complex organization is ►alternative splicing. This mechanism amplifies the complexity of the 30,000 human genes to astronomic numbers. Furthermore, alternate splicing mechanisms may act on top of an already sophisticated transcriptional control system, and these combined mechanisms enable the development of complex organisms. Here we review how differential splicing regulates glial cell maturation in flies and mammals.

Characteristics

Several known examples indicate that alternative splicing may result in distinct and even opposite functional consequences, either during embryonic development or in adult life. A prime example has been established for sex specification in *Drosophila*. In this system, the presence of the ►Sex lethal splice factor results in the differential ►3' splice junction choice that routes an animal towards female (or in its absence, into a male) development [1]. Moreover, sexual dimorphisms in the nervous system are brought about by sex-specific alternative variants of the *fruitless* gene, *fruitless^m* or *fruitless^f*, to induce either male or female behavior [2]. Another example is the alternative splicing of Apolipoprotein 2 (Apoer2), which induces an ►NMDA receptor isoform at postsynaptic sites that is sensitive to Reelin-dependent phosphorylation, thereby enhancing long term potentiation [3].

Terminal differentiation of cells is most often regulated by transcriptional activity and/or by cell/cell interactions. Interestingly, it was recently shown that differential splicing also plays an important and decisive role in cell differentiation. *Drosophila* glial cell differentiation depends on alternative splicing, which surprisingly, appears to be conserved during evolution. Two major components that control glial cell differentiation in *Drosophila*, Crooked Neck (Cn) and Held Out Wings (HOW) were identified. In mutants lacking either

of these genes, glial cells are correctly specified and initiate their normal migration towards their final destination. However, late glial cell differentiation, manifested by **►axonal wrapping**, is impaired. Both Crn and HOW mediate alternative splicing of specific target genes essential for glial cell differentiation [4].

Crn is a Conserved Splice Factor

The Crooked neck protein is conserved from yeast to humans. Yeast cells show little alternative splicing activity, though the molecular mechanisms underlying the splice reaction are conserved. The role of the yeast Crooked neck-like protein (Clfp1) is to promote assembly of a functional **►spliceosome**. The yeast clfp1 mutant has been successfully complemented by the expression of the Drosophila Crn protein, demonstrating that the proteins not only share sequence conservation but also exhibit similar functional properties. In addition to its role in yeast, the function of Crn in the regulation of splicing was demonstrated in a number of examples in the *Drosophila* system. Crn proteins do not bind directly to RNA. Rather, through multiple TPR repeats that mediate protein-protein interactions, Crn proteins can function as assembly platforms.

STAR Proteins Mediate Alternative Splicing in Specific Tissues

Proteins belonging to the **►STAR** (**►Signal Transduction and Activation of RNA**) family of RNA-binding proteins have long been viewed as candidates for mediating alternative splicing decisions. These proteins share a single maxi **►KH domain**, which binds to RNA and is highly conserved from *C. elegans* to humans [5]. Members of this family exhibit tissue-specific distribution. For example, *C. elegans* Gld-1 is expressed in the gonads of the nematodes, mammalian Quaking is expressed in **►oligodendrocytes**, **►astrocytes** and in **►Schwann cells**, as well as in the heart, and *Drosophila* HOW is expressed in tendon, glial and muscle cells. Importantly, several members of this family were shown to regulate splicing of specific targets. For example, mammalian Quaking was shown to mediate the alternative splicing of the myelin-associated glycoprotein, MAG [6] in oligodendrocytes of the mouse brain. Thus, viable *quaking* mutants suffer from a severe **►demyelination** phenotype.

The *Drosophila* HOW and Crn Proteins Mediate Alternative Splicing Required for Glial Cell Differentiation

Recently, an association was demonstrated between the *Drosophila* STAR protein, Held Out Wing (HOW), and the splicing factor Crooked Neck (Crn) [4,7]. These two proteins appear to function together to regulate critical differentiation steps of both glia and tendon cells, suggesting that they form part of a general mechanism

that mediates alternative splicing in a tissue specific manner. Similar to other STAR family members, the *how* gene itself produces at least two major protein **►isoforms** by alternative splicing, HOW(L) and HOW(S). The nuclear HOW(L) isoform had been shown to mediate mRNA degradation, thereby reducing the levels of specific target mRNAs. In contrast, the HOW(S) isoform shuttles between the nucleus and the cytoplasm where it can interact specifically with the splicing factor, Crn, to induce alternative splicing of specific targets.

The functional link between the HOW-Crn-dependent alternative splicing events and tissue differentiation has been demonstrated recently in two distinct tissues, glia and tendon cells. In a genetic screen, *crooked neck* (*crn*) mutants were identified based on their glial differentiation phenotype. In *crn* mutant embryos, **►peripheral glial** cells exhibit aberrant migration and fail to wrap the axons. While *crn* mutants exhibit additional phenotypes in other tissues, overall embryonic development proceeds relatively normally, possibly due to the contribution of maternal *crn* transcript (**►maternal transcript**). The glial-specific nature of the *crn* phenotype indicates that the process of glial cell maturation and its ability to wrap the axons is hypersensitive to the reduction of Crn levels. Since the general splicing machinery is still intact in the mutant, it is likely that Crn is involved in specific splicing events required for glial cell maturation. Analysis of *how* mutants revealed a glial phenotype similar to that of *crn*, in which the peripheral glia also fails to wrap the axons. Moreover, a genetic interaction between the two gene products was demonstrated. Crn was shown to enhance a gain of function phenotype in the wing following ectopic expression of HOW(S); reducing Crn levels partially rescues the HOW(S)-gain of function phenotype. These and additional experiments strongly suggested that both Crn and HOW form a protein complex in the cytoplasm that functions together to mediate glial cell maturation.

To reveal the basis for the alternative splicing-dependence of glial cell differentiation it was essential to identify glial-specific targets that are spliced in response to Crn-HOW complex formation. The **►HOW-response element** (HRE) was recently characterized as a penta-nucleotide sequence (ACUAA), which is unfortunately too short to be used for bioinformatic screening as a tool for target gene identification [8]. Therefore, to find such genes that are differentially expressed in wild type versus *crn* mutants, we followed a **►GFP-exon trap** approach. This procedure identified two proteins, NrxIV (Casper homolog) and Nervana2 (beta subunit of the Na⁺/K⁺ ATPase), whose expression was greatly reduced in the nervous system of *crn* mutants.

Both NrxIV and Nervana 2 are required for the formation of **►autocellular septate junctions** formed by the glial cells that wrap the peripheral axons. Additional experiments strongly support a mechanism by which

nrxIV pre mRNA is associated with HOW, and undergoes specific splicing in the presence of both HOW and Crn. Glial specific splicing of *nrxIV* may help to establish tight temporal control of the formation of the autocellular junctions. Transcriptional regulation may provide a pool of pre-mRNAs that, upon an as yet unidentified signal, are processed to form autocellular junctions required to insulate axons at a very specific developmental stage.

The Mechanisms that may Regulate Glial Specific Crn-HOW-Dependent Alternative Splicing

Taken together, our data suggest a model in which the HOW-Crn protein complex is shuttled from the cytoplasm into the nucleus to regulate the splicing and/or RNA stability of specific mRNAs required for the induction of glial cell differentiation. This process would contribute to the specific gene expression profile characteristic of the mature differentiation state of glial cells.

The mammalian STAR protein, Sam 68, undergoes phosphorylation by the protein tyrosine kinases Src and Fyn, as well as by ERK kinases. These phosphorylation events could affect different aspects of Sam 68 activity as they alter the subcellular distribution of Sam 68 (nuclear versus cytoplasmic) as well as its affinity to RNA. For example, the Sam 68-dependent inclusion of exon5 into the CD44 mRNA is induced upon ERK phosphorylation of Sam 68 [9]. Similarly, HOW-dependent splicing activity could be regulated by ERK-dependent signaling. Recently, it was shown that Fyn, a kinase of the Src family, phosphorylates the STAR protein, Quaking, which is essential for oligodendrocyte maturation [10]. The absence of Fyn activity in oligodendrocytes leads to specific alternative splicing of the Myelin Basic Protein, resulting in ►hypomyelination in the brain, a phenotype that is shared with viable *quaking* mutants in mice. It remains to be shown that the loss of Fyn-dependent phosphorylation of Quaking is the primary cause for the hypomyelination phenotype. Similarly, HOW phosphorylation may regulate its promotion of splicing in glial cells. These results are consistent with a model in which an external regulatory signal that leads to ERK, or Src-dependent phosphorylation of HOW, promotes the Crn-HOW interaction leading to alternative splicing only when glial cells undergo terminal differentiation.

Control of cellular differentiation needs to be carefully regulated. It makes sense that glial differentiation must not be initiated before all the cells are correctly localized; however, once they are, the signal for differentiation needs to be fast and efficiently executed. We speculate that this is one of the advantages provided by differential splicing. ►Pre-mRNA molecules can be generated and ready for use, but are rapidly spliced into the correct isoform only upon cells receiving a, still-elusive, signal.

In summary, the identification of the HOW-Crn complex, and its involvement in glial cell differentiation may represent a paradigm for a tissue-specific mechanism of alternative RNA splicing. Future elucidation of the mechanisms involved in the regulation of the HOW-Crn complex formation, and/or the promotion of developmentally-regulated alternative splicing, as well as the identification of glial-specific target mRNAs are essential for understanding how alternative splicing of specific targets is linked to glial cell differentiation.

References

- Christiansen AE, Keisman EL, Ahmad SM, Baker BS (2002) Sex comes in from the cold: the integration of sex and pattern. *Trends Genet* 18:510–516
- Demir E, Dickson BJ (2005) Fruitless splicing specifies male courtship behavior in *Drosophila*. *Cell* 121:785–794
- Beffert U, Weeber EJ, Durudas A, Qiu S, Masiulis I, Sweat JD, Li WP, Adelmann G, Frotscher M, Hammer RE et al. (2005) Modulation of synaptic plasticity and memory by Reelin involves differential splicing of the lipoprotein receptor Apoer2. *Neuron* 47:567–579
- Edenfeld G, Volohovsky G, Kruckert K, Naffin E, Lammel U, Grimm A, Engelen D, Reuveny A, Volk T, Klämbt C (2006) The splicing factor crooked neck associates with the RNA-binding protein HOW to control glial cell maturation in *Drosophila*. *Neuron* 52:969–980
- Vernet C, Artzt K (1997) STAR, a gene family involved in signal transduction and activation of RNA. *Trends Genet* 13:479–484
- Wu JI, Reed RB, Grabowski PJ, Artzt K (2002) Function of quaking in myelination: regulation of alternative splicing. *Proc Natl Acad Sci USA* 99:4233–4238
- Volohovsky G, Edenfeld G, Klämbt C, Volk T (2007) Muscle-dependent maturation of tendon cells is induced by post-transcriptional regulation of stripeA. *Development* 134:347–356
- Israeli D, Nir R, Volk T (2007) Dissection of the target specificity of the RNA-binding protein HOW reveals dpp mRNA as a novel HOW target. *Development* 134:2107–2114
- Matter N, Herrlich P, Konig H (2002) Signal-dependent regulation of splicing via phosphorylation of Sam 68. *Nature* 420:691–695
- Lu Z, Ku L, Chen Y, Feng Y (2005) Developmental abnormalities of myelin basic protein expression in fyn knock-out brain reveal a role of Fyn in posttranscriptional regulation. *J Biol Chem* 280:389–395

Altricial

Definition

Altricial refers to animals that are born rather immature.

► Neural Correlates of Imprinting

Altruistic Behavior

Definition

Unselfish behavior; thus, the opposite of selfish behavior. In a strict sense a behavior that decreases the fitness of an animal. If individuals sacrifice their own reproduction for the reproduction of relatives, this is not, in a strict sense altruistic, because it will increase their fitness through kin selection.

Alveus of Hippocampus

Synonyms

► Alveus hippocampi

Definition

The efferent fibers of the large pyramidal cells of the hippocampus course on the ventricular surface of the hippocampus. This lamella is called the alveus of hippocampus. It bundles to form the fimbria of the hippocampus and later enters the crus of fornix via which the fibers pass as part of the fornix into the direction of the diencephalon (hypothalamus).

► Telencephalon

Alzheimer's Disease (AD)

Definition

AD is a disabling neurological disorder that afflicts about 11% of the population over age 65. It involves widespread intellectual impairment, personality changes, sometimes delirium, and culminates in ►dementia, the loss of reason and ability to care for oneself. A person with Alzheimer's disease usually dies of some complication that affects bedridden patients, such as pneumonia. Brains of Alzheimer individuals show three distinct structural abnormalities: great loss of neurons in specific regions (e.g., ►hippocampus and ►cerebral cortex), plaques of abnormal proteins deposited outside neurons (amyloid plaques), tangled protein filaments within neurons (neurofibrillary ►tangles). Its causes are unknown, and it has no cure at the

present time, although drugs that inhibit acetylcholinesterase (AchE) mitigate the symptoms in 5% of patients.

► Memory and Dementia

Alzheimer's Disease – Oxidative Injury and Cytokines

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Synonyms

Alzheimer's disease; Senile dementia of the Alzheimer's type; Senile dementia

Definition

Alzheimer's disease is a progressive dementing illness, typically fatal within eight to ten years due to intercurrent infections such as pneumonia. At autopsy there is generalized shrinking of the brain. Microscopically the hallmarks are β -amyloid laden plaques and tau protein laden tangles. Current belief is that the disease is caused by toxicity from β -amyloid or tau protein.

Characteristics

Alzheimer's Disease is not Caused by β -Amyloid

Tomb stones do not kill, unless they fall upon the living. Tomb stones mark where the dead reside. To discover the cause of death, the body needs to be exhumed and analyzed. Even then, the cause of death may not be discovered.

For three decades, scientists pursued plaques (β amyloid) and tangles (tau protein) as causal Alzheimer's disease (AD) [1]. It is not the first time science went in a wrong direction. Plaques and tangles are tombstones. But, evidence has been shown that β amyloid and tau protein are toxic to neurons [1,2]. Yes. But this is similar to dropping tomb stones on the living.

What, then, causes AD? When does it start?

A logical hypothesis with substantial support is that various CNS insults initiate oxidative injury with a pathologic immune response resulting in smoldering CNS microlocalized inflammation (mLI) [2]. The mLIs create plaques and tangles. Over two or more decades these pockets of inflammation metastasize to other areas of the brain. Ultimately this preclinical state is called mild cognitive impairment (MCI). As time

passes, this becomes Alzheimer's which leads down the familiar path to death.

What are the initiating brain insults? The general classes would be mechanical trauma (sports, auto accidents); infections (herpes simplex viruses, cytomegalovirus, HIV, chlamydia pneumoniae, syphilis); anoxia (stroke, cardiac arrest, hemodynamic shock, pulmonary emboli, sleep apnea syndrome); metabolic (diabetes, B12 deficiency, hypothyroidism, obesity, hypertension, homocysteinemia); and toxic (iron, mercury, bismuth) [2,3]. The list of CNS insults that are related to AD is growing.

The Role of Excitotoxin Neurotransmitters and the Release of Free Radicals

The CNS insult must result in focal neuron death by either necrosis or secondary apoptotic damage. This results in massive release of the excitatory amino acid, glutamate into the extraneuronal space [3]. L-glutamate, the most abundant excitatory neurotransmitter, binds to AMPA and NMDA receptors to precipitate localized neuronal apoptosis. This is accomplished by Na^+ ion influx with acute osmotic damage followed by apoptosis. Or it is accomplished by Ca^{2+} influx and delayed apoptosis. Both necrosis and apoptosis release free radicals (ROS/RNS) into the intracellular space. Indeed L-glutamate is a neurotransmitter free radical. However, release of mitochondrial contents injects metals (copper, zinc, iron, etc) into the intracellular space. Homeostasis is threatened. This is where nitric oxide (NO), antioxidants, Beta amyloid and cytokines come into play.

NO is a free radical, but is part of homeostasis [3]. Rapidly formed, it interacts with superoxide radicals (O_2^-) to form more innocuous products which antioxidant mechanisms can manage.

Oxidative Injury

Metabolism produces reactive oxygen species (ROS) and reactive nitrogen species (RNS) which is approximately balanced by antioxidant defense systems of the body. Anoxia, blunt trauma, infections, and any cause of inflammations create an excess of ROS/RNS. Serious imbalance between production of ROS/RNS and the antioxidant defense results in oxidative injury or disruption of DNA, proteins (enzymes), and lipids.

The brain is uniquely vulnerable to oxidative injury [2]. In the milieu of local necrosis/apoptosis, the free radicals test the ability of the brain to protect lipid membranes. 50–80% of neurons by weight are lipids. The brain has antioxidant methods to protect the neuronal membrane [2,4]. As these local defenses fail, markers of oxidative damage should be evident. Indeed activated NF κ B, 8-OHdG, protein carbonyls, nitrotyrosine, 4-HNE, and other markers of oxidative injury are elevated in AD. Further these markers are associated with senile plaques and paired helical filaments [4].

Cytokines

Concomitant with and as the mLI persists, cytokines come into play. Cytokines are low molecular weight regulatory proteins secreted by cells to orchestrate host immune processes [2,5]. They regulate proliferation, maturation, enhanced inflammation or dampened inflammation. Important properties of cytokines are: (i) pleiotropy (one cytokine has multiple targets and multiple actions) (ii) redundancy (several different cytokines have similar actions) (iii) countervailing actions (one cytokine may stimulate or inhibit production of others) (iv) cytokines precipitate or truncate cascades of other cytokines (v) cytokines increase or decrease receptor sensitivity for other cytokines or even themselves (vi) CNS cytokines stimulate or inhibit both local cytokine response and distant (non-CNS) cytokine response.

Only recently has it been recognized that cytokines are produced by all four major CNS cell groups. These are neurons, oligodendrocytes, astrocytes, and microglia. Over two hundred distinct cytokines identified to date are divided into three groups and 12 sub groups (families) [2,5] Chemokines are a subgroup of 50 small cytokines that are central to mediation of inflammatory responses. Most of these are produced by CNS cells [6]. Some cytokines tend to be proinflammatory and promote apoptosis. Example are TNF- α , IFN- γ , IL1 β , IL-6, IL-8, IL-18, MCP-1, MIP-1 α , MIP-1 β , IP-10, and RANTES. Some CNS cytokines tend to down regulate inflammation and promote growth/ repair. These would include BDNF, β -NGF, GDNF, G-CSF IL-1 β , IL-4, IL-10, IL-13, and NT-3, 4/6, 6. This list changes near daily. Further one cytokine may be found to be proinflammatory in one region or circumstance, and have an opposite effect under other circumstances. CNS cytokines may stimulate distant response. For example, blood levels of IL-2 correlate with severity of Alzheimer's disease. External application of cytokines can induce CNS patterned responses. For example, administration of IL-2 will induce depressive symptoms.

Sustained elevations of cytokine productions are associated with pathologies. In the case of AD, the key cytokines are IL-1 which induces iNOS expression by astrocytes and then potentiates NMDA – glutamate neurotoxicity [7]. IL-1 may also be neuroprotective. Interleukin-6, produced by neurons, astrocytes and microglia co-localizes with A β plaques. Peripherally, IL-6 is a marker of chronic inflammation. Elevated IL-6 is seen in chronic simple anemia, rheumatoid arthritis, Crohn's disease and others [5]. IL-6 is involved in protecting neurons from methylmercury [7]. It is probably involved with A β neuroprotection by neutralizing metalloproteins ROS/RNS produced by apoptosis [2,8]. TNF-alpha typically is a harbinger that calls forth other inflammatory cytokines. In AD there is mixed evidence at the present time. Macrophage Colony Stimulating

Factor (MCSF, CSF-1) appears to be involved with upregulated cytokine/iNOS response to A β [7]. A growing list of chemokines is involved with AD. Transforming growth factor (TGF- β) cytokine family, which includes the neurotrophin subfamily, are expressed by neurons, astrocytes, and microglia. The neurotrophin subfamily include nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), insulin like growth factor (ILGF), glial derived neurotrophic factor (GDNF), and erythropoietin (EPO) [2,5,9] These stimulate repair, growth, and neurogenesis [2,10].

The Role of A β in Alzheimer's Disease

Perry, Smith, et al offer a logical explanation [2,8] A β is actually part of the brain's efforts to maintain homeostasis. Apoptosis and necrosis resulting from mLI cause release of mitochondrial metalloproteins and metals (iron, zinc, copper, etc) into an acidic extracellular matrix. A β is induced by cytokines. A β binds copper, zinc, iron and others. A β absorbs these ROS/RNS as part of homeostasis. Adequate circulation should allow clearance of the A β -metal complexes. When the microglia are activated, and when the ROS/RNS are overwhelming, myeloid-specific enzyme myeloperoxidases (MPO) consume them to produce MPO-H₂O₂. This MPO-H₂O₂ creates cross linkage with A β protein to precipitate it into insoluble plaques [2].

With plaque formation, activated microglia, highly reactive ROS (including glutamate) the table is set for distant penumbra effect. The mLI can trigger distant microinflammations by transaxonal/transsynaptic flow, intracellular flow, and vascular dispersion of ROS/RNS. So plaques and tangles develop elsewhere in the CNS, and after decades the victim dies of AD.

Possible Interventions in Alzheimer's Disease

Use of cytokines, anti-cytokines, cytokine receptor modulators is not a current therapeutic intervention. The pleiotropy, redundancy, and unexplored effects of cytokine cascades would result in unanticipated adverse side effects [2,5] Down modulating the effects of glutamate is both practical and available. NMDA antagonists memantine and amantadine are available, and by personal experience of the authors effective early in the course of AD [7]. Third, are anti-inflammatory medications. These have been disappointing to date, possibly due to the drawbacks noted for cytokines [1]. Vaccinations against A β are fraught with problems, as one is developing immunity against a homeostatic mechanism. Finally there are antioxidants. Inexpensive vitamins and herbs are available and have increasing scientific support [2,4,11]. Traditional medicine discounts these, while pursuing patentable pharmaceuticals. Further research on synergistic combinations of antioxidants may prove effective.

Because the authors were limited to eleven references, the choice was made to cite recent books with a larger number of specific references.

References

- Behl C (2002) Neuroprotective strategies in Alzheimer's disease. In: Alzheimer C (ed) Molecular and cellular biology of neuroprotection in the CNS. Kluwer Academic/Plenum, New York, pp 475–496
- Summers WK (2004) Alzheimer's disease, oxidative injury, and cytokines. *J Alzheimers Dis* 6:651–657
- Gillesen T, Budd SL, Lipton SA (2002) Excitatory amino acid neurotoxicity. In: Alzheimer C (ed) Molecular and cellular biology of neuroprotection in the CNS. Kluwer Academic/Plenum, New York, pp 3–40
- Halliwell B, Gutteridge JMC (2001) Free radicals in biology and medicine, 3rd edn. Oxford University Press, Oxford, pp 617–859
- Vilcek J (2006) Cytokines: wherefrom and whereto. In: Ransohoff RM, Benveniste EN (eds) Cytokines and the CNS. Taylor & Francis, New York, pp 23–37
- Dey N, Durden DL, Van Meir EG. Cytokine expression and signaling in brain tumors. In: Ransohoff RM, Benveniste EN (eds) Cytokines and the CNS. Taylor & Francis, New York, pp 194–228
- Murphy GM, Saravanapavan P (2006) Cytokines and neurodegeneration. In: Ransohoff RM, Benveniste EN (eds) Cytokines and the CNS. Taylor & Francis, New York, p163–191
- Castellani RJ, Lee H, Perry G, Smith MA (2006) Antioxidant protection and neurodegenerative disease: the role of amyloid- β and tau. *Am J Alzheimers Dis Oth Demen* 21:126–130
- Dechant G, Neumann H. Neurotrophins (2002) In: Alzheimer C (ed) Molecular and cellular biology of neuroprotection in the CNS. Kluwer Academic/Plenum, New York, pp 303–334
- Unsicker K, Kriegstein K (2002) TGF- β s and their roles in the regulation of neuron survival. In: Alzheimer C (ed) Molecular and cellular biology of neuroprotection in the CNS. Kluwer Academic/Plenum, New York, pp 353–374
- Packer L, Ong CN, Halliwell (eds) (2004) Herbal and traditional medicine. Marcel Dekker, New York

Amacrine Cell

Definition

A group of lateral interneurons in the vertebrate retina, interacting with bipolar cells, other amacrine cells and ganglion cells in the inner plexiform layer (synaptic layer).

- Inherited Retinal Degenerations
- Retinal Bipolar Cells

- Retinal Color Vision in Primates
- Retinal Direction Selectivity and Starburst Amacrine Cells
- Retinal Ganglion Cells

Ambiens Gyrus

Definition

The ambiens gyrus borders on the uncus and is partially surrounded by the semilunar gyrus. Both are components of the hippocampus.

- Telencephalon

Amiculum of Olive

Synonyms

- Amiculum olivare

Definition

Shortly before reaching the dentate nucleus, some afferents of this nucleus form, around the inferior olive, a dense, superficial fiber bundle at the rostral end of the laterodorsal myelencephalon, which is called the amiculum of olive.

- Myelencephalon

4-Aminopyridine

Definition

High-potency blocker of some types of potassium (K^+) channels, including those of the Kv3 family and a subset of Kv1 family subunits, and less potent blocker of other K^+ channels, including those of the Kv4 family.

- Action Potential
- Neuronal Potassium Channels

Ammons Horn/Cornu Ammonis

- Hippocampal Formation

Amnesia

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Synonyms

Memory loss; Memory impairment; Memory dysfunction

Definition

► **Amnesia** refers to an impaired ability to learn new information or recall details from the past.

Characteristics

The definitive characteristic of amnesia is profound forgetfulness. It can be caused by brain injury, neurological disease, a cardiovascular event (e.g., stroke), as well as by neurodegenerative and psychological disorders. Amnesia can occur simultaneously with impairment in other cognitive domains (e.g., visuospatial, language, attention disorders), or in the absence of additional cognitive deficits. For this reason, patients with amnesia can perform in the average to above average range on intelligence tests (e.g., Wechsler Adult Intelligence Scale – Third Edition), while simultaneously performing in the severely impaired range on tests of memory (e.g., the Wechsler Memory Scale – Third Edition). This impairment in memory can be observed regardless of the sensory modality (e.g., auditory, visual) in which the information is presented. Interestingly, amnestic individuals can retain intact language and social skills, as well as intact memories for the remote past. Immediate memory remains intact as well. This is illustrated by their ability to retain information up to several minutes provided there is no distraction; the presented material does not exceed immediate memory capacity (e.g., eight or more items); and they are able to rehearse the material. These preserved characteristics explain why individuals with amnesia can appear quite normal in casual conversation. It is only when information must be recalled after an extended delay or distraction-filled interval that a memory impairment becomes apparent.

In 1957, Scoville and Milner detailed the discovery of the critical involvement of the medial temporal

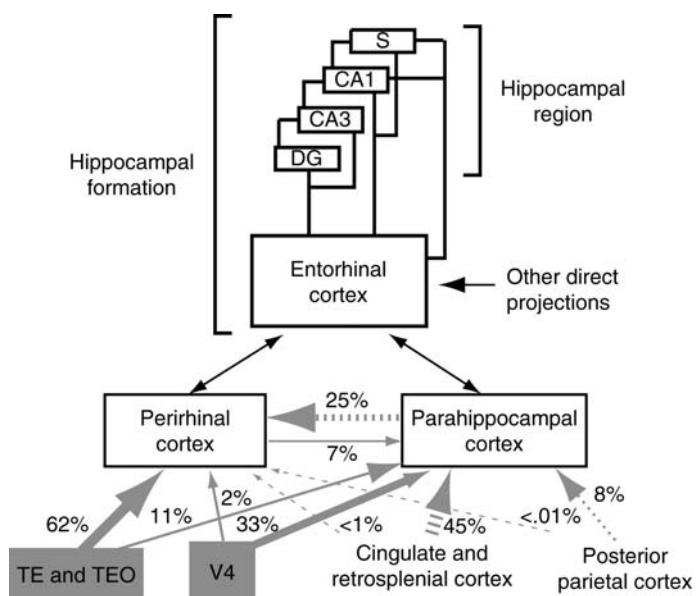
lobe in amnesia in a report on famed patient, H.M., who underwent bilateral medial temporal lobe resection, and subsequently suffered severe memory impairment as a result [1]. A great deal has been learned about amnesia from well-studied amnesic patients such as H.M., as well as from the development of the animal models of human amnesia. Methodical work with the non human primate model subsequently revealed the system of medial temporal lobe structures recognized to be crucial for memory. This system consists of the hippocampal region (CA fields, dentate gyrus and subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices [1,2]. There are continued efforts to try to further elucidate the types of memory properties (e.g., object versus spatial memory) processed by these regions within the medial temporal lobe (Fig. 1) [3].

Regions outside the medial temporal lobe, such as the diencephalon and basal forebrain, are also known to impair memory when injured. The essential structures within each of these areas for memory is still in need of further investigation. Suspected regions include the mediodorsal thalamic nucleus, the anterior nucleus, the internal medullary lamina, the mammillothalamic tract, and the mammillary nuclei. Amnesia resulting

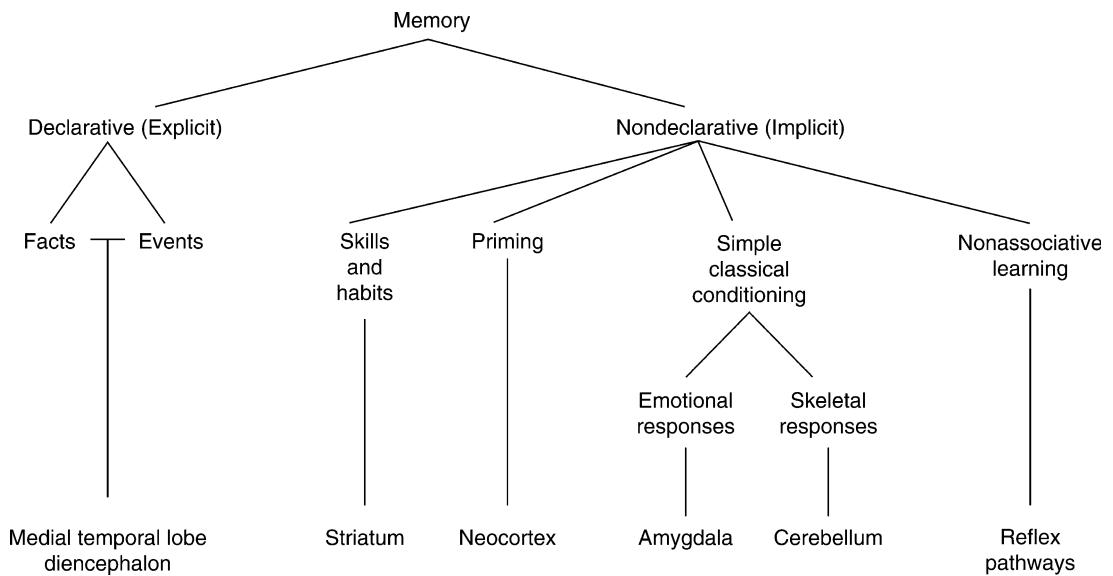
from lesions in medial diencephalic structures (e.g., medio-dorsal thalamic nucleus, mammillary nuclei) is referred to as “►medial diencephalic disorder” or “diencephalic amnesia.” The behavioral presentation of diencephalic amnesia and ►medial temporal lobe amnesia can be similar. Therefore, it is thought that these two regions together perhaps form an anatomically linked, functional system.

Multiple Memory Systems

Decades of research on amnesia have highlighted the fact that memory is not a single faculty but instead is composed of multiple separate systems (Fig. 2), only one of which is generally impaired in amnesia [5]. Human amnesia impairs the ability to acquire information about facts and events (►declarative memory or ►explicit memory), while typically sparing the capacity for skill learning, probabilistic classification learning, certain kinds of conditioning and habit learning, as well as the phenomenon of priming (collectively referred to as ►nondeclarative memory or ►implicit memory) [2]. Declarative memory is largely dependent upon the integrity of the medial temporal lobe and diencephalon, whereas nondeclarative memory largely relies on



Amnesia. Figure 1 Schematic view of the medial temporal lobe memory system (adapted from references [3] and [2]) showing the percentage of cortical input from unimodal and polymodal association areas to the perirhinal and parahippocampal cortices in the medial temporal lobe (*black boxes*). The percentages of cortical input shown on this schematic are from Suzuki and Amaral [4]. The thickness of the lines approximate the relative percentages of cortical input. Buffalo et al. [3] suggest that the perirhinal cortex might be more important for object memory (grey solid lines and boxes) while the parahippocampal cortex might be more important for spatial memory (grey dashed lines and boxes). Additionally, they hypothesize the possibility that the perirhinal cortex is involved in both spatial and object memory due to the large amount of spatial information it receives via the parahippocampal cortex. See also ►Spatial Learning and ►Object recognition, visual. Abbreviations: S, subiculum; CA1, hippocampal field CA1; CA3, hippocampal field CA3; DG, dentate gyrus; TE, inferotemporal cortex area TE; TEO, infero temporal cortex area TEO; V4, visual area V4.



Amnesia. **Figure 2** A taxonomy of long-term memory systems together with specific brain structures involved in each system (adapted from reference [2]).

different brain systems than those damaged in amnesia (Fig. 2) [2].

The label “amnesia” is a broad term that describes the presence of some type of memory impairment. However, there are a variety of amnesic presentations. The following text explains more specifically what particular type of memory difficulties a person with a certain type of amnesia might experience. Additionally, given the majority of research that suggests that nondeclarative memory typically remains preserved in amnesic patients [5], the kinds of amnesia described below concentrate on what could be observed as a result of an impaired declarative memory system.

Types of Amnesia

► **Anterograde amnesia** refers to an impaired ability to learn new information. An individual who experiences anterograde amnesia can have significant difficulty remembering new people, recent conversations, and new surroundings subsequent to the onset of amnesia. For example, Scoville and Milner [1] described patient H.M. as having severe anterograde amnesia. They detailed an incident where H.M. could not remember meeting a particular physician despite his having had a conversation with the physician only minutes earlier. It is important to note that the degree of severity of anterograde amnesia produced by medial temporal lobe damage is variable. However, research has demonstrated that damage limited to the hippocampus alone is sufficient to produce memory impairment. Additionally, work performed with both amnesic patients and animal models of amnesia suggest that memory impairment is exacerbated when damage

includes cortical regions adjacent to the hippocampus. In other words, the severity of anterograde amnesia can increase as more regions of the medial temporal lobe memory system are involved in the injury.

► **Retrograde amnesia** is characterized by an impaired ability to remember facts or events that occurred prior to the onset of amnesia. It may or may not occur in conjunction with anterograde amnesia. Similar to anterograde amnesia though, the severity of retrograde amnesia can vary as a function of the extent of damage to cortical regions adjacent to and including the hippocampus. Furthermore, although memory for events close in time to the amnesic episode can be significantly impaired (e.g., details of an accident that resulted in head injury), memories for very remote events are typically preserved (e.g., childhood memories). This phenomenon is referred to as ► **temporally graded retrograde amnesia**. Scoville and Milner’s report on H.M. [1] supplies a fine illustration of temporally graded retrograde amnesia. They described H.M. as having very poor memory for events occurring several before and up to his surgery, while retaining relatively intact memories from his youth. This sparing of remote memories is generally attributed to the process of ► **memory consolidation**. This term refers to the cortical processing and reorganization of neural substrates involved when forming memories. Memory formation is initially thought to be dependent on the medial temporal lobe system, but its role appears to diminish as more permanent memory is established elsewhere, presumably in neocortex [6]. Research suggests that memory consolidation processes for remote memories have had a sufficient amount of

time to be completed. Recently acquired memories have not had the same amount of time to undergo reorganization, and are thus more vulnerable to medial temporal lobe injury, whose structures are presumed to be involved in the early stages of memory consolidation [6].

► **Source amnesia** or ► **contextual amnesia** is a phenomenon that occurs when an individual can recall a fact or an idea, but cannot recall when or where the information was learned. In other words, the individual has access to and can recall information previously presented to them, but cannot recall the context in which the information was acquired. Source memory and source amnesia have been associated with frontal lobe function (or dysfunction in the case of source amnesia) due to its suspected processing of spatial-temporal (i.e., where-when) information [7,8]. Source amnesia can be commonly seen in young children as well as in the elderly. This observation has been attributed to the slow maturation of the frontal lobes relative to other brain regions during development, as well as the relatively increased vulnerability of the frontal lobes to the effects of normal aging. Additionally, source amnesia can be observed in normal adults when newly learned information is assessed after long periods of delay. An increase in the duration of the delay before testing corresponds to an increase in frequency of source memory errors [8]. Patients with frontal lobe lesions can often exhibit source memory difficulties. The pattern of deficits on memory tests suggest they fail to employ efficient memory strategies (e.g., semantic clustering) to enhance encoding and retrieval of previously learned information [7]. It is important to note that a person with anterograde amnesia does not necessarily have to also have source amnesia. Its appearance is variable in amnestic patients and seems to be a separate deficit that can occur in addition to impaired declarative memory. The variability of its co-occurrence with anterograde amnesia lends support to the idea that source amnesia is associated with regions outside the medial temporal lobe, such as the frontal lobes [7].

► **Transient global amnesia** is characterized by a sudden onset of both ► **anterograde** and retrograde amnesia, with no other obvious cognitive disturbances present. It can last for a few to several hours, but usually resolves within a day. It is most commonly observed in middle age to elderly individuals. The person experiencing transient global amnesia typically complains of memory impairment, but remains fully conscious and self-aware. Complete recovery is usually expected. However, research has demonstrated persistent mild cognitive deficits after transient global amnesia has resolved [9]. Its etiology is still unknown, although hypothesized causes include focal ischemic lesions, brain tumors, and migraine headaches. The medial temporal lobe is known to be particularly susceptible to the effects of stress, which could suggest its possible role. A recent study involving diffusion-weighted imaging has

demonstrated the involvement of the hippocampus in the pathophysiology of transient global amnesia, providing structural evidence indicative of ischemic dysfunction in this particular brain region [10]. Given the pattern of advance in structural and functional brain imaging procedures, improved methods show promise in providing more substantial evidence of the neuroanatomical substrates involved in transient global amnesia.

► **Mnestic block syndrome** is sometimes referred to as “functional retrograde amnesia,” or “psychogenic amnesia,” and it is the type of memory disorder with which the average layperson is probably most familiar. It is also this kind of amnesia that has been most popularized by television and film. Mnestic block syndrome is characterized by a sudden onset of severe retrograde amnesia, in the absence of significant anterograde amnesia. This is reflected by the individual’s memory loss for personal identity and autobiographical detail (e.g., cannot recall name or date of birth), as well as a period of wandering. It can also include impaired ► **semantic memory** and ► **episodic memory**. This collection of symptoms is often referred to as a “fugue state” [5]. Additionally, when a person recovers, he or she may have no recollection of what took place during their amnestic state. The extent of retrograde amnesia experienced by the individual can range from an inability to recall past memories for a limited time period, to complete lack of recollection for most memories prior to amnestic onset. Incidents of mnestic block syndrome are usually precipitated by premorbid periods of severe psychological stress (e.g., death of loved one, financial collapse, marital discord), hence the term “psychogenic amnesia.” A recently proposed model tries to explain the psychogenic nature of mnestic block syndrome by hypothesizing an interaction between psychosocial stress factors and brain regions pertinent to autobiographical memory retrieval and personal identity. The model suggests that severe stress can directly inhibit the frontal control/executive brain system, which in turn negatively affects retrieval of memories [5]. Episodes of mnestic block syndrome generally resolve over a short period of time, but can last anywhere from a few hours to a few months. However, prolonged “fugue states” can raise the suspicion of simulation [5].

References

1. Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21
2. Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci USA* 93:13515–13522
3. Buffalo E, Bellgowan P, Martin A (2006) Distinct roles for medial temporal lobe structures in memory for objects and their locations. *Learn Mem* 13:638–643

4. Suzuki WA, Amaral DG (1994) Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J Comp Neurol* 350:497–533
5. Kopelman M (2002) Disorders of memory. *Brain* 125:2152–2190
6. Squire LR, Stark CEL, Clark RE (2004) The medial temporal lobe. *Annu Rev Neurosci* 27:279–306
7. Baldo J, Shimamura A (2002) Frontal lobes and memory. In: Baddeley A, Kopelman M, Wilson B (eds) *Handbook of memory disorders*, 2nd edn. Wiley & Sons, Inc., Chichester, pp 363–380
8. Schacter D, Harbluk J, MacLachlan D (1984) Retrieval without recollection: an experimental analysis of source amnesia. *J Verbal Learn Verbal Behav* 23:593–611
9. Le Pira F, Giuffrida S, Maci T, Reggio E (2005) Cognitive findings after transient global amnesia: role of prefrontal cortex. *Appl Neuropsychol* 12:212–217
10. Cianfoni A, Tartaglione T, Gaudino S, Pilato F, Saturno E, Tonali P, Di Lazzaro V (2005) Hippocampal magnetic resonance imaging abnormalities in transient global amnesia. *Arch Neurol* 62:1468–1469

Amnesic Aphasia

Definition

A type of aphasia in which word-finding difficulty in spontaneous speech and in picture or object naming is the predominant symptom, with other language abilities being relatively spared. Despite the name, patients with “amnesic” aphasia do not exhibit amnesia or episodic memory deficits. Synonymous with anomia aphasia.

► Verbal Memory

Amnesic Shellfish Poison

► Domoic Acid Neurotoxicity

Amniote Egg

Definition

An egg that contains everything needed for the development of an organism on land – protective shell

and membranes (amnion, chorion, allantois), respiratory surfaces, and food and water reserves.

► The Phylogeny and Evolution of Amniotes

Amniotes

Definition

A group of vertebrates whose embryos develop inside extensive membranes that allow the offspring to be laid as eggs or carried by the female and born live. Early amniotes were known as reptiles, but they are now called early amniotes to distinguish them from the separate lines that led to present-day reptiles and mammals.

► Evolution of the Brain in Reptiles

► Evolution of the Somatosensory System: in Mammals

Amorphosynthesis

Definition

Inability of patients with ► Balint’s syndrome to construct an internal representation of the external world.

► Visual Neuropsychology

AMPA

Definition

α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid is an amino acid derivative that binds to the AMPA-type glutamate receptor.

► AMPA Receptors

AMPA Receptors

Definition

Ionotropic receptors for the excitatory neurotransmitter glutamate. AMPA receptors consist of GluR1

(GluR α 1), GluR2 (GluR α 2), GluR3 (GluR α 3) and GluR4 (GluR α 4) subunits and are localized at the postsynaptic site on the dendritic spine. The composition of the subunits determines the properties of AMPA receptor channels. When glutamate binds to the receptor channel, the channel opens and monovalent cations permeate through the receptor channel. Mainly, sodium ions permeate into the neuron at the resting membrane potential, resulting in the depolarization of the neuron.

- ▶ Associative Long-term Potentiation (LTP)
- ▶ Long-Term Potentiation (LTP)
- ▶ Memory
- ▶ Molecular Mechanisms

Amperometry

Definition

A sensitive electro-chemical method to detect the release of transmitters or hormones (e.g. dopamine or adrenaline) that can be catalyzed to undergo a redox reaction by a voltage applied to the tip of an electrode (typically made of a carbon fiber). This method can monitor the rate of release of certain transmitters and hormones from individual vesicles in millisecond timescale.

- ▶ Dopamine
- ▶ Noradrenaline

Amphibian Cerebral Cortex

- ▶ Evolution of the Pallium: in Amphibians

Amphibians

- ▶ Evolution of the Brain: Amphibians

Amphisbenid (Type)

Definition

Refers to a family (Amphisbaenidae) of burrowing lizards.

- ▶ Evolution of the Brain: At the Reptile-Bird Transition

Amplification

- ▶ Hearing Aids

Amplitude Spectrum

Definition

Most often used in acoustics and the analysis of electrical signals. An amplitude spectrum shows the strength of each frequency over the whole range of all sine and cosine waves of unknown frequencies that make up a signal.

- ▶ Electric Fish

Ampulla

Definition

Enlarged portion at the base of each semicircular canal that contains the crista, the cupula and canal receptor hair cells.

- ▶ Ampullar Receptors
- ▶ Semicircular Canals
- ▶ The Peripheral Vestibular Apparatus

Ampulla of Lorenzini; Tuberous Organ

- ▶ Electoreceptor Organs

Ampullar Receptors

Definition

Labyrinthine receptors located over a protrusion of the epithelium (ampullary crista) within the ampullae of semicircular canals. Their cilia are embedded in a gelatinous structure (cupula) having the same density as the endolymph. These receptors are stimulated by the movement of the endolymph within the semicircular canals elicited by head angular accelerations. Opposite directions of fluid motion induce opposite effects on the receptors.

- Semicircular Canals
- The Peripheral Vestibular Apparatus

Ampullary Organs

Definition

Primitive receptor of the electrosensory system.

Sensitive to weak direct-current (DC) and low-frequency electric fields.

- Evolution of Mechanosensory and Electrosensory Lateral Line Systems

Amygdala

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Synonyms

Amygdaloid body; Amygdalar nuclear complex

Definition

The amygdala (Latin, almond) is a subcortical cluster of brain nuclei located in the temporal lobe of the cerebral hemispheres. It is involved in a wide range of functions, including emotion, biologically based behaviors, attention, memory and learning. It exhibits pathological and pathophysiological changes in several important neurological and psychiatric diseases including temporal lobe epilepsy, Alzheimer's disease, schizophrenia, anxiety disorders and depression.

Characteristics

Anatomical Organization

The amygdala is a part of the ►limbic system located in the temporal lobe of the cerebral hemispheres [1,2] (Figs. 1 and 2).

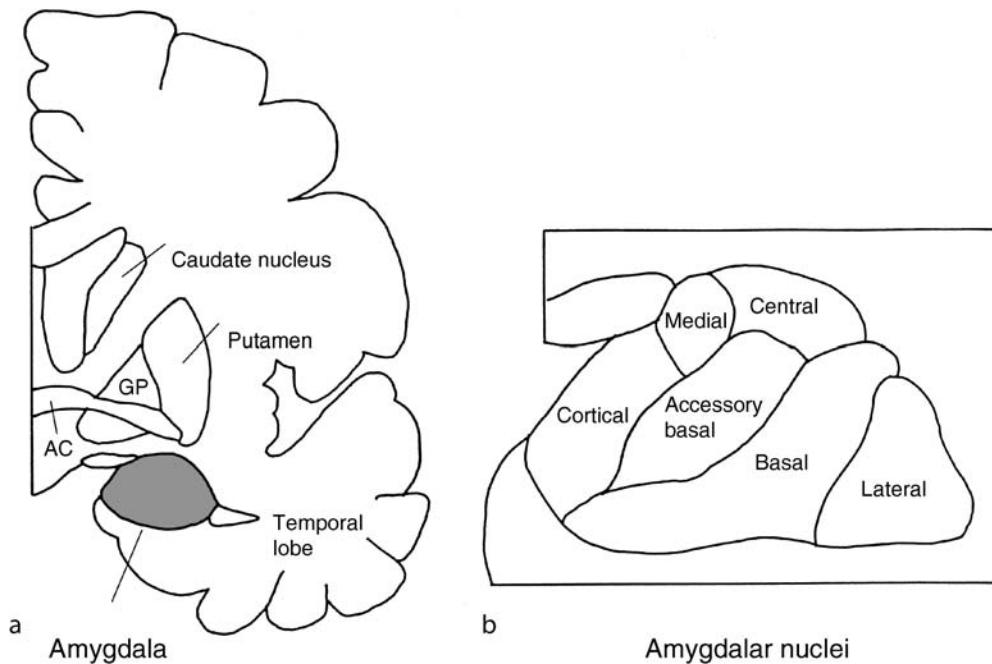
It is customary to categorize the amygdalar nuclei into groups that exhibit distinctive anatomical or functional characteristics. Traditionally, two major amygdalar nuclear groups were recognized, a superficial “corticomedial” group (including the cortical, medial and central nuclei) and a deeper “basolateral” group (including the lateral, basal and accessory basal nuclei) (Fig. 1). Recent studies however, indicate that the central and medial nuclei exhibit anatomical and histochemical characteristics that are distinct from those of the cortical nucleus. Therefore, it has been suggested that the amygdalar nuclei should be divided into a corticobasolateral nuclear group and a centromedial nuclear group [3]. In addition, attenuated portions of the centromedial nuclear group extend forward to become continuous with a brain region called the bed nucleus of the ►stria terminalis, which is located in the septal region adjacent to the anterior commissure. The term “►extended amygdala” has been used to collectively designate the centromedial amygdala and bed nucleus of the stria terminalis [4].

Cell types in the basolateral and cortical nuclei are very similar to each other. Most of the neurons in both groups are termed pyramidal cells because they resemble the pyramidal neurons in the cerebral cortex. The pyramidal cells are the main “projection neurons” of the cortical and basolateral nuclei (i.e. their axons project out of the amygdala and allow the amygdala to activate other brain regions). Pyramidal cells utilize the amino acid ►glutamate as an excitatory ►neurotransmitter. The remaining cell types in the basolateral and cortical nuclei are nonpyramidal neurons. The axons of these cells establish synaptic contacts with neighboring amygdalar neurons but do not extend beyond the amygdala (i.e. they are ►interneurons). They utilize γ -aminobutyric acid (►GABA) as an inhibitory neurotransmitter.

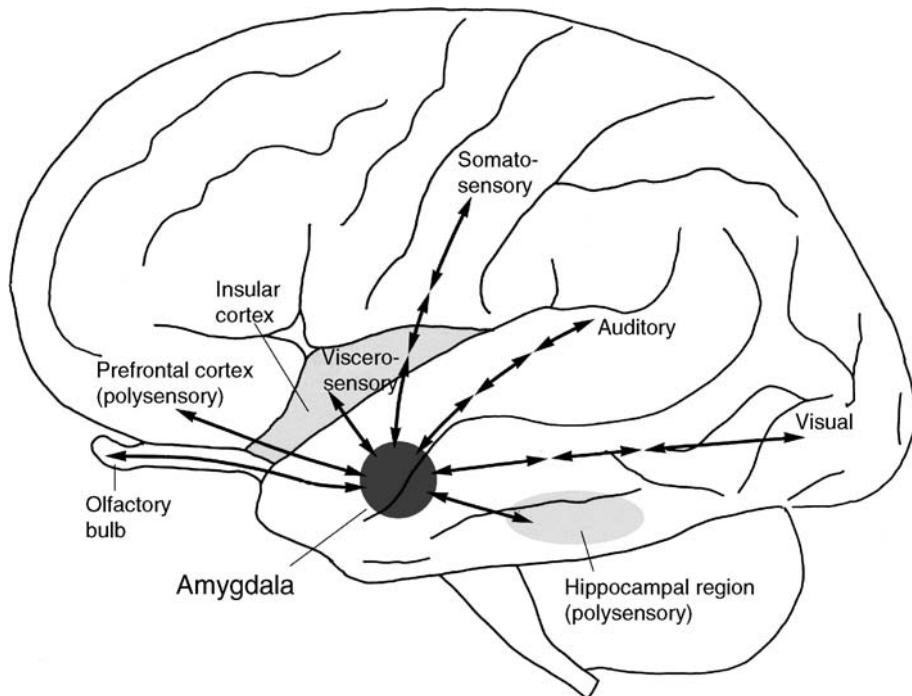
In contrast to the basolateral and cortical nuclei, neurons of the centromedial nuclei and the bed nucleus of the stria terminalis resemble neurons of the adjacent striatum (part of the ►basal ganglia) rather than the cerebral cortex. Most of these neurons utilize GABA as an inhibitory neurotransmitter, and many also contain ►neuropeptides that function as neurotransmitter-like substances.

Functional Anatomy

In their classic study performed in 1937, Klüver and Bucy [5] found that lesions of the amygdalar region produced a profound loss of fear in monkeys (“►Klüver-Bucy syndrome”). These animals also exhibited



Amygdala. **Figure 1** (a) Coronal section through the human brain at the level of the amygdala (only the right half of the brain is shown; the amygdala is actually found on both sides of the brain). Note that the amygdala (shaded area) is located in the anteromedial part of the temporal lobe. (b) Enlargement of the amygdala at the level shown in (a), illustrating the locations of the main amygdalar nuclei. AC anterior commissure; GP globus pallidus. Reprinted from Encyclopedia of the Neurological Sciences with permission from Academic Press.



Amygdala. **Figure 2** Lateral view of the human brain illustrating the anatomy of the main cortical pathways conveying sensory information to the amygdala. Note that somatosensory, auditory and visual information is transmitted to the amygdala over polysynaptic cortical pathways; only higher order cortical areas involved in processing the most complex sensory information in these modalities have projections to the amygdala. Reprinted from Encyclopedia of the Neurological Sciences with permission from Academic Press.

inappropriate sexual and feeding behavior. In general, it appeared that these amygdalectomized monkeys were unable to recognize the emotional or behavioral significance of visual stimuli. Subsequent studies revealed that animals with amygdalar lesions also did not respond appropriately to auditory, somatosensory and olfactory cues. Thus, it appears that the amygdala is critical for producing appropriate behavioral responses to biologically relevant sensory stimuli and events in the external world. In fact, the amygdala is thought to constitute an essential link between brain regions that process sensory information (e.g. the ►cerebral cortex and ►thalamus) and brain regions responsible for eliciting emotional and motivational responses (i.e. the ►hypothalamus, ►brainstem and ►striatum). For this reason, the amygdala has been called the “sensory gateway to the emotions.”

The amygdala receives sensory information through its connections with the olfactory bulb and sensory association areas in the cerebral ►cortex (Fig. 2). The cortical and medial nuclei receive olfactory information from the olfactory cortex and from the main and accessory olfactory bulbs. The latter structure is part of the vomeronasal system, which is involved in detecting special odors (pheromones) that are produced by individuals of the same species. Pheromones elicit hormonal and behavioral responses involved in species-specific reproductive and social activities. The amygdala receives visual and auditory information from the temporal lobe, ►somatosensory and viscerosensory (including gustatory) information from the insular lobe and polysensory information from the ►prefrontal cortex and ►hippocampus. These nonolfactory inputs primarily target the basolateral nuclei. The basolateral nuclei also have reciprocal projections back to these same cortical regions. It has been suggested that these amygdalocortical projections may be important for attention to emotionally and behaviorally significant stimuli and for the storage of emotional memories.

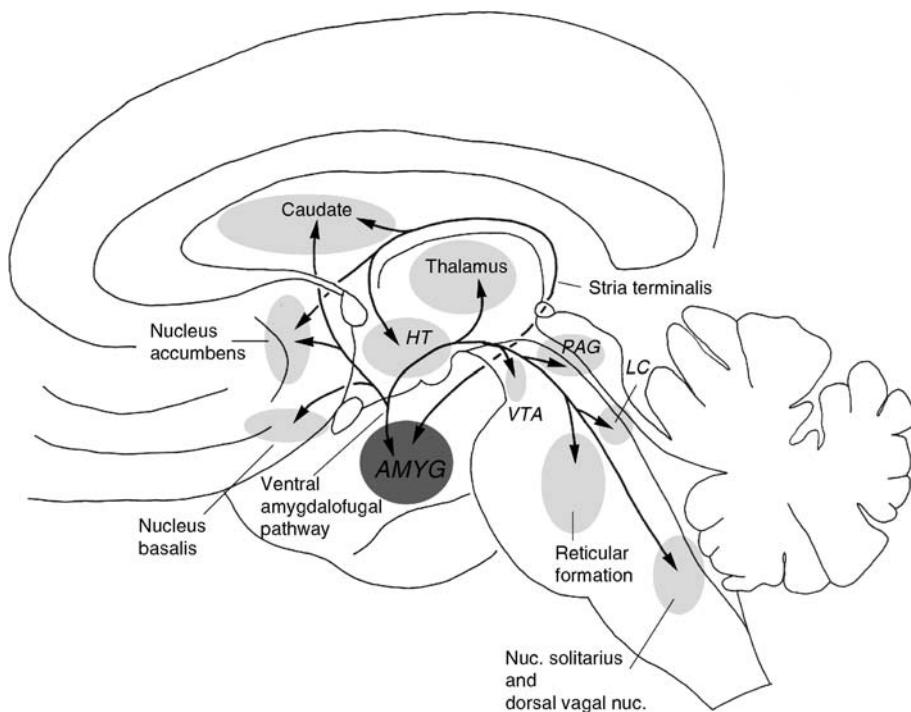
Projections from the ►thalamus to the amygdala arise mainly from the midline thalamic nuclei and from the medial part of medial geniculate nucleus and adjacent posterior thalamic nuclei. These projections, which terminate primarily in the basolateral and central amygdalar nuclei, convey auditory, somatosensory, viscerosensory and visual information to the amygdala. Amygdalothalamic projections are more limited and consist of projections from the central nucleus to the midline thalamic nuclei and from the basolateral amygdala to the mediodorsal thalamic nucleus. Since the latter nucleus has extensive reciprocal connections with the prefrontal cortex, it provides an indirect link by which the amygdala can influence the activity of the prefrontal region.

The amygdala produces emotional responses by way of its connections with several subcortical regions,

including the ►hypothalamus, brainstem, striatum and ►basal forebrain. Some of these fibers course in the ►ventral amygdalofugal pathway, which runs (Fig. 3) near the inferior surface of the brain. Others course in a thin fiber bundle termed the ►stria terminalis, which takes a more circuitous route above the thalamus (Fig. 3). There are extensive reciprocal connections between the medial portions of the hypothalamic region and the amygdala, particularly the medial amygdalar nucleus, cortical nuclei and medial portions of the basolateral amygdala. Consistent with these connections, stimulation and lesion studies in experimental animals have shown that the amygdala is involved in behavior related to biological drives and motivation, including arousal, orienting and sleep, fight or flight, feeding and drinking and social, reproductive and maternal behavior. In humans, these behaviors are typically associated with emotional feelings (e.g. fear with flight and anger and rage with fighting and defensive behavior). In each of these affective states, the amygdala appears to elicit a coordinated response consisting of autonomic, endocrine and behavioral components by way of its projections to various subcortical regions, especially the hypothalamus. The endocrine responses produced by amygdalar stimulation are due to its indirect activation of the pituitary via the hypothalamus. Interestingly, many of the hormones secreted by the glands targeted by pituitary hormones can affect the activity of the amygdala via receptors expressed by amygdalar neurons. Thus, there is a very high density of estrogen and androgen receptors in the medial and cortical nuclei. Glucocorticoid receptors, activated during stress, are located in all portions of the amygdala, but particularly high levels are found in the centromedial nuclear group.

Another important subcortical target of the amygdala that is important for producing behavioral responses is the striatum (caudate, putamen and nucleus accumbens) (Fig. 3). This projection mainly originates in the basolateral nuclei and terminates primarily in the ventral and medial portions of the striatum, including the nucleus accumbens. Lesion studies indicate that the projections of the basolateral amygdala to the striatum are important for controlling behavior related to the reinforcing properties of sensory stimuli.

The central nucleus is the main amygdalar region exhibiting connections with the brainstem and basal forebrain. Among these targets are several brainstem areas involved in visceral function, including the parabrachial nucleus, ►dorsal vagal nucleus and ►nucleus solitarius. It also has projections to the ►periaqueductal gray and ►reticular formation, which are important for pain modulation and behavioral responses to stress. In addition, the central nucleus innervates several brain regions that give rise to neurotransmitter specific fiber systems that target the



Amygdala. **Figure 3** Medial view of the human brain illustrating the connections of the amygdala (AMYG) with subcortical brain regions. All connections are reciprocal except those to the caudate and nucleus accumbens, which do not have projections back to the amygdala. HT, hypothalamus; LC, locus ceruleus; PAG, periaqueductal gray; VTA, ventral tegmental area. Reprinted from Encyclopedia of the Neurological Sciences with permission from Academic Press.

amygdala and other forebrain areas. These regions include the locus ceruleus (noradrenergic), the substantia nigra and ventral tegmental area (dopaminergic), the raphe nuclei (serotonergic) and the nucleus basalis (**►cholinergic**). These transmitter specific systems, also known as **►ascending modulatory projections**, are activated in certain behavioral states, particularly during stress and can modulate amygdalar activities related to emotion, attention and memory.

Involvement in Neurological and Psychiatric Diseases

In agreement with the results of animal experiments, recent investigations of the human amygdala have shown that it is critical for the recognition of the emotional significance of auditory, visual and olfactory stimuli, including facial expressions, vocal intonation and expressive body movements. It has also been demonstrated that electrical stimulation of the human amygdala elicits fear, rage or other emotions. In addition, the human amygdala plays an important role in emotional learning, consistent with animal studies showing that the amygdala is essential for classical **►Pavlovian fear conditioning** to simple sensory cues, as well as to complex sensory representations such as the context in which an emotional event has occurred

[6,7]. Studies in both humans and animals have demonstrated that the release of noradrenaline in the amygdala is essential for the formation and recall of memories involving emotional events [8] and that there is over-activation of the amygdala in patients with post-traumatic stress disorder (PTSD).

The amygdala exhibits pathological and pathophysiological changes in several additional neurological and psychiatric diseases including **►temporal lobe epilepsy**, **►Alzheimer's disease**, schizophrenia, **►anxiety disorders** and **►depression**. Temporal lobe epilepsy (TLE) is the most common type of epilepsy and is often characterized by psychiatric disturbances. The amygdala exhibits cell loss in TLE and altered activity has been noted in recording studies. Studies in the rat have shown that the amygdala has the lowest threshold for "**►kindling**," a phenomenon that has attracted a considerable amount of interest as a model of TLE. The amygdala is also a major target of the classic neuropathological changes seen in Alzheimer's disease and it has been suggested that degeneration of the amygdala may be responsible for the emotional liability seen in this disease.

There is also amygdalar degeneration in schizophrenia and recording studies have detected abnormal activity in the amygdala in this condition. **►Dopamine**

levels are increased in the amygdala in schizophrenia and this brain region may be one of the main sites of action of atypical ►antipsychotic drugs such as clozapine. Consistent with numerous rodent studies implicating the amygdala in fear and anxiety, there is evidence that anxiety disorders in humans are associated with excessive activity in the amygdala. Moreover, studies in animals and humans have shown that the amygdala has very high levels of benzodiazepine receptors and is a critical site of action for the anxiolytic effects of these drugs. Recent functional imaging investigations have demonstrated that there is increased activity in the human amygdala in major depression and that administration of ►antidepressants, which modulate levels of serotonin and noradrenaline in the amygdala, cause a decrease in amygdalar activity that is associated with amelioration of depressive symptoms [9].

References

- Aggleton JP (ed) (2000) The amygdala: a functional analysis. Oxford University Press, Oxford, NY
- Price JL, Russchen FT, Amaral DG (1987) The limbic region. II: the amygdaloid complex. In: Björklund A, Hökfelt T, Swanson LW, (eds) Handbook of chemical neuroanatomy, vol 5. Elsevier, Amsterdam, pp 279–388
- McDonald AJ (2003) Is there an amygdala and how far does it extend?: an anatomical perspective. Ann NY Acad Sci 985:1–21
- Alheid GF, Heimer L (1988) New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience 27:1–39
- Klüver H, Bucy PC (1937) “Psychic blindness” and other symptoms following bilateral temporal lobectomy in rhesus monkeys. Am J Physiol 119:352–353
- Davis M, Falls WA, Campeau S, Kim M (1993) Fear-potentiated startle: a neural and pharmacological analysis. Behav Brain Res 58:175–198
- LeDoux J (1996) The emotional brain. Simon & Schuster, New York
- McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27:1–28
- Drevets WC (2003) Neuroimaging abnormalities in the amygdala in mood disorders. Ann NY Acad Sci 985:420–444

Amygdalar Nuclear Complex

- Amygdala

Amygdaloid Body

Synonyms

- Corpus amygdaloideum

Definition

The amygdala is a large nuclear complex in the dorsomedial portion of the temporal lobe, at the inferior horn of the lateral ventricle. Reciprocal connections with the rhinencephalon, hypothalamus, thalamus, brainstem and some cortical areas. The amygdaloid body receives highly preprocessed sensory impressions and is responsible for initiation and integration of somatic and autonomic responses, associated with affective behavior.

- Telencephalon
- Amygdala

Amygdalospinal Fibers

Definition

Fibers, predominantly from the central amygdaloid nucleus which pass further through the brainstem into the spinal cord, where they may be involved in the regulation of autonomic processes.

- Pathways

Amyloid Plaques

Definition

These aggregates of primarily amyloid proteins and other carbohydrates are found in the brains of patients suffering from amyloidopathies, typically in Alzheimer’s disease, and rarely in brain disorders of viral origin such as Acquired Immune Deficiency Syndrome (AIDS). The amyloid plaques can either be well defined or can occur as diffuse plaques, and play an important role in the pathogenesis of neurodegenerative disorders.

- Alzheimer’s Disease
- Central Nervous System Disease – Natural Neuro-protective Agents as Therapeutics

Amyotrophic Lateral Sclerosis (ALS)

Definition

ALS is also called Lou Gehrig's disease, is ultimately fatal and results from progressive degeneration of cortical neurons giving rise to corticospinal fibers and motor neurons in ►brainstem and ►spinal cord (cause unknown). Amyotrophy here denotes the neurogenic atrophy of skeletal muscle, and lateral sclerosis refers to the hardness of the lateral spinal cord resulting from astrocyte proliferation and scarring consequent to degeneration of the ►corticospinal tracts. ►Tendon reflexes are increased (►hyperreflexia), while sensation is normal.

Analeptics

► Stimulants

Analgesia

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Synonyms

Antinociception

Definition

The word analgesia comes from the Greek words of An (negative) and Algesis (►pain) hence not sensing pain. We can think of analgesia as the process in which the sensation of pain is attenuated or inhibited. This is most often accomplished by the use of pharmaceuticals such as opioids that inhibit the activation of the neuronal pathways that relay pain sensations from the periphery to the central nervous system.

Characteristics

Description of Pain and Analgesia

Pain is described as an unpleasant sensation associated with a specific part of the body [1] (►Nociception). It is produced by processes that either damage, or are

capable of damaging, the tissues. Such damaging stimuli are called ►noxious and are detected by specific sensory nerve fibers called ►nociceptors [2]. These nociceptors are free nerve endings with cell bodies in the dorsal root ganglia and terminate in the superficial layers of the dorsal horn of the spinal cord. Here they relay messages of noxious stimulation by releasing neurotransmitters such as glutamate [3], substance P and calcitonin gene related peptide (CGRP) [4,5]. These "pain" neurotransmitters will result in the activation of the second order neurons *via* their corresponding receptors. The second order neurons cross the spinal cord to the contralateral side and travel up the spinothalamic tract until they reach the thalamus. From there the third order neurons are activated, traveling from the thalamus to the somatosensory cortex, hence allowing for the perception of pain. In addition to the activation of second order neurons that ascend *via* the spinothalamic tract, there are second order neurons that activate lower motor neurons in the ventral horn of the spinal cord provoking a reflex withdrawal from the ►noxious stimulus. Likewise, there are enkephalin and endorphin containing interneurons at the level of the spinal cord and brainstem that will modulate the neurotransmission of pain.

Analgesic Actions Along the Pain Pathways

Several sites for analgesic actions can be identified in the neural processing of noxious signals. Nociceptive afferent fibers are typically pseudounipolar neurons, with a peripheral terminal and a central terminal. Neurotransmitters that are produced within the cell body (i.e. in the dorsal root ganglia) are the same at both the central and peripheral ends of the nerve fiber. The neurotransmitters are released at both ends, participating in the pain signal peripherally and centrally. The release of neurotransmitters from the peripheral terminals of the afferent fibers is actually an "efferent" function of these afferent neurons. Peripheral release of neurotransmitter substances leads to the classic "axon reflex". This reflex leads to peripheral changes which are recognized as indicators of pain – redness, swelling, tenderness [6]. The peripheral terminals have ►opioid receptors on which compounds such as morphine, codeine, fentanyl, etc. or endogenous opioids such as enkephalin and endorphins can act to inhibit the release of such pain neurotransmitters that contribute to the activation of the nociceptors themselves. Opioid receptor activation (G-protein coupled receptors) results in the indirect opening of potassium channels. Potassium with its positive charge flows out of the ►nociceptor leaving the inside of the neuron more negative. The enhanced intracellular negative charge hyperpolarizes the nociceptor, resulting in a decrease in nociceptor activity (i.e. ►analgesia).

The periphery is the site of other analgesics including steroids (i.e. corticosteroids) and the family of

non-steroidal anti-inflammatory drugs (\blacktriangleright NSAIDs) (i.e. ibuprofen, indomethacin, aspirin). Steroids and NSAIDs result in \blacktriangleright analgesia by inhibiting the pro-inflammatory and pro-nociceptive family of prostaglandins.

Opioids can act on the presynaptic terminal of the primary afferent nociceptor at the level of the spinal cord *via* the opioid receptor (G-protein coupled receptors) by indirectly blocking voltage gated calcium channels, as well as opening potassium channels. The inhibition of calcium entry into the presynaptic terminal as well as the efflux of potassium (hyperpolarization) results in the inhibition of pain neurotransmitter release from the primary afferent fibers, hence \blacktriangleright analgesia. Opioids have a second site of action at the level of the spinal cord. Opioid receptors on the postsynaptic nerve (the second order neuron), when activated by an opioid, indirectly open potassium channels resulting in hyperpolarization of the second order neuron, producing further \blacktriangleright analgesia.

The inhibition of pain, analgesia, also occurs by the activation of the cortical descending neural system. Activation of the cortical/bulbar/spinal descending pain inhibitory system to further promote \blacktriangleright analgesia is induced by the release of endorphins and, enkephalin, as well as by exogenously administered opioids acting again via opioid receptors. Thus far we know that these systems are activated in and around the periaqueductal gray (PAG) region of the midbrain. Such neurons then project to sites in the medullary reticular formation and the locus ceruleus (the major source of norepinephrine cells in the brain). These neurons that are opioid sensitive are activated through disinhibition - that is, inhibition of a tonically active inhibitory interneuron. Opioids are known to hyperpolarize neurons as detailed above, yet when given into these CNS regions activate neurons by simply attenuating the inhibitory GABAergic neurons (i.e. opioids act to remove the "GABA brake"). These descending fibers then project to the dorsal horn of the spinal cord along a tract called the dorsolateral funiculus (located in the dorsolateral portion of the spinal cord) to synapse with either the incoming primary afferent neuron, the second order pain transmission neuron, or interneurons. These descending pain modulatory neurons either (i) release neurotransmitters in the spinal cord, especially serotonin (5HT) and norepinephrine (NE) or (ii) activate small opioid containing interneurons in the spinal dorsal horn to release endogenous opioid peptides. The released NE and 5HT in the end (i) inhibit the release of pain transmitters from the incoming nociceptive afferent signal, and (ii) inhibit the second order pain transmission cell, hence producing \blacktriangleright analgesia. Activation of the descending pain modulatory system is a good example of why subjects report not feeling pain at all under conditions of stress, or perhaps other situations, where

even though the pain is felt, the degree appears to be greatly modulated [7].

Summary of Analgesic Sites

We can identify several analgesic sites. (i) activating opioid receptors in the periphery to inhibit the activation of the nociceptors, as well as use NSAIDs or steroids to inhibit the release of inflammatory mediators, (ii) activating opioid receptors at the central terminals of nociceptors to stop the release of pain neurotransmitters in the spinal cord, (iii) activating opioid receptors on the second order pain transmission cells to prevent the ascending transmission of the pain signal, and (iv) activating the opioid receptors in the midbrain and "turning on" the descending pain inhibitory systems (through disinhibition).

Intracellular Mechanisms of Opioid Analgesia

Recent cloning has identified three distinct genes for the μ , κ and δ opioid receptors (this needs to be corrected by the author) [8–11]. All three receptors belong to the G-protein coupled receptor (GPCR) family. Agonist binding to opioid receptors leads to a conformational change in the opioid receptor resulting in the activation of an intracellular protein called a G-protein. The G-protein is made up of three separate protein subunits termed alpha, beta and gamma. The alpha portion of the G-protein associates with guanosine diphosphate (GDP). The alpha portion with its GDP will associate with the beta and gamma subunits and exist as an intracellular trimeric protein. An opioid bound to an opioid receptor undergoes a conformational change in the receptor resulting in the exchange of the GDP for a GTP on the α_i subunit. It is this exchange of GDP for GTP that activates the G-protein complex. Opioid receptors typically couple to a α_i subunit and once the exchange of GDP for GTP has occurred, the α_i subunit will dissociate from the $\beta\gamma$ subunit and inhibit the activity of adenylate cyclase, a nearby membrane bound enzyme. Under resting conditions, adenylate cyclase converts ATP into cAMP at some basal rate. cAMP acts as a second messenger within the cell resulting in several events including the activation of protein kinases and gene transcription proteins. Opioid receptor activation by an opioid will result in the activation of the α_i subunit and inhibit adenylate cyclase enzyme, hence significantly decreasing intracellular basal levels of cAMP. This opioid via opioid receptor-induced decrease in cAMP indirectly results in the inhibition of voltage dependent calcium channels on presynaptic neurons. These voltage dependent calcium channels are important in the release of neurotransmitter and transduction of neuronal communication, in this case pain transmission. Opioid receptors located on the presynaptic terminals of the nociceptive fibers, when

activated by an opioid agonist, will indirectly inhibit voltage dependent calcium channels via decreasing cAMP levels hence blocking the release of pain neurotransmitters such as glutamate, substance P and calcitonin gene related peptide (CGRP) from the nociceptive fibers resulting in ►analgesia.

In addition to the indirect inhibition of voltage gated calcium channels by opioid receptors, the $\beta\gamma$ subunit of the G-protein will open inward rectifying potassium (GIRK) channels allowing K^+ to flow down its concentration gradient and out of the cell carrying its (+) charge. This results in a more negatively charged environment within the cell termed hyperpolarization. This opioid-induced hyperpolarization results in a decrease in cell excitability hence attenuating neuronal transmission [12] and ►analgesia.

►Development of Nociception

References

- Melzack R, Katz J (eds) (2006) Pain assessment in adult patients. Textbook of Pain, 5th edn. Elsevier Churchill Livingstone, Edinburgh, UK, pp. 291–304
- Sherington CS (1906) The integrative action of the nervous system. Scribner, New York
- Jeftinija S, Jeftinija K, Liu F, Skilling SR, Smullin DH, Larson AA (1991) Excitatory amino acids are released from rat primary afferent neurons in vitro. *Neurosci Lett* 125:191–194
- Lawson SN, Crepps BA, Perl ER (1997) Relationship of substance p to afferent characteristics of dorsal root ganglion neurons in guinea-pigs. *J Physiol* 505:177–191
- Lawson SN, Crepps BA, Perl ER (2002) Calcitonin gene related peptide immunoreactivity and afferent receptive properties of dorsal root ganglion neurons in guinea-pigs. *J Physiol* 540:989–1002
- Schmelz M, Petersen LJ (2001) Neurogenic inflammation in human and rodent skin. *News Physiol Sci* 16:33–37
- Mayer DJ, Price DD (1976) Central nervous system mechanisms of analgesia. *Pain* 2:379–404
- Evans CJ, Keith DE Jr, Morrison H, Magendzo K, Edwards RH (1992) Cloning of a delta opioid receptor by functional expression. *Science* 258:1952–1955
- Kieffer B, Befort K, Gaveriaux-Ruff C, Hirth C (1992) The delta opioid receptor: isolation of a cDNA by expression cloning and pharmacological characterization. *Proc Natl Acad Sci USA* 89:12048–12052
- Chen Y, Mestek A, Liu Y, Hurley J and Yu L (1993) Molecular cloning and functional expression of an In-opioid receptor from rat brain, *Mol. Pharmacol.* 44:8–12.
- Yasuda K, Raynor K, Kong H, Breder C.D., Takeda J, Reisine T and Bell GI (1993) Cloning and functional comparison of K and S opioid receptors from mouse brain. *Proc Nat Acad Sci USA* 90:6736–6740.
- Jordan B, Devi LA (1998) Molecular mechanisms of opioid receptor signal transduction. *Br J Anaesth* 81:12–19

Analogous (Phylogenetic)

Definition

Similar in function, but without phyletic continuity (e.g., human hands and the tongue of a chameleon used for prey catching: they both do the same thing at one time, but their origins are completely different).

Analytical Behaviorism

►Behaviorism, Logical

Analytical Functionalism

Definition

This is a version of functionalism which says that it is a conceptual truth about our folk psychological concepts that every mental state of an organism can be characterized by its causal relations to perceptual input, other internal states, and the behavioral output of that organism.

- Behaviorism
- Functionalism
- Logical

Analytical Mechanics

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Definition

A formulation of the laws of ►mechanics based on the geometric concept of ►configuration space. In this approach, forces (or, more precisely, generalized forces) are considered as linear operators on vectors tangent to the configuration space (virtual displacements, or virtual velocities).

Description of the Theory

The concept of *configuration space* is briefly discussed in the article on classical mechanics (q.v.), and the use of *generalized coordinates* has been introduced in the article on the ►principle of virtual work (q.v.). To effect the transition to ►analytical mechanics the so-called ►principle of D'Alembert, briefly discussed in the article on statics (q.v.), may be invoked. According to this principle the equations of motion of a system can be regarded as equilibrium equations that include fictitious inertia forces. Applying this idea to the principle of virtual work, the virtual work of the forces of inertia associated with the free motion of a single particle in space may be calculated. Working in an inertial frame, the force of inertia, as defined in the article on statics (q.v.), is equal to $-\dot{\mathbf{p}}$. Since the particle is free, any arbitrary virtual displacement $\delta\mathbf{x}$ is admissible. The virtual work of the force of inertia is, therefore, given by:

$$-\dot{\mathbf{p}} \cdot \delta\mathbf{x} = -m\dot{\mathbf{v}} \cdot \delta\mathbf{x}. \quad (1)$$

According to D'Alembert's principle, the incorporation of this extra term to the virtual work of the applied forces will deliver (by means of the principle of virtual work) the equations of motion of the particle. In fact, in many practical applications, including the derivation of approximate numerical algorithms for finding the motion of a system, this is all that is needed. But analytical mechanics does not stop at this point, since its inspiration came from a philosophical point of view (initially advocated in France during the eighteenth century by, among others, Maupertuis) according to which the laws of Nature must represent in some sense the most efficient possible way for phenomena to take place. This principle has its historical origins in the *principle of least time* of optics (already known for reflected rays to Heron of Alexandria and extended to refraction problems by Fermat), according to which light rays travel in a trajectory that minimizes the time of travel (or, at least, renders it stationary with respect to neighboring trajectories). Maupertuis advocated the existence of a similar principle in mechanics, except that the quantity to be optimized was not necessarily time, but some vaguely defined quantity called *action*. This general idea was further developed and made mathematically precise by Euler, Lagrange and Hamilton. To understand these developments, it is useful to realize that, even in the case of the rays of light, the quantity to be minimized is not an ordinary function of several variables, but rather a *functional*, namely, a function whose independent variables are themselves entire functions. Consider, for example, the trajectory of a ray of light in a refractive medium whose index of refraction varies smoothly from point

to point. The time-minimizing trajectory is, therefore, expected to be a smooth curve (rather than a zigzag of straight pieces). In principle, all smooth trajectories starting at the source and ending at the receptor must be considered in an equal footing. The time of travel is thus a function of the whole trajectory, a function to be evaluated for each candidate curve, namely, a functional given by an integration over a curve of a certain function of the index of refraction and the element of length of the curve. Returning to Eq. 1 for the virtual work of the force of inertia for a single particle and integrating it between an initial time t_0 and a final time t_1 :

$$\begin{aligned} \int_{t_0}^{t_1} -m\dot{\mathbf{v}} \cdot \delta\mathbf{x} dt &= \int_{t_0}^{t_1} -\frac{d}{dt}(m\mathbf{v} \cdot \delta\mathbf{x}) dt + \int_{t_0}^{t_1} m\mathbf{v} \cdot \delta\dot{\mathbf{x}} dt \\ &= -m\mathbf{v} \cdot \delta\mathbf{x}|_{t_0}^{t_1} + \int_{t_0}^{t_1} m\mathbf{v} \cdot \delta\mathbf{v} dt \\ &= -m\mathbf{v} \cdot \delta\mathbf{x}|_{t_0}^{t_1} + \delta \int_{t_0}^{t_1} K dt, \end{aligned} \quad (2)$$

where K is the ►kinetic energy of the particle:

$$K = \frac{1}{2}m\mathbf{v} \cdot \mathbf{v}. \quad (3)$$

There are several subtleties involved in the derivation of Eq. 2. One is that the variations $\delta\mathbf{x}$ are vector-valued *functions of time*. In other words, they consist of entire variations (or perturbations) of a motion between the initial and the final times. So far, these variations have been permitted to be arbitrary, but now they must vanish at the end points. This is tantamount to saying that, although the actual trajectory of the particle is unknown, its positions for the initial and the final times are assumed to be known and that is why a non-zero variation is no longer being allowed at these times. Under these restricted conditions, the integrated virtual work of the force of inertia is exactly equal to the integral of the kinetic energy of the particle between the initial and the final times. Naturally, the kinetic energy depends on the trajectory chosen and thus its integral is not an ordinary function but a functional of the trajectory; for each candidate trajectory (always starting and finishing at specified points) a different value of the integral of the kinetic energy is obtained.

Having calculated the integrated virtual work of the force of inertia, the integrated virtual work of the actual forces impressed on the particle may be calculated. Assume that this force is conservative, namely, it is equal to minus the derivative of a ►potential energy function V (see the article on the ►principle of virtual

work). In that case, the integrated virtual work of the impressed forces is:

$$\int_{t_0}^{t_1} \mathbf{f}^{ext} \cdot \delta \mathbf{x} dt = - \int_{t_0}^{t_1} \delta V dt = - \delta \int_{t_0}^{t_1} V dt. \quad (4)$$

Since, according to D'Alembert's principle, along the actual trajectory of the particle, the total virtual work must vanish at each instant of time, it follows that the integrated virtual work will also vanish identically. Collecting the results of Eqs. 2 and 4, and defining the ►Lagrangian density L as the difference between the kinetic and the potential energies, namely,

$$L = K - V, \quad (5)$$

along the actual trajectory of the particle the variation of the integral of the Lagrangian density must vanish, viz.:

$$\delta \int_{t_0}^{t_1} L dt = 0. \quad (6)$$

This result can be interpreted as follows. Among all the possible trajectories starting and ending at specified points and at specified times, the particle will choose a trajectory that, when compared with any of its neighboring trajectories starting and ending in the same way, renders the integral of the Lagrangian density stationary (for example, minimum).

An in-depth treatment of this important topic is beyond the scope of this article. Nevertheless, the validity of this principle extends to all conservative mechanical systems of a finite number of degrees of freedom with purely geometrical constraints. Systems with so-called ►non-holonomic constraints (constraints on the velocities rather than the positions of the system) require a special treatment.

The kinetic energy of a rigid body can be calculated on the basis of Eq. 9 of ►Newtonian mechanics (q.v.) as:

$$K = \frac{1}{2} M \dot{\mathbf{x}} \cdot \dot{\mathbf{x}} + \frac{1}{2} \Omega \cdot \mathbf{J} \Omega. \quad (7)$$

The Lagrangian density L will in general be a function of the generalized coordinates q^i and of their time-derivatives \dot{q}^i (or, *generalized velocities*). According to the principles of the *calculus of variations* (the mathematical discipline dealing with the determination of stationary values of functionals), a functional of the type shown in Eq. 6 is stationary if the functions $q^i(t)$ satisfy the so-called *Euler-Lagrange differential equations*:

$$\frac{\partial L}{\partial q^i} - \frac{d}{dt} \left(\frac{\partial L}{\partial \dot{q}^i} \right) = 0 \quad (8)$$

These equations are not partial but ordinary differential equations. The partial derivatives appearing therein are nothing but indications of the operations to be performed with the Lagrangian density (seen as a function of the $2n$ independent variables, the generalized coordinates and the generalized velocities) to obtain the equations. The total time-derivative appearing in Eq. 8, on the other hand, needs to be calculated by the chain rule of differentiation, namely, taking into consideration that the generalized coordinates and velocities are ultimately functions of time. The Euler-Lagrange equations represent an alternative procedure for the derivation of the equations of motion of the system. Although they were derived by means of a time-wise global conceptual framework (the stationary value of an integral over time), they ultimately yield a time-wise local result (a system of differential equations). As compared with the derivation of the equations of motion by means of Newtonian mechanics (q.v.) the advantages are clear. In analytical mechanics only the expression of two scalar functions, the kinetic and the potential energy of the system, need be known. The rest is delivered automatically by the calculus of variations, thus avoiding the pitfalls of derivations based on free-body diagrams. These pitfalls are particularly severe in those cases in which extra geometric constraints are imposed whose associated forces are not easily represented in free-body diagrams (for example, a constraint of area preservation of a panel comprised between several bars). Even if these constraints are not easily factored out in the choice of generalized coordinates, the calculus of variations provides techniques for their straightforward incorporation in the formulation of analytical mechanics.

This is an elementary sketch of the so-called *Lagrangian mechanics*. There exists an equivalent formulation known as *Hamiltonian mechanics* in which the primary concept is the so-called *phase space*, rather than the configuration space. In phase space the generalized coordinates and the generalized momenta are given symmetric roles. In spite of the long-standing tradition of these two versions of analytical mechanics, there is still much research being carried out today. The discovery of a strong canonical geometric structure in phase space for example, has given rise to the *symplectic formalism*, which is specially suited to the definition of physically meaningful quantities in a global intrinsic way, rather than in terms of local coordinate expressions. These topics are beyond the scope of this article.

References

1. Whittaker ET (1947) A treatise on the analytical dynamics of particles and rigid bodies, 4th edn. Cambridge University Press, Cambridge

2. Goldstein H (1950) Classical mechanics. Addison-Wesley, Cambridge
3. Neimark JI, Fufaev NA (1972) Dynamics of nonholonomic systems. In: Translations of Mathematical Monographs, vol 33. American Mathematical Society, Providence
4. Lanczos C (1970) The variational principles of mechanics, 4th edn. Toronto University Press, Toronto
5. Abraham RA, Marsden JE (1982) Foundations of mechanics, 2nd edn. Addison-Wesley, Redwood
6. Arnold VI (1989) Mathematical methods of classical mechanics. In: Graduate texts in mathematics, 2nd edn. vol 60. Springer, New York

Anandamide

Definition

Anandamide also known as arachidonoylethanolamide or AEA, is an endogenous cannabinoid neurotransmitter. It was isolated and its structure was elucidated in the Laboratory of Raphael Mechoulam, at the Hebrew University in Jerusalem in 1992. The name is taken from the Sanskrit word ananda, which means “bliss”. Its structure represents arachidonic acid linked to ethanolamine via an amide linkage.

► Cannabinoids

Anapsida

Definition

The most ancient, extinct group of Amniota, without temporal openings for the masticatory muscles. Formerly turtles were held the extant representatives of the group. The advanced amniotes have two evolutionary lines: Synapsida, with one large temporal opening, it comprises mammals, and their extinct, reptile-like ancestors, and Diapsida, with two temporal openings: birds, extant reptiles, and extinct groups, like dinosaurs and pterosaurs.

► Evolution of the Brain: At the Reptile-Bird Transition

Anatomical Coordinate System

Definition

An orthonormal set of coordinate axes attached to a bone, and defined using bony anatomical landmarks

or other points of anatomical significance to the segment.

► Motion Analysis

Anatomy

Definition

The branch of biology that explores the structure and organization of tissues.

Anatomy and Function in the Respiratory Network

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Synonyms

Anatomy of Breathing; Central Respiratory Mechanisms; Models of Respiration

Definition

Breathing is an automatic somatomotor behavior serving homeostasis for O₂ and CO₂. The rhythm and pattern of breathing is shaped by an interconnected series of neural modules located mainly in the rhombencephalon (medulla and pons). Breathing is also voluntary in that it can be consciously started or stopped as well as its depth and frequency altered.

Characteristics

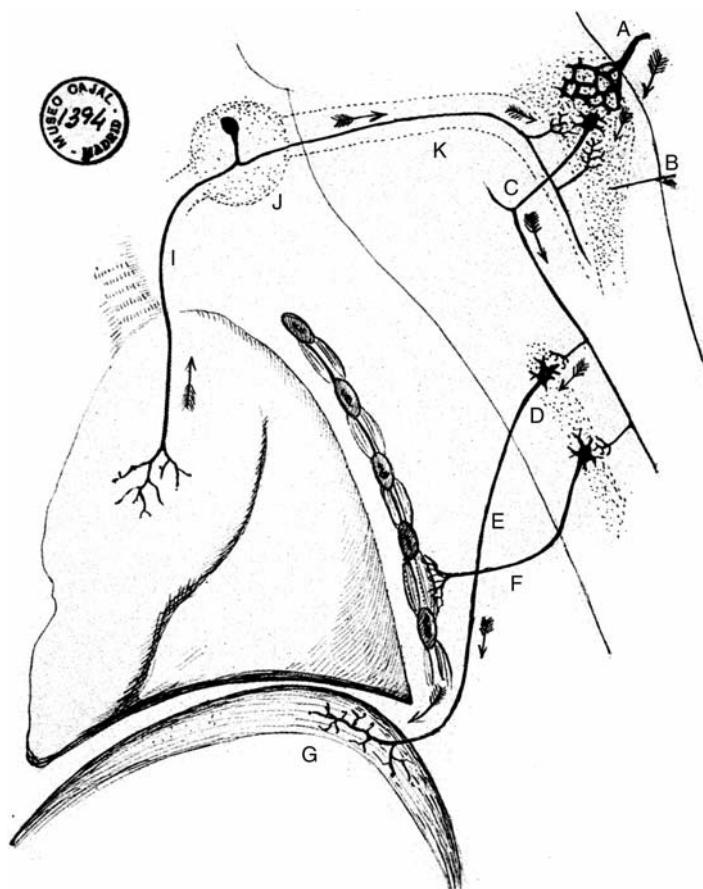
Breathing is an essential homeostatic behavior persisting without significant interruption throughout life. Although it can be voluntarily controlled, respiration is served by highly automated central rhythmic oscillators located in the rhombencephalon. In general, the frequency (rhythm) and volume of respiration is unconsciously adjusted over a wide range. Brainstem reflexes respond to central and peripheral chemosensors monitoring the partial pressures of oxygen (PO₂) and carbon dioxide (PCO₂) in the arterial blood and in the brain parenchyma, as well as responding to receptors in the upper airways and lungs monitoring inflation or deflation (stretch receptors) or signaling the presence of toxins or irritants in the airways.

In addition to its vital role in homeostasis, breathing may be arbitrarily altered to serve other non-homeostatic behaviors ranging from walking and talking to postural adjustments. Breathing is also an (involuntary) component of emotional behaviors; it may be enhanced or inhibited relative to orienting and defensive responses, modulated within emotional state and in conditions such as panic disorder where hyperventilation may contribute to the dysphoria experienced by the affected individual. As a basic component of vocalization, the precise control of expiration and muscle contractions in the upper airways (including the larynx and tongue) underlies the

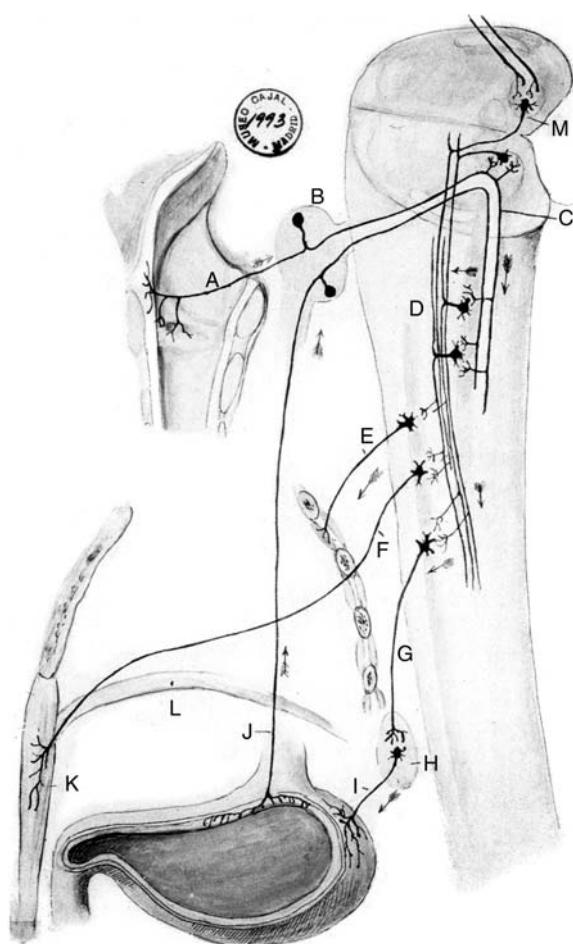
motor output for one of the most complex cognitive activities of the brain.

Functional Neuroanatomy

The importance of the brainstem in the control of breathing was appreciated relatively early on in the history of neuroscience, Cajal [3] for example, provided a relatively accurate overview of mammalian afferent and efferent pathways regulating breathing (Figs. 1 and 2). These include: (i) ascending sensory information from the airways that travel via the vagus to reach the nucleus of the solitary tract (NTS), (ii) integration by brainstem



Anatomy and Function in the Respiratory Network. **Figure 1** Diagram of respiratory circuits and the output to inspiratory muscles. This diagram provides an overview of the anatomical circuits controlling breathing, and, in particular, respiratory motor output via inspiratory pump muscles. Specifically, peripheral pulmonary stretch receptors (I,J,K), and peripheral chemoreceptors that monitor arterial O₂ and CO₂ (not shown – see text) provide afferents that terminate centrally in the nucleus of the solitary tract (B). Central chemoreceptors in this nucleus (A, and elsewhere in the brainstem – see Fig. 8) monitor CO₂ levels and brainstem respiratory rhythm generators in the ventrolateral medulla (see Fig. 3) integrate this information with feedback from pulmonary stretch receptors. Respiratory premotor neurons in the medulla (C, and see Fig. 5) give rise to descending axons that innervate inspiratory motoneurons in the cervical spinal cord (D – phrenic nucleus, E – phrenic nerve) and thoracic spinal cord (F) that innervate the inspiratory pump muscles. The latter include the diaphragm (G) and external intercostal muscles (F). From Cajal SR 1897–1899. "Textura del sistema nervioso del hombre y de los vertebrados," copyright Herederos de Santiago Ramón y Cajal. [English Transl Pasik P & Pasik T, 1999–2002] With the kind permission of María Angeles Ramón y Cajal.



Anatomy and Function in the Respiratory Network. **Figure 2** Diagram of respiratory circuits and their output to expiratory muscles. This diagram, initially intended to illustrate anatomical circuits involved in coughing and vomiting, also provides an overview of the respiratory motor output via expiratory pump muscles. Airway receptors (A – larynx) and pulmonary stretch receptors (see Fig. 1) provide afferents to the nucleus of the solitary tract (M) which relays this information to respiratory circuits in the medulla (D) and pons (see Fig. 3). The latter circuits provide afferents to spinal projecting expiratory premotor neurons in the medulla (D and Fig. 5) controlling the rhythm and pattern of activity on their axons which terminate on thoracic motoneurons innervating expiratory pump muscles, including abdominal (K) and internal intercostal muscles (E). From Cajal SR 1897–1899. “Textura del sistema nervioso del hombre y de los vertebrados,” copyright Herederos de Santiago Ramón y Cajal. [English Transl Pasik P & Pasik T, 1999–2002 with the kind permission of María Angeles Ramón y Cajal.

neurons of vagal respiratory afferent information with the central detection of CO₂ levels, and the control of brainstem premotor neurons. (iii) The latter innervate spinal motoneurons in the phrenic nucleus and thoracic

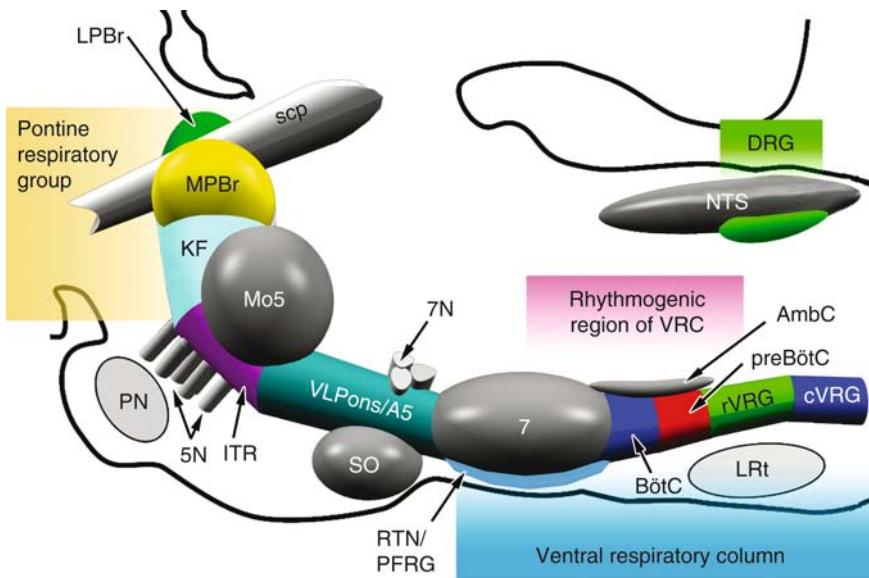
spinal cord that activate the inspiratory pump muscles (i.e., the diaphragm and external intercostal muscles), and (iv) innervate motoneurons in the thoracic spinal cord that activate the expiratory pump muscles (i.e., internal intercostal and abdominal muscles). Over the past century physiological and anatomical research has resulted in considerable elaboration of this basic outline, including the identification of multiple compartments within the brainstem whose coordinated activity precisely controls breathing.

Brainstem Respiratory Neurons

Neurons demonstrating bursts of action potentials phase-locked to the respiratory cycle, and dependant on a centrally generated respiratory rhythm are operationally defined as “respiratory neurons.” These are distinguished from non-phasic firing respiratory related neurons, such as neurons in chemosensory pathways providing tonic inputs to respiratory neurons.

Not surprisingly, rhomencephalic respiratory neurons tend to fire in phase with either the inspiratory or expiratory phase of the respiratory cycle. Prominent brainstem collections of respiratory neurons are concentrated in three regions (Fig. 3). The first is located dorsally within the medulla in ventrolateral portions of the NTS and was accordingly designated the “dorsal respiratory group” (DRG). A second region, in the dorsolateral pons in and around the complex formed by the parabrachial and Kölliker-Fuse nuclei, was originally termed the “pontine pneumotaxic region,” but more recently, the “pontine respiratory group” (PRG). The third consists of an elongated column of neurons in the ventrolateral medulla which is termed the “ventral respiratory column” (VRC).

It is argued that three respiratory phases are necessary to characterize the breathing cycle, the inspiratory phase and early and late expiratory phases (Fig. 4). Specifically, activity on the phrenic nerve starts contraction of the diaphragm, expanding the lungs and beginning the inspiratory phase. Following lung inflation, action potentials on the phrenic nerve decline abruptly. At this point, the inherent elastic recoil of the lungs and thorax begin the expiratory phase of respiration. During normal relaxed breathing in humans, expiration generally depends on the passive recoil of the lungs and chest wall with little expiratory muscle contraction (e.g., abdominal and internal intercostal muscles). As the demand for gas exchange increases (for example during running) phasic activation of expiratory muscle activity is recruited. During the early part of expiration, adduction of the larynx slows expiratory airflow. There may also be residual activity on the phrenic nerve. This expiratory activity on a nerve innervating the major inspiratory muscle (the diaphragm) prompted the designation of early expiration as post-inspiration. If activity on expiratory muscles occurs (e.g., abdominal, internal

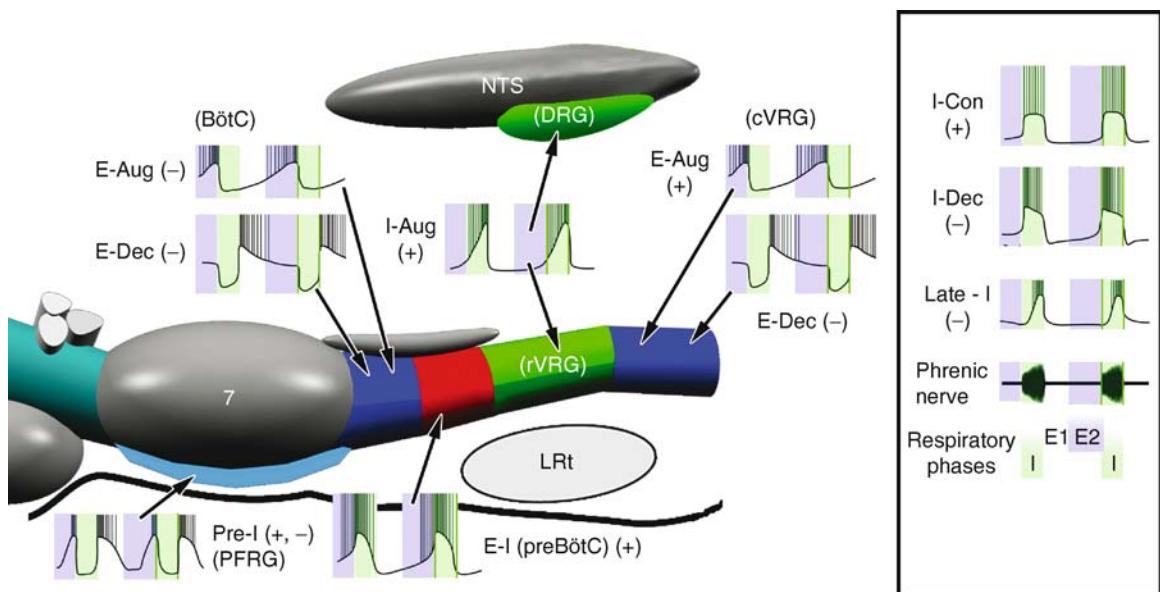


Anatomy and Function in the Respiratory Network. **Figure 3** Brainstem respiratory neurons and compartments. Respiratory related regions of the rhombencephalon (pons + medulla) are diagrammed by colored coded compartments against a parasagittal section of the rat brain (as viewed from the midline). Nearby landmark structures are shaded in gray. Brainstem respiratory neurons are concentrated in three regions: (i) The dorsal respiratory group (DRG) located in the region of the ventral and ventrolateral subnuclei of the solitary tract, (ii) the pontine respiratory group composed of several subdivisions of the parabrachial complex along with the Kölliker-Fuse nucleus, (iii) the ventral respiratory column (VRC) extending from the level of the facial nucleus caudally to the spinal-medullary junction. The VRC is composed of a serial succession of physiologically distinct compartments (see text) which are responsible for the automatic generation of the respiratory rhythm (particularly in the rostral portions of the VRC, see magenta shaded region) and integrating this rhythm with patterned activity on respiratory spinal-projecting premotor neurons (mainly in caudal portions of the VRC, see text and Fig. 5). The VRC is essentially continuous with the PRG, via respiratory-related neurons located along the boundaries of the facial nucleus that recollect in the ventrolateral pons and continue into the intertrigeminal region (ITR) before merging with the Kölliker-Fuse nucleus (KF). Abbreviations: 5N, trigeminal nerve; 7, facial nucleus; 7N, facial nerve; A5, A5 noradrenergic neurons; Ambc, nucleus ambiguus compact part; Botc, Bötzinger complex; cVRG, caudal part of ventral respiratory group; DRG, dorsal respiratory group; ITR, intertrigeminal region; KF, Kölliker-Fuse nucleus; LPBr, lateral parabrachial area; LRT, lateral reticular nucleus; Mo5, motor trigeminal nucleus; NTS, nucleus of the solitary tract; MPBr, medial parabrachial area; PFRG, parafacial respiratory group; preBötC, preBötzinger complex; pRG, pontine respiratory group; RTN, retrotrapezoid nucleus; VRG, rostral part of ventral respiratory group; PN, basilar pontine nuclei; Scp, superior cerebellar peduncle; SO, superior olive; VLPons, ventrolateral pons; VRC, ventral respiratory column.

intercostal muscles) it is usually most prominent during late expiration. It is notable that the extent to which the expiratory muscles participate in breathing varies considerably across the energy demands of the individual.

Individual respiratory neurons tend to fire with particular phase relationships to the respiratory cycle (Fig. 4), and the firing pattern as well as the synaptic interactions of individual respiratory neurons have been used to infer different functional roles. While a standardized nomenclature has not been agreed upon, the basic types include inspiratory (I) and expiratory (E) neurons as well as phase-spanning neurons whose activity spans the temporal limits between inspiration and expiration. Within the inspiratory or expiratory phase of the respiratory cycle, neurons have been

further categorized by their augmenting (Aug), decrementing (Dec), or constant rate (Con) of firing within a specific respiratory phase, and whether the activity of a particular cell occurs in the early or late within the inspiratory or expiratory phase of respiration. Using these qualifications, types of respiratory neurons commonly identified include E-I phase spanning neurons, I-Con, I-Dec, I-Aug, and Late-I neurons, as well as E-Dec (or post-I) and E-Aug neurons. Additionally, a “pre-I” cell type has been described whose activity begins at the end of expiration, is actively inhibited during inspiration, and fires again at the beginning of expiration. The firing patterns of these various types of neurons are generally a result of their circuit interactions within the rhombencephalon



Anatomy and Function in the Respiratory Network. Figure 4 Medullary respiratory neurons. This figure depicts the activity patterns for a representative sample of respiratory neurons on a parasagittal view of the rat medulla. These neurons are distinguished by the timing of their bursts of action potentials with respect to the inspiratory phase, or with respect to one of the two postulated expiratory phases of the respiratory cycle and the accompanying changes in their membrane potentials, and (when possible) by their axonal projections (see Fig. 5). Most of the respiratory compartments in the VRC are associated with “typical” (but not exclusive) concentrations of particular classes of inspiratory or expiratory neurons; the firing patterns of these neurons are depicted in relation to a sagittal diagram of the VRC and with respect to the DRG. Respiratory neuronal types commonly recorded in the VRC but not readily associated with a particular brainstem compartment are shown in the inset at the right side of the figure along with the “normal” pattern of firing for the phrenic nerve. For all of the respiratory neurons depicted, the inspiratory (I) part of the respiratory cycle is identified by the green shading. The first part of the expiratory phase (E1) is not shaded, while the second part of the expiratory phase (E2) is identified by purple shading. The characteristic excitatory or inhibitory nature of the particular neuronal types is indicated by plus or minus signs. Note that in some instances a single firing pattern may be associated with both inhibitory and excitatory neurons, as is the case for E-Aug neurons in the BötC or cVRG (respectively), or for pre-I neurons in the parafacial region. It should be further noted that the terminology used for respiratory neurons is not entirely uniform between different investigators in this field, and the depicted excitatory and inhibitory bursting patterns do not represent an exhaustive catalog of the possible respiratory neuronal types. Abbreviations: E1, early expiratory phase E2, late expiratory phase; E-Aug, expiratory neurons with an augmenting depolarization starting at the begin of E2; E-Dec, expiratory neurons with a decrementing depolarization beginning in E1; E-I, phase-spanning neurons with a depolarization beginning at the end of E2 and continuing into the inspiratory phase; I, inspiratory phase of respiratory cycle; I-Aug, inspiratory neurons with augmenting depolarization and firing pattern; I-Con, inspiratory neurons with a constant depolarization; I-Dec, inspiratory neurons with decrementing depolarization; Late-I, inspiratory neurons depolarizing at later portion of inspiratory phase; Pre-I neurons, phase spanning neurons characterized by depolarization beginning in E2, which are then actively inhibited during inspiration, and subsequently depolarized at the beginning of E1; (other abbreviations as in Figure 3).

and particularly within the medulla. Ultimately, the pattern of activity at motoneurons giving rise to nerves innervating the airways and pump muscles reflects premotor input to these motoneurons from various combinations of brainstem respiratory neurons.

The Nucleus of the Solitary Tract

The NTS is compartmented and multifunctional, relaying visceral information from various peripheral organs relevant to physiological homeostasis and central

reflexes. Afferents arising from the lung and airways as well as arterial chemoreceptors (carotid and aortic bodies) travel mainly in the vagus and glossopharyngeal nerves, and target neurons in caudal aspects of the NTS. Relative to breathing, pulmonary stretch receptors monitor the level of inflation of the lungs and via inhibitory second order NTS neurons increasingly inhibit inspiration as maximal lung volume is reached. Receptors in the airways additionally detect irritants, and their afferents to the NTS initiate protective reflexes

such as a cough or sneeze. Peripheral chemoreceptors for breathing are located mainly in the carotid body. They are activated by decreases in PO₂ or pH or an increase in PCO₂ of arterial blood and generally facilitate respiration during developing hypoxia or hypercapnia. Evidence suggests that a subset of neurons in the NTS also functions as central chemosensors for CO₂/pH. The targets of NTS second or higher order sensory relay neurons are predominantly within the VRC and the pontine respiratory group; a subset of these targets includes direct synapses on cranial motoneurons within the region of the VRC. Thus the respiratory related elements of the NTS function as sensory relays, as chemosensors, and as premotor neurons. The topography of respiratory related afferents to the NTS and the central reflexes they serve are discussed in greater detail elsewhere in this volume (*McCrimmon and Alheid, respiratory reflexes*).

Populations of Respiratory Neurons

Dorsal Respiratory Group (DRG; Fig. 3)

The dorsal respiratory group is comprised of “respiratory neurons” (predominantly inspiratory) located mainly in the ventral and ventrolateral NTS. These neurons receive a central respiratory drive that persists in the absence of peripheral afferent input. Interestingly, although they receive vagal and glossopharyngeal afferent input, they do not appear to be required for the production of peripheral reflexes which are relayed largely through neurons in other NTS subregions. Particularly in the cat, significant numbers of these DRG neurons are premotor with terminations in the phrenic nucleus, including monosynaptic input to phrenic motoneurons.

The Ventral Respiratory Column (VRC; Fig. 3)

The VRC refers to a succession of six contiguous but physiologically distinctive collections of respiratory neurons in the ventrolateral medulla. This includes the principal neuronal circuits responsible for the intrinsic generation of respiratory rhythm, and for the pattern of respiratory activity on nerves innervating the muscles of the airways as well as on nerves innervating the pump muscles. In the caudal half of the VRC, premotor neurons for spinal respiratory motoneurons are concentrated within a region termed the “ventral respiratory group” (VRG). The VRG is divided into rostral (rVRG) and caudal (cVRG) components reflecting a predominance of inspiratory neurons rostrally and expiratory neurons caudally. The rVRG and cVRG represent the main foci of excitatory (glutamatergic) bulbospinal inspiratory (augmenting; I-Aug) and expiratory (Augmenting; E-Aug) neurons (respectively). They provide the alternating (phasic) central drive mainly responsible for determining the pattern of activity for spinal motoneurons of the respiratory pump muscles (Fig. 5). At least within the

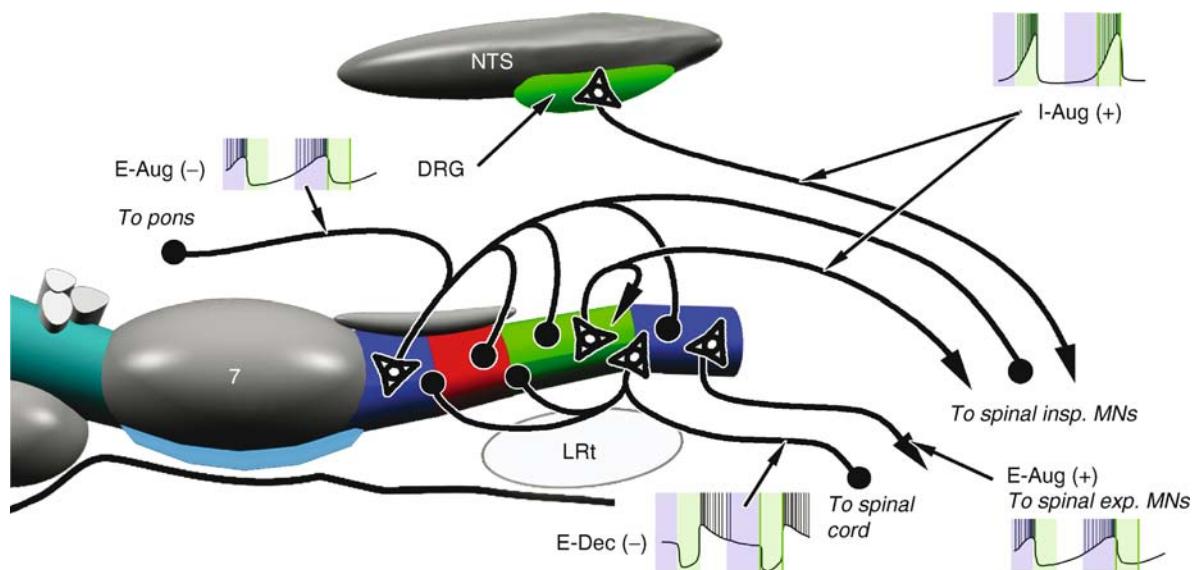
bulbospinal inspiratory neurons of the rVRG, enkephalin appears to be a co-transmitter with glutamate. Neurons in rVRG and cVRG appear to integrate afferents arising from second- or higher-order sensory relay neurons in the NTS as well as from respiratory-related neurons located throughout the ventrolateral medulla and pons (Figs. 6 and 7).

In the rostral half of the VRC, four additional concentrations of respiratory neurons have been identified, each with a distinctive physiological profile. From caudal to rostral, these include the pre-Bötzinger complex (preBötC), the Bötzinger complex (BötC), the retrotrapezoid nucleus (RTN) and the parafacial respiratory group (PFRG). At the most rostral end of the VRC, RTN neurons appear to be chemosensory, increasing their firing rate in proportion to central CO₂ (or inversely proportional to pH) and activating respiratory neurons in the other VRC compartments. The remaining three anterior VRC compartments (PFRG, BötC, preBötC) appear to play a significant role in respiratory rhythm generation. In contrast, spinal premotor neurons in the posterior part of the VRC (rVRG, cVRG) provide the major source of rhythmic excitatory input to pump muscle motoneurons in the spinal cord but do not appear to contribute to the generation of respiratory rhythm. Chemical blockade in the cVRG, for example, blocks respiratory activity at abdominal muscles but does not change the respiratory rate measured on the phrenic nerve. It should be noted, however, that the transition between anterior rhythmogenic and posterior spinal premotor portions of the VRC is not abrupt. This may reflect the fact that the respiratory neuronal types (Fig. 4), characterizing a particular VRC region have distributions whose tails overlap with those of neuronal types typifying adjacent compartments.

The Retrotrapezoid Nucleus (and Central Chemosensitive Brainstem Regions)

The RTN consists of a narrow layer of chemoresponsive neurons located near the surface of the brainstem ventral to the facial nucleus (Figs. 3 and 8). Specifically, hypercapnic solutions or acidification of these superficial regions, cause increased firing of glutamatergic neurons that project widely to medullary and pontine areas related to breathing, resulting in increased ventilation. RTN neurons also increase their firing in response to stimulation of peripheral chemoreceptors. This is consistent with the presence of excitatory projections from the commissural NTS, which is the primary target region of peripheral chemoreceptor afferent neurons. Consequently, it has been argued that the RTN integrates peripheral and central chemoreceptor information and provides a drive to respiratory circuits.

In addition to the RTN several other chemosensitive brainstem regions have been identified, including the preBötC, the caudal raphe nuclei (raphe magnus,



Anatomy and Function in the Respiratory Network. Figure 5 Bulbospinal respiratory neurons. This parasagittal diagram of the rat medulla depicts various types of respiratory neurons in the VRC and DRG that provide the spinal premotor input that ultimately determines the activity of the respiratory pump muscles. Some of the neurons sending axons to the spinal cord also provide collaterals to the VRC; for I-Aug neurons in the rVRG (see Fig. 3), some of these collaterals appear to target other inspiratory bulbospinal neurons ipsilaterally or contralaterally, while other collaterals of I-Aug neurons appear to target cranial motoneurons (e.g., laryngeal, hypoglossal motoneurons). Also notable is the difference between E-Aug neurons that in the cVRG are excitatory (glutamatergic) and do not have medullary collaterals compared to E-Aug neurons in the BötC which are largely inhibitory and project extensively throughout the VRC and in some instances also send ascending axons to the pons. For the depicted E-Aug and E-Dec neurons the diagram is a summary of the axon collaterals since the individual neurons do not necessarily reach every potential target of these populations. Finally, many neurons in the NTS relay respiratory related afferents to the VRC and pons; these are not shown here but are depicted elsewhere in this volume (McCrimmon & Alheid, *Respiratory Reflexes*). For abbreviations see legends for Figures 3 and 4.

pallidus, and obscurus), the locus coeruleus, the fastigial nucleus of the cerebellum, as well as a subset of NTS neurons (Fig. 8). The occurrence of multiple chemosensitive brainstem sites related to brainstem respiratory circuits may reflect alternative redundant systems for this important function.

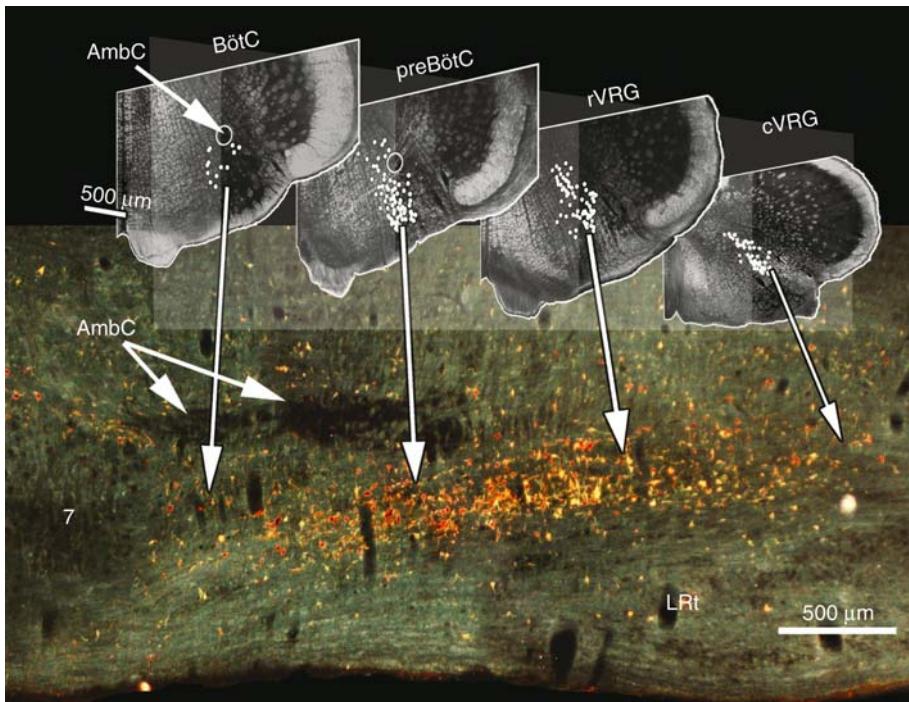
Attention has also been focused on the chemosensory role of neurons in the caudal raphe nuclei (raphe magnus, raphe pallidus, and raphe obscurus), by clinical pathology relating aberrations in serotonergic neurons and serotonergic receptors at the ventromedial surface of the brain (in the medullary arcuate nucleus of human brains), to sudden infant death syndrome (SIDS). The caudal raphe nuclei have a diffuse system of projections including the brainstem and spinal cord, and descending serotonergic projections appear to be important both for the tonic activation of motoneurons and for the modulation of sensory afferents. Serotonergic neurons appear to be chemosensitive and are activated by increasing CO₂/decreasing pH when tested using cultured neurons or brain slices. In addition to their role as potential central chemoreceptors, serotonergic projections to the phrenic

nucleus are essential for the occurrence of long-term facilitation to intermittent hypoxia, a model of plasticity in central respiratory circuits.

The Parafacial Respiratory Group and the RTN

Recently, it has been argued that “pre-I” neurons in the vicinity of the RTN function as an expiratory oscillator complementing an inspiratory oscillator located in the preBötC. *In vitro* imaging experiments of neonatal rat brainstems implicated neurons beneath lateral portions of the facial nucleus in the generation of rhythmic respiratory activity [9]. While not entirely separate topographically from the area normally associated with the RTN the term “parafacial respiratory group” (PFRG) has been used to designate this conceptually distinctive functional group.

The PFRG and preBötC are proposed to operate together as mutually inhibitory, coupled oscillators in the generation of the respiratory rhythm [5]. Data derived from *in vitro* and *in vivo* experiments (mainly on neonatal or juvenile rat brains) suggest that PFRG neurons are capable of generating rhythmic activity on



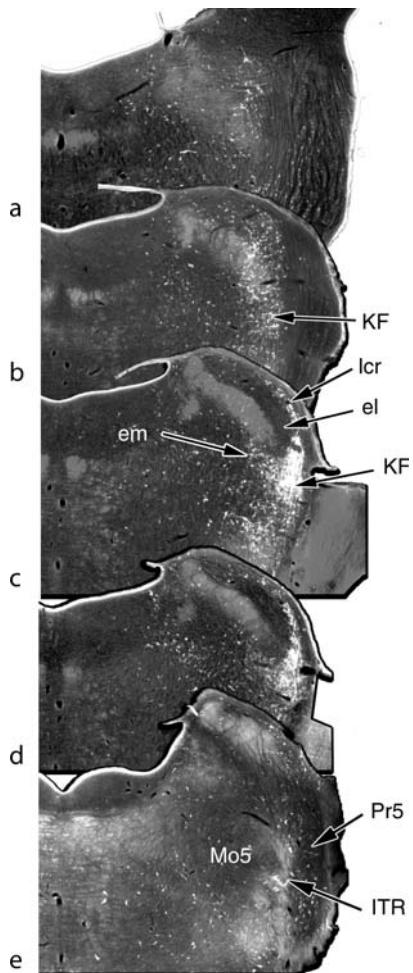
Anatomy and Function in the Respiratory Network. **Figure 6** Retrogradely labeled neurons in the ventral respiratory column of the rat brain. The anatomical location of respiratory neurons in the VRC is depicted after an injection of a retrograde tracer (FluoroGold) in the contralateral rVRG of two brains, one sectioned in the coronal plane (shown in perspective in the upper sections) and one in the parasagittal plane (lower section). Note that retrograde labeling is lighter in the RTN and in the BötC than in the more caudal portions of the VRC since the former regions have projections that preferentially target the ipsilateral side of the medulla. The parasagittal plane depicted is at the lateral level of the compact division of the nucleus ambiguus. This is indicated in the upper (coronal) sections by the parasagittal cutting plane indicated in light gray. In the coronal sections the location of the FluoroGold fluorescent labeling is identified by white dots mapped against darkfield images of the same sections in which the fluorescent cells were observed. In the lower parasagittal section, the Fluorogold labeling was enhanced by detection with an antibody to FluoroGold and a subsequent immunoperoxidase reaction to label the neurons with polymerized diaminobenzidine (DAB). (Color version of monochrome figure published in Alheid et al., *J Neurocytol* 31:693–717, 2002, with kind permission from Springer Science and Business Media). For abbreviations see legends for Figures 3 and 4.

the nerves innervating expiratory pump muscles, even following pharmacological blockade of neuronal activity in the preBötC. Based on *in vitro* experiments the PFRG appears to include both excitatory and inhibitory pre-I neurons. It is not at present clear whether some of the neurons comprising the PFRG are coincident with those cells serving chemosensory functions in the region of the RTN. The latter, however, appear to be exclusively excitatory (glutamatergic). It is also the case that for the adult brainstem, a clear physiological description of PFRG neurons functioning as an expiratory oscillator is still lacking. The concept of a brainstem expiratory oscillator has broad implications for the studies in the neurobiology of breathing. These have been addressed in the context of the evolution of vertebrate respiratory circuits and with respect to the

pre- and post-natal developmental course of respiratory circuits [4]. Consequently, the topic of the PFRG and its persistence in the adult brainstem remains topics under intense scrutiny.

The Bötzingер Complex

The BötC is located in the ventrolateral medulla immediately caudal to the facial nucleus (Fig. 3), and is identified physiologically by its content of expiratory, and mainly inhibitory (glycinergic) neurons (Fig. 4; augmenting or decrementing; E-Aug or E-Dec neurons). These projects widely to other respiratory related regions of the brainstem, and a subset of these neurons also provides descending projections to the spinal cord, including terminations in the phrenic nucleus (Figs. 1 and 5). BötC neurons (together with other inhibitory



Anatomy and Function in the Respiratory Network.
Figure 7 The anatomical distribution in the rat brain of pontine neurons projecting to the VRC shown in coronal sections. Neurons were retrogradely labeled after a tracer (FluoroGold) injected in the ipsilateral rVRG. A, the most rostral section in the series, is located at the mesencephalic-pontine border. The labeling of the neurons was enhanced by immunodetection and conversion to DAB. The darkfield images of the labeled sections were combined with inverted brightfield images of the densely DAB labeled neurons. (From Jiang et al., *Respir Physiol Neurobiol* 143:215–233, 2004, with permission from Elsevier). Abbreviations: DAB, diaminobenzidine; em, external medial subnucleus of the lateral parabrachial complex; el, external lateral subnucleus of the lateral parabrachial complex; Icr, lateral crescent subnucleus of the lateral parabrachial complex; PrS, principal (sensory) trigeminal nucleus; For other abbreviations see legends for Figures 4 and 5.

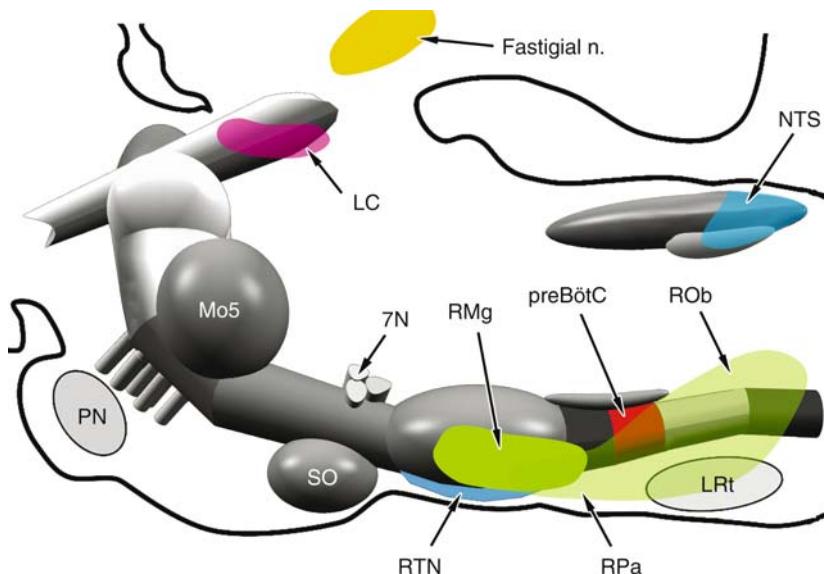
expiratory neurons scattered throughout the VRC presumably account for the pronounced phasic inhibition of inspiratory neurons in the brainstem and spinal cord during the expiratory phase of breathing.

The PreBötzinger Complex

Interposed between the BötC and the rVRG is the preBötC; this compact region contains excitatory phase-spanning neurons [10] essential for the generation of the respiratory rhythm, and particularly for the expression of rhythmic inspiratory activity. Even when isolated *in vitro* from the remainder of the medulla, neurons in the preBötC are capable of sustaining an inspiratory-like rhythmic bursting activity [5]. The latter derives mainly from excitatory local circuits within the preBötC since its oscillating activity persists after blockade of inhibitory transmitters. Compared to other portions of the VRC the preBötC appears to be distinguished by a particular set of neurons having an expiratory-inspiratory (E-I) pattern of activity, which use glutamate as a transmitter, and which express neurokinin-1 (substance P) and μ -opioid receptors. Recent observations in the rat indicate that somatostatin is also present in relatively high concentrations within preBötC neurons and is a likely co-transmitter with glutamate; somatostatin containing neurons are, however, not confined to the preBötC in this area of the medulla. The preBötC has widespread projections to other ipsilateral and contralateral brainstem respiratory regions, but at least in the rat characteristically lacks neurons with spinal projections.

The Ventral Respiratory Column and Nucleus Ambiguus

Intermingled with or adjacent to VRC neurons are the cranial motoneurons in the dorsal portions of nucleus ambiguus (Fig. 9 and [2]). These include motoneurons of the larynx, pharynx, and esophagus. The activity of these motoneurons is not uniquely tied to respiration and serves a variety of additional behaviors including feeding, drinking, vomiting, and vocalizations. These types of homeostatic, protective, and social orofacial behaviors are served by neural networks in the forebrain and brainstem that are, to some extent, distinct from one another, and from the brainstem circuits underlying rhythmic respiratory activity. Nonetheless, these behaviors are often multiplexed with ongoing respiratory activity at the level of relevant cranial motoneurons. In fact, phasic respiratory activity is generally present on the cranial nerves innervating the airways, such as those supplied by pharyngeal and laryngeal motoneurons. Respiratory activity is also evident on subsets of motoneurons outside of nucleus ambiguus such as in the trigeminal, facial, and hypoglossal nuclei. Accordingly, axon collaterals from subsets of respiratory neurons in the VRC (including both propriobulbar and bulbospinal neurons) contribute premotor input to airway cranial motoneurons. Such connections have been shown for inspiratory bulbospinal neurons in the rVRG which also elaborate axon collaterals locally within the medulla. Similarly, expiratory neurons in the cVRG provide ascending axons that



Anatomy and Function in the Respiratory Network. **Figure 8** Chemosensitive regions of the rhombencephalon. A parasagittal view of central chemosensitive regions depicted in color against brainstem regions (gray) related to breathing (see Fig. 3). Chemosensitive regions are identified by neurons with relatively early responses to hypercapnia (excess CO₂) or the accompanying low pH levels. Relative to breathing, a number of candidate regions have been identified in the rhombencephalon that both show chemosensitivity and are interconnected with brainstem or spinal areas involved in respiration. These are the fastigial nucleus (one of the efferent nuclei of the cerebellum), the locus coeruleus (LC; which projects widely throughout the forebrain, brainstem, and spinal cord), the retrotrapezoid nucleus (RTN), the preBötzinger complex (preBötC), the nucleus of the solitary tract (NTS, see text), and the caudal raphe nuclei (RMg, raphe magnus, RPa, raphe pallidus; ROb, raphe obscurus). For other abbreviations see legends for Figures 4 and 5.

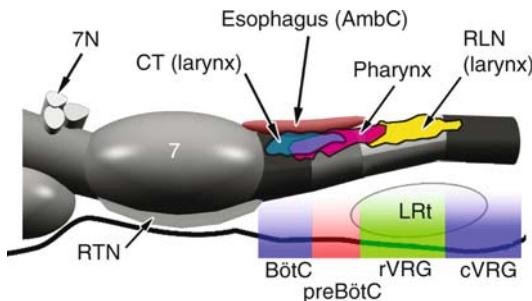
innervate laryngeal and pharyngeal motoneurons; such projections may be of particular significance for vocalizations rather than for other laryngeal reflexes, since the latter appear to survive pharmacological inactivation of the cVRG while vocalizations (and the accompanying laryngeal activation) elicited by electrical stimulation of the midbrain periaqueductal gray do not.

In addition to its role in the expiratory phase of respiration, the cVRG, or as it is alternatively termed, “the retroambiguus nucleus,” is identified as an important medullary focus for vocalizations, controlling a significant part of the activity of laryngeal muscles necessary for vocalizations, as well as providing for the activation of abdominal expiratory muscles. Abdominal muscles are involved in a variety of non-respiratory behaviors including vomiting, postural adjustments, and reproductive behaviors such as lordosis, all of which may access abdominal premotor neurons in the cVRG/retroambiguus region. The cVRG is consequently a particularly striking example of a respiratory compartment that is multiplexed with other behaviors. Whether individual cVRG neurons are recruited for multiple functions or whether distinct subgroups of these neurons are specialized for different behaviors is not entirely clear. Populations of “silent” neurons that are only activated under specific functional demands have been observed in cVRG, while some

cVRG neurons with axons reaching the lower segments of the lumbar spinal cord demonstrate expiratory rhythmicity despite the absence of potential motoneuron targets serving respiration.

Pontine Respiratory-Related Circuits

The brainstem column of neurons related to respiration does not end abruptly with the VRC at the facial nucleus. Neurons related to the control of breathing and connected with the VRC or with airway motoneurons in nucleus ambiguus are scattered around the margins of the facial nucleus, and continue rostral to it, forming an attenuated but essentially continuous and interconnected column in the lateral pons (Fig. 3 and [1]). At its rostral end this column expands into the larger aggregate of neurons in the region of the parabrachial and Kölliker-Fuse nuclei (Fig. 7). As with the VRC, respiratory-related neurons in the lateral pons do not appear to represent a functionally homogeneous column, but may be tentatively divided into distinct compartments. These include the ventrolateral pons/A5 region, the inter-trigeminal region, the Kölliker-Fuse nucleus, and medial and lateral nuclei of the parabrachial complex. As mentioned earlier, respiratory neurons in the parabrachial complex and Kölliker-Fuse nucleus together comprise the area designated as the pontine respiratory group.



Anatomy and Function in the Respiratory Network.

Figure 9 Nucleus ambiguus cranial motoneurons and the ventral respiratory column. This figure depicts the topography of cranial motoneurons of the upper airways and esophagus (colored polygons; *based on Fig. 9 in [2]*) located in the dorsal portions of nucleus ambiguus and overlapping with the VRC (gray, also see *Fig. 3*). In addition to spinal motoneurons controlling the pump muscles (see *Figs. 1, 2 and 5*) the respiratory circuits of the VRC provide afferents to cranial motoneurons of the upper airways. These motoneurons, however, are also activated in a variety of other behaviors (see text) and are not exclusively controlled by the circuits controlling the rhythm and pattern of breathing. The subdivisions of the VRC are indicated by the labeled colored bands.

Abbreviations: CT, motoneurons projecting to the crico-thyroid muscles of the larynx; RLN, motoneurons projecting to the larynx via the recurrent laryngeal nerve. For other abbreviations see legends for Figures 4 and 5.

Ventrolateral Pons/A5 Region

At pontine levels just rostral to the facial nucleus is an area variously referred to as the A5 region and/or the ventrolateral pons (*Fig. 3*). The A5 noradrenergic cell group is located within the ventrolateral pons near the ventral surface of the brain. A5 neurons are reported to project to the adjacent facial nucleus and to ventrolateral medulla, but also send axons terminating throughout much of the spinal cord including terminations at sympathetic preganglionic neurons in the intermediolateral column of the spinal cord. It is important to note that the major proportion of neurons projecting to the VRC from the ventrolateral pons is not catecholaminergic. A specific role of the ventrolateral pons/A5 region in breathing has not been determined in any detail. Electrical or chemical (glutamatergic) stimulation in this region facilitates expiration (i.e., lengthens expiration time while reducing respiratory frequency). It has additionally been reported that the ventrolateral pons may be a necessary relay for a similar facilitation of expiration evoked by stimulation in the medial parabrachial region.

The ventrolateral pons has also been identified as an important area for vocalizations [*7*] and some of the

interactions of the ventrolateral pons with the respiratory circuits in the VRC presumably reflect this function. It is argued that neurons in the ventrolateral pontine reticular formation are necessary for the organization of specific voluntary vocalizations (as opposed to emotional vocalizations), particularly including those sets of vocalizations requiring integration with auditory feedback. Consistent with this interpretation, some neurons in the ventrolateral pontine reticular formation both demonstrate a respiratory rhythm and receive auditory input.

The Intertrigeminal Area

Rostrally and dorsally, the ventrolateral pons merges with the intertrigeminal region (ITR; *Figs. 3 and 7*). This region consists of neurons located between the pontine principal (sensory) trigeminal nucleus and the motor trigeminal nucleus. Apneas appear to be readily elicited from the ITR with low doses of glutamatergic stimulation. The relevance of this observation for normal breathing is not entirely clear, but are potentially related to upper airway protective reflexes.

The Pontine Respiratory Group

Neurons in the parabrachial complex and Kölliker-Fuse nucleus are included within the pontine respiratory group (PRG). This region of the pons includes significant populations of respiratory neurons and is designated as the pontine respiratory group. Compared to the on-off firing pattern of most VRC neurons, the PRG has a larger percentage of neurons with tonic activity that is phasically modulated by the respiratory cycle.

The Kölliker-Fuse Nucleus

The Kölliker-Fuse nucleus is an ill-defined but fairly large aggregate of neurons located at the rostral and lateral boundaries of the pons (*Figs. 3 and 7*). The Kölliker-Fuse nucleus has the largest aggregate of neurons extrinsic to the medulla that project to the VRC; it densely innervates every compartment of the VRC. Targets include bulbospinal neurons in the rVRG, cranial motoneurons in the ambiguus and hypoglossal nuclei, and phrenic motoneurons in the spinal cord. Despite the extensive knowledge about the circuitry of the Kölliker-Fuse nucleus, its specific functional role remains unclear. It has been suggested that the Kölliker-Fuse nucleus is part of the network coordinating orofacial and/or airway protective reflexes.

The Parabrachial Complex

The parabrachial complex is composed of several functionally distinct subnuclei characterized by extensive and topographically specific reciprocal connections

with the NTS, as well as providing diverse (and to some extent reciprocated) efferents to the rhombencephalon and basal forebrain. The parabrachial complex surrounds the axons in the superior cerebellar peduncle (a.k.a. “*brachium conjunctivum*”) as they exit the deep cerebellar nuclei. At its ventral limits the parabrachial complex merges with the dorsal portions of the Kölliker-Fuse nucleus. Only a subset of the multiple compartments that make up the parabrachial complex appear to be directly related to breathing. Based on retrograde labeling, these particularly include the lateral crescent subnucleus, the external medial subnucleus, and rostral portions of the external lateral subnucleus (Fig. 7). Only scattered neurons in the more dorsal parts of the medial parabrachial complex appear to directly target the VRC, and similarly there is only a dispersed field of VRC projecting neurons in the subcoeruleus region located just medial to the medial parabrachial complex and ventral to the locus coeruleus. Projections from the medial parabrachial region may also reach the VRC via relays in the ventrolateral pons.

The parabrachial complex plays a significant role in relaying viscerosensory information (a substantial portion of which originates in the NTS) via ascending axons, to the thalamus, hypothalamus, and basal forebrain. Nociceptive afferents also reach the parabrachial region directly from the spinal cord and from the sensory trigeminal nuclei. Via descending projections, the parabrachial complex in part reciprocates the projections it receives from the NTS but also targets neurons in the caudal pontine reticular formation (medially and laterally), and sends projections to the ventrolateral medulla. Via these descending projections, the parabrachial region appears to function as a relay integrating visceral reflexes with descending forebrain afferents. Together these forebrain afferents and the substantial parabrachial projections to the brainstem form part of the emotional motor system. The latter is responsible for evoking the involuntary motor and visceral responses that accompany strong emotions.

Differential effects on breathing follow stimulation in the medial vs. lateral parabrachial nuclei. When stimulated, the lateral part of the parabrachial complex appears to provide a facilitation of inspiration. In contrast, stimulation in the medial parabrachial region (and to some extent in the adjacent dorsal portions of the Kölliker-Fuse nucleus) leads to a facilitation of expiration. Facilitation of breathing during locomotion, or in response to painful stimuli, appears to involve relays in the lateral part of the parabrachial complex. One parabrachial region that appears to be involved in these responses is the lateral crescent, which receives direct projections relevant to painful stimuli from the dorsal horn of the spinal cord and which sends projections directly to the VRC.

Periaqueductal Gray

Neurons surrounding the central canal in the mesencephalon play an important role as a relay to motor areas of the brainstem for a variety of behaviors originating in the forebrain. These include emotional vocalizations, reproductive reflexes, orienting responses, as well an antinociceptive role presumably related to facilitating adaptive responses in spite of bodily damage. Stimulation in lateral portions of the periaqueductal gray reliably evokes vocalizations that have been related to emotional behavior. Periaqueductal gray neurons directly and indirectly target the VRC and particularly, the cVRG. Respiratory changes occurring during other behaviors such as the orienting response appear to require an obligatory relay from the periaqueductal gray to the parabrachial complex.

Higher Order Neurons in the Hypothalamus, Basal Forebrain, and Cortex

Higher order neurons in the hypothalamus, basal forebrain, and cortex also influence respiration, but with the exception of cortical regions related to vocalizations, most forebrain regions are not exclusively related to breathing. Nonetheless, in addition to vocalizations, the influence of neuroendocrine systems, thermoregulatory systems, locomotor regions, and emotional behaviors on breathing is an important and complex topic. This is, unfortunately, beyond the scope of the present survey of the functional circuitry of respiration.

References

1. Alheid GF, Milsom WK, McCrimmon DR (2004) Pontine influences on breathing: an overview. *Respir Physiol Neurobiol* 143(2–3):105–114
2. Bieger D, Hopkins DA (1987) Viscerotopic representation of the upper alimentary tract in the medulla oblongata in the rat: the nucleus ambiguus. *J Comp Neurol* 262(4):546–562
3. Cajal SR (1897–1899) Texture of the nervous system of man and the vertebrates. (transl. by Pasik P, Pasik T, 1999–2002). Springer, Vienna/New York
4. Chatonnet F, Borday C, Wrobel L, Thoby-Brisson M, Fortin G, McLean H, Champagnat J (2006) Ontogeny of central rhythm generation in chicks and rodents. *Respir Physiol Neurobiol*
5. Feldman JL, Del Negro CA (2006) Looking for inspiration: new perspectives on respiratory rhythm. *Nat Rev Neurosci* 7(3):232–242
6. Feldman JL, McCrimmon DR (2002) Neural control of breathing. In: Squire LR, Bloom FE, McConnell SK, Roberts JL, Spitzer NC, Zigmond MJ (eds) (2003) Fundamental neuroscience, 2nd edn. Elsevier-Academic Press, San Diego, pp 967–990
7. Hage SR, Jurgens U (2006) Localization of a vocal pattern generator in the pontine brainstem of the squirrel monkey. *Eur J Neurosci* 23(3):840–844

8. McCrimmon DR, Alheid GF. Respiratory reflexes. In: Binder M, Hirokawa N, Martin MC, Winhorst U (eds) Encyclopedia of Neuroscience. Springer, Berlin
9. Onimaru H, Homma I (2003) A novel functional neuron group for respiratory rhythm generation in the ventral medulla. *J Neurosci* 23(4):1478–1486
10. Sun QJ, Goodchild AK, Chalmers JP, Pilowsky PM (1998) The pre-Botzinger complex and phase-spanning neurons in the adult rat. *Brain Res* 809(2):204–213

affected are often not able to assign objects they see to specified expressions. Instead of using the correct expression, they engage in circumlocutions in which the expression does not occur.

► **Telencephalon**

Anatomy of Breathing

- Anatomy and Function in the Respiratory Network

Andersen Syndrome

Definition

- Familial Periodic Paralyses

Anencephaly

Definition

Lack of encephalon resulting from failure of the neural tube to close.

- Neural Tube

Angular Gyrus

Synonyms

- Gyrus angularis

Definition

The angular gyrus lies in the parietal lobe, and shaped like an angle, it surrounds the posterior end of the superior temporal sulcus Functionally, it is between the secondary auditory cortex and the area 18. And indeed the angular gyrus does play an important role in linking visual impulses with linguistic concepts. Damage to the angular gyrus causes alexia and agraphia. Those

Angular Momentum

Definition

In classical (particle) mechanics, the angular momentum of a particle with respect to a point is defined as the cross product of the vector joining this point with the particle times the linear momentum of the particle. In continuum mechanics, the angular momentum density with respect to a point in space is obtained in a similar manner, using the linear momentum density. The total angular momentum is then obtained as the integral over the body of the angular momentum density.

- Mechanics

Angular Vestibulo-Ocular Reflex (aVOR)

Definition

The angular or rotational vestibulo ocular reflex (aVOR or rVOR) is the compensatory eye movement generated in response to an angular rotation of the head. The reflex is mediated by semicircular canals and the vestibular nuclei.

- Velocity Storage
- Vestibulo-Ocular Reflexes

Animal Communication

Definition

Interaction between two or more animals. A sender encodes and sends out a signal through a channel. A receiver decodes the signals and interprets it. For more information see essay on “Communication in electric fish.”

Animal Model

Definition

Species that have been used to study principles of neural and behavioral processing. Synonym: model system. Famous model systems are squids (for the investigation of the mechanisms underlying the action potential), *caenorhabditis* (genetics), *drosophila* (genetics), mouse (genetics), bats (biosonar), electric fish (acetylcholine receptor).

Animat

Definition

Artificial animal. Robot or computer simulation with sensors, actuators and nervous system that are directly inspired by actual living organisms.

► Computer-Neural Hybrids

Anisocoria

Definition

Pupils of unequal diameter. This is generally indicative of disruption of sensory, central, or lower motor neuronal components of the reflex circuitry.

► Neural Regulation of the Pupil

Anisotropic

Definition

Not invariant with respect to direction.

► Anisotropy

Anisotropy

Definition

Materials that have properties that change as the material is tested in different orientations are called “anisotropic materials.” For example, if the uniaxial stress-strain behavior of a material is stiffer in one material direction than another (possibly because there is more collagen laid down in that direction), the material is anisotropic.

Ankle Strategy

Definition

A fixed support (feet in place) reaction to anteroposterior postural perturbation where the predominant stabilizing action involves active generation of ankle torque. Also commonly referred to as the “early automatic postural response” (APR).

► Postural Strategies

Anomalous Monism

Definition

Anomalous monism is the thesis in the philosophy of mind, formulated by D. Davidson, that every event with a mental description, i.e. a mental event, is also physical, i.e. has a physical description, but no strict, precise and exceptionless laws link the mental and the physical. If there are no psychophysical laws relating events under mental descriptions in terms of “believing/desiring/hoping that snow is white” with events under physical descriptions in terms of, say, oscillatory patterns in the brain, then there can be no conceptual reduction of the mental to the physical. Anomalous monism is a form of monism, because it claims that all events are physical, but it is “anomalous” (“a nomos” – not governed by law), because it denies the possibility of strict psychophysical laws, which would allow conceptual reduction of the mental to the physical. It offers a non-reductive conception of the relation of the mental and the physical, which accepts ontological monism, but preserves the autonomy of the mental with its concepts of belief, desire, reasons and actions.

► Theory Theory (Simulation Theory, Theory of Mind)

Anomia

Definition

Word-finding difficulty in naming a picture, object, or definition as well as in spontaneous speech. Anomia is found in various pathological cases resulting from brain damage, such as aphasia, Alzheimer's disease, semantic dementia and herpes simplex virus encephalitis (HSVE or HSE).

- Alzheimer's Disease
- Aphasia
- Verbal Memory

Anorexia Nervosa

Definition

Serious loss of appetite. The patient becomes greatly emaciated. Neurobiological risk factors are becoming apparent.

- Neuroendocrinology of Eating Disorders

Anorgasm

Definition

Anorgasm refers to difficulty achieving or lack of orgasm.

- Sexual Reflexes

Anosmia

Definition

A temporary or permanent loss of the sense of smell, which may be selective to a small number of odorants or affect detection of all odorants. Acute nasal infection can cause temporary loss of smell. Permanent loss often involves neural damage in the olfactory system, for example due to close head injury damaging the olfactory nerve or brain disease.

- Smell Disorders

Anosognosia

Definition

Denial or unawareness of one's handicap. After stroke or traumatic brain injury, usually with involvement of the non-dominant hemisphere (right side in 95% of people).

- Stroke

Anoxic

Definition

Conditions characterized by the absence of free oxygen.

Ansa Lenticularis

Definition

Fiber tract of the subthalamus. The lenticular fasciculus and ansa lenticularis together form the pallidothalamic projection, the biggest efferent of the globus pallidus. The fibers terminate in the ventral lateral thalamic nucleus, which in turn projects to parts of premotor cortex (area 6) and of the supplementary motor area. They arrive at the thalamic nuclei via the thalamic fasciculus.

Ansa Peduncularis

Definition

In the ansa peduncularis short tracts project from the amygdaloid body to the hypothalamus and to the medial thalamic nucleus.

Antagonist Muscle

Definition

Muscle acting to produce opposite motion or torque at a joint.

- Impedance Control

Antagonistic Innervation

Definition

Antagonistic innervation refers to the case in which an organ is controlled by two different kinds of nerves (double innervation), and the effects of nerves on the organ are antagonistic. An example would be the effect of sympathetic innervation of the heart which is facilitatory versus that of parasympathetic innervation which is inhibitory.

Antennal Lobe

Definition

First central area of the insect olfactory system. This structure receives input from the olfactory nerve in the antennae and projects to the mushroom body. The architecture is very similar to the vertebrate olfactory bulb.

► Olfactory Information

Anterior Cerebellar Lobe

Synonyms

► Lobus cerebelli ant; ► Anterior lobe of cerebellum

Definition

The anterior lobe is the part of the cerebellum rostral to the primary fissure, and is composed of vermis (lingula, central lobule and culmen) as well as hemispheres (quadrangular lobe, anterior part, and ala lobuli centralis). Functionally this subdivision has practically no significance, since the cerebellum evidences a functional arrangement in a vertical direction (vermis, intermediate part, lateral part).

► Cerebellum

Anterior Cingulate Cortex

Definition

The anterior cingulate cortex is the area of the cerebral cortex located in the medial wall of the cerebral

hemispheres, just above the corpus callosum. The anterior cingulate has a major role in behavioral drive and regulation of affective behavior. It has extensive connections with the prefrontal cortex, amygdala, thalamus, and striatum; receives inputs from pain pathways, and contributes to the corticospinal tract.

Anterior Column

Synonyms

► Funiculus ant; ► Anterior funiculus

Definition

The white matter between anterior median fissure and ventral root forms the anterior column, containing:

- Anterior pyramidal tract
- Medial longitudinal fasciculus

► Medulla Spinalis

Anterior Commissure

Synonyms

► Commissura ant.

Definition

The anterior commissure is a bundle of nerve fibers connecting both hemispheres. It crosses the midline anterior to the third ventricle. The anterior commissure runs between parts of the temporal lobes (e.g. parahippocampal gyrus, amygdala) as well as between olfactory areas of the two hemispheres.

► Telencephalon

Anterior Commissure, Anterior Limb

Synonyms

► Commissura ant., pars ant; ► Anterior commissure, anterior part

Definition

Very narrow branch of the anterior commissure passing to the anterior perforated substance, where it joins the olfactory tract.

► Diencephalon

Anterior Commissure, Posterior Limb

Synonyms

► Commissura ant., pars post; ► Anterior commissure, Posterior part

Definition

Main part of the anterior commissure passing to the frontal portion of the temporal lobe, hippocampus and amygdaloid body.

► Diencephalon

Anterior Corticospinal Tract

Synonyms

► Tractus corticospinalis ant.

Anterior Forceps

Synonyms

► Forceps minor; ► Minor forceps

Definition

The commissural fibers running in the splenium of the corpus callosum from the occipital lobe embark on a U-shaped course and are shaped like forceps. They are called the posterior forceps. The anterior forceps is formed from similar U-shaped fibers in the frontal lobe.

► Telencephalon

Anterior Gray Commissure

Synonyms

► Commissura grisea ant.

Definition

In the gray commissure, the nuclear regions, more precisely the intermediate substance, of both halves of spinal cord meet each other. Whereas the anterior gray commissure runs ventrally to the central canal, the posterior gray commissure passes dorsally to the spinal canal.

► Medulla Spinalis

Anterior Group Hox Genes

Definition

Hox genes expressed in the anterior region and located toward the 3 end of Hox clusters, this group includes Hoxa1.

► Hox Gene-Related Respiratory Control Disturbance

Anterior Horn

Synonyms

► Cornu ant; ► Anterior horn of the spinal cord

Definition

In the anterior horn are situated the large alpha motoneurons which innervate the skeletal muscles. But the gamma motoneurons responsible for innervation of intrafusal fibers are also encountered here. They play an important role in the refinement of muscle-spindle sensitivity. The anterior horn evidences a somatotopic arrangement and has two zones:

- Medial motor cells
- Lateral motor cells

► Medulla Spinalis

Anterior Hypothalamic Nucleus

Synonyms

►Nucl. ant. hypothalami; ►Anterior nucleus of hypothalamus

Definition

The anterior hypothalamic nucleus has myriad diverse afferents, e.g. from the limbic system, other hypothalamic nuclei and the Mesencephalon. Efferents go to the surrounding hypothalamic nuclei, but also to the rhombencephalic nuclear regions.

Functionally, the nucleus is involved in regulation of body temperature, respiration and cardiovascular tasks (context: affective defense behavior).

►Diencephalon

Anterior Limb of Internal Capsule

Synonyms

►Capsula interna, crus ant; ►Anterior limb of internal capsule

Definition

The internal capsule features the following pathways: posterior limb of internal capsule:

- Pyramidal tract
- Superior thalamic peduncle
- Posterior thalamic peduncle
- Parietopontine tract
- Corticopontinal fibers

Anterior limb of internal capsule:

- Frontopontine tract
- Anterior thalamic peduncle

►Telencephalon

Anterior Lobe of Cerebellum

Definition

Several classifications are used to subdivide the cerebellum based on anatomical, phylogenetic and

functional (i.e. termination of cerebellar afferents and efferents) findings. Anatomically, both sagittal and horizontal subdivisions can be distinguished. The cerebellum consists of two large lateral parts called the hemispheres and a midline structure, the vermis.

The cerebellum is further subdivided into three major horizontal components, the flocculonodular, anterior and posterior lobes, the latter two forming the corpus cerebelli. The anterior lobe is separated from the posterior lobe by the primary fissure and the flocculonodular lobe is separated from the posterior lobe by the posterolateral fissure.

►Posture Role of Cerebellum

Anterior Lobe of the Hypophysis

Synonyms

►Adenohypophysis

Definition

The glandular tissue of the anterior lobes produce gonadotropic hormones that regulate the secretion of peripheral hormone glands (ACTH → NNR hormones, TSH → thyroid gland hormones, inter alia) but also effector hormones that act directly (PRL → mammary gland, FSH → gonads inter alia). Regulation is effected via releasing and release-inhibiting factors secreted by neurons of the hypothalamus (infundibular nucleus) into the portal system of the gland.

►Diencephalon

Anterior Median Fissure

Synonyms

►Fissura mediana ant.

Definition

Fissure in the ventral side of the spinal cord.

►Medulla Spinalis

Anterior Occipital Sulcus

Definition

Relatively constant continuation of the preoccipital notch.

The sulcus could be called a “three-lobe corner,” since here the occipital lobe, parietal lobe and temporal lobe meet.

► Telencephalon

the olfactory nerve (Cranial Nerve I) to the olfactory bulb, an evagination of the ventral forebrain that is the rostral-most portion of the telencephalon and is commonly found just behind (or above) the nasal cavity. The general circuitry of the olfactory bulb is similar to that of the retina in that a) incoming sensory information is parsed into separate data streams, and b) it contains two layers of inhibitory interactions to reinforce the differences between these data channels. Axons of the two major output neurons, the mitral and tufted cells, travel caudally and ventrally in the bulb, coalescing to form the lateral olfactory tract (LOT) that courses along the ventrolateral surface of the forebrain.

The area directly behind the olfactory bulb is often referred to as the ►olfactory peduncle (or retrobulbar area, Fig. 1). The peduncle contains the anterior olfactory nucleus (AON) as well as two other much smaller regions, the *tenia tecta* (or dorsal hippocampal rudiment) and the dorsal penduncular cortex. The olfactory peduncle merges caudally with the ►olfactory tubercle on the medial side and with the piriform cortex laterally. The core of the peduncle is formed by a subependymal layer that is continuous with the rostral extension of the lateral ventricle, and comprises the

Anterior Olfactory Cortex

► Anterior Olfactory Nucleus

Anterior Olfactory Nucleus

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Synonyms

Anterior olfactory cortex

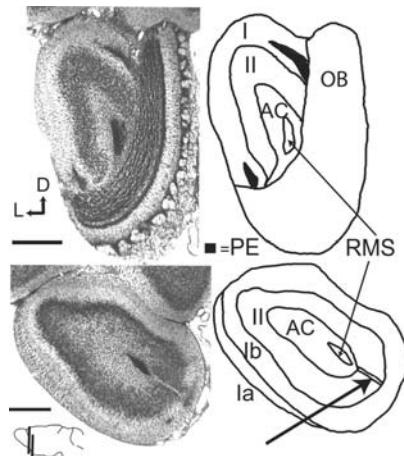
Definition

The primary component of the region of the telencephalon located between the olfactory bulb and the ►piriform cortex.

Characteristics

The olfactory system is highly developed in vertebrates, particularly in “macroscopic” mammals (such as many rodents) where olfaction is the primary sensory system used to navigate in the world. As olfactory ability has evolved, there has been a concurrent increase in the size and complexity of cortical structures dedicated to encoding and deciphering olfactory information (►cortical circuitry). Below is an overview of one of these cortical regions, the ►anterior olfactory nucleus (AON), which plays a central, though largely uncharted role in olfactory information processing [1].

In vertebrates, odor information is transduced by olfactory receptor neurons that line the nasal cavity (or olfactory rosette in fishes). The information is sent via



Anterior Olfactory Nucleus. Figure 1 *Left panels:* Photomicrographs of coronal Nissl-stained sections at two levels of the rat olfactory peduncle (Small panel on bottom left shows the approximate location of these two sections). *Right panels:* diagrams of cytoarchitectural features in the left panels. The two top panels show an anterior section that includes *pars externa* (PE). The bottom panels depict a section approximately 600 µm more caudal, where *pars principalis* predominates. Abbreviations: I = Layer I of the AON; Ia, Ib = sublaminae within Layer I; II = Layer II of *pars principalis*; LOT = Lateral olfactory tract; RMS = Rostral migratory stream; AC = Anterior limb of the anterior commissure; OB = Olfactory bulb; D, L = dorsal and lateral. Scale bars = 150 µm.

“rostral migratory stream” that provides new interneurons to the olfactory bulb throughout life. Overlying the rostral migratory stream is the anterior or olfactory limb of the anterior commissure, the source of centrifugal fibers, including some from the medial forebrain bundle, to the region.

The Anterior Olfactory Nucleus is Comprised of two Separate Structures

The first is a thin ring of cells encircling the rostral end of the olfactory peduncle known as “*pars externa*.” *Pars externa* contains large cells with apical dendrites that have long and thin dendritic spines. Evidence gathered from injections of neuronal tracers suggests that there are topographical projections from the olfactory bulb to *pars externa*: cells in the lateral and medial portions of the bulb project to corresponding regions in *pars externa*. No evidence for patterning in the rostral-caudal dimension has been reported. Axons from *pars externa* travel via the anterior commissure to the contralateral olfactory bulb where they synapse in the internal plexiform layer.

The second and largest region, “*pars principalis*,” appears as a two-layered structure in coronal sections from rodents (Fig. 1). The deepest (Layer II) is a thick ring of cell bodies surrounding the anterior limb of the anterior commissure. Many of the resident neurons are similar to neocortical pyramidal cells with a thick apical dendrite, several basal dendrites, and dense dendritic spines. The outer layer has been subdivided into a superficial zone (Layer Ia, which contains the output axons from the olfactory bulb) and a deeper area (Layer Ib) where these axons synapse with the dendrites of Layer II neurons. The subdivisions of Layer I are easily discernable in Nissl-stained sections based on patterns of glial staining.

Since the only landmark in *pars principalis* is a small, cell-free gap in the ventromedial region of Layer II (Fig. 1), most studies divide the region on the basis of the “compass points,” yielding *pars dorsalis*, *pars ventralis*, *pars medialis*, *pars lateralis*, and *pars posterioralis* (often combined with *pars ventralis* to form “*pars ventroposterioralis*”). However, since there are few obvious ways to make these subdivisions, the boundaries employed are often arbitrary and exhibit wide variations, leading to considerable confusion [2].

Pars lateralis is often defined as the area that lies directly under the major portion of the lateral olfactory tract. Caudally, *pars lateralis* merges with the piriform cortex. The transition occurs with the emergence of a deep polymorphic cell layer (Layer III, the “polymorphic cell zone” of the piriform cortex), and the emergence of the pre-endopiriform and endopiriform nuclei.

Pars medialis appears in anterior regions caudal to the remnant of the granule cell layer of the olfactory bulb. In posterior regions the structure is replaced by the ventral tenia tecta. The ventral border of the subregion

is the cell-free notch in Layer II, while the dorsal border can be difficult to delineate and is often determined by examining variations in cell size and density.

Pars dorsalis is typically defined by exclusion: it is found between *pars lateralis* and *pars medialis* on the dorsal aspect of the AON. The superficial plexiform layer overlying both *pars dorsalis* and *pars medialis* has few myelinated fibers except in the area of transition with *pars lateralis*, reflecting a relatively small innervation by the olfactory bulb. The caudal border of *pars dorsalis* occurs with the emergence of the dorsal peduncular cortex and the transition zone between the AON and the frontal neocortex.

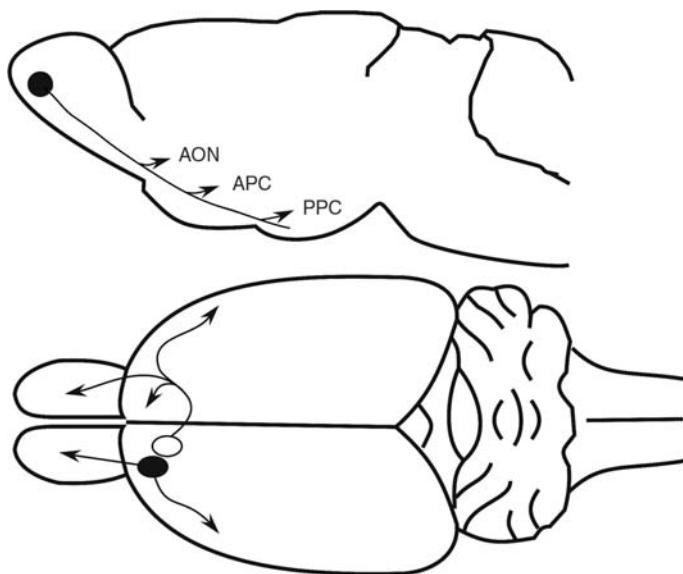
Pars ventralis can also be defined by exclusion as the area between *pars lateralis* and *pars medialis* on the ventral surface. It is relatively small, often only slightly larger than *pars medialis* in coronal sections. In caudal areas, *pars ventralis* merges with *pars posterioralis*. In posterior regions this area forms the caudomedial boundary of the AON with the olfactory tubercle.

Role in the Olfactory Information Processing

The position of the AON in the olfactory circuit suggests that it plays a crucial role in olfactory information flow (Fig. 2). The fact that the region receives a substantial input from the olfactory bulb has been known for a century; indeed, Ramon y Cajal formed his “law of dynamic polarization” (information flows from the axon of one cell to the dendrites of the next) partly by observing the projection of mitral and tufted cell axons onto the dendrites of AON cells. There is a broadly topographical organization in the anterior olfactory peduncle and LOT, with fibers from the dorsal olfactory bulb contacting the dorsal AON, ventral bulb to ventral AON, etc. The LOT continues through the olfactory peduncle to innervate the piriform cortex. The projection appears to be organized in that deep relay cells in the bulb (e.g., mitral cells and the deep tufted cells) send axons all the way to the entorhinal cortex while more superficial tufted cells rarely project caudal to the AON and rostral piriform cortex. Evidence for more specific topographical patterns is difficult to find, indeed, it appears that individual projection neurons innervate broad regions in both the AON and PC.

The AON sends a substantial reciprocal input back to the olfactory bulb. The connections are so widespread that the AON is capable of interacting at nearly every synaptic step in bulb processing. Significant regional differences have been observed these projections. Converging evidence indicates that *pars medialis* fibers are heaviest in the deep granule cell layer of the ipsilateral bulb, while *pars externa* predominately innervates the contralateral internal plexiform layer. The remaining regions have bilateral projections to broader regions.

The AON projects predominantly to the ventromedial portion of anterior piriform cortex (APC), primarily to the region deep to the LOT and extending from the



Anterior Olfactory Nucleus. Figure 2 Schematic view of a mouse or rat brain from the lateral (top) and dorsal (bottom) sides. Top panel depicts the trajectory of the lateral olfactory tract, leaving the olfactory bulb (on left) and distributing information to the anterior olfactory nucleus AON, anterior piriform cortex APC and posterior piriform cortex PPC. Bottom panel shows the ipsilateral (bottom) projections of the AON (to the olfactory bulb and anterior piriform cortex) and contralateral (top) projections (to opposite AON, olfactory bulb, and APC).

olfactory tubercle laterally to just beyond the border of the LOT. Axons run primarily in deep Layer Ib, adjacent to the compact cell body layer. A broad topography exists, with the heaviest projections from *pars dorsalis*, *pars lateralis* and *pars ventroposterioralis* going to the dorsolateral, central, and ventromedial APC respectively. There is an abrupt decrease in labeled fibers at the boundary with the posterior piriform cortex.

Back-projections from the piriform cortex to the AON are also complex. The APC projects primarily to *pars lateralis*, with a smaller projection to both *pars dorsalis* and *pars ventroposterioralis*, and maintains the broad medial-to-lateral topography displayed in the projections from AON. Interestingly, connections from PPC to the AON are apparently plentiful to all parts of the AON except for *pars externa*.

While much remains to be learned about the precise nature of the projections into and out of the AON, it is obvious that the region is involved in the feedforward regulation of information passing from the bulb to the anterior piriform cortex, and in the feedback regulation of the return circuit. Further, it regulates information flow between the left and right olfactory bulbs via the anterior commissure, and it serves a similar role in distributing information to the left and right piriform cortices.

Development

AON neurons in the rat are generated during the last week of embryonic development in two distinct

patterns. All divisions exhibit a caudal-to-rostral gradient of neurogenesis similar to that seen in the PC. A second superficial-to-deep gradient is also observed which contrasts with the “inside-out” sequence typical of cortical areas. Patterns of axonal ingrowth from the bulb follow the sequence of cell proliferation. Axonal projections from *pars externa* develop sooner than those from other, deeper AON regions. Similarly, the earliest contralateral projections of *pars lateralis* arise from its caudal- and superficial-most regions, while more rostral, deeper cells send projections 2–3 days later. Finally, three different patterns in the postnatal growth of the subregions of the AON have been reported: a) relatively little expansion (*pars lateralis*), b) moderate growth with overshooting of size and subsequent reduction (*pars medialis*), and c) exuberant growth with subsequent size reduction (*pars dorsalis* and *pars ventroposterior*). Such independent development of the various subregions is compelling evidence that they may serve different functions.

Anterior Olfactory Nucleus or Anterior Olfactory Cortex?

Several have suggested that the AON would more properly be labeled the anterior ▶olfactory cortex. Arguments include the fact that the area is rigidly laminated and populated by pyramidal-shaped cells characteristic of the cerebral cortex, and that it gradually merges with the three-layered piriform cortex. An argument based on functional attributes has been made by Haberly [3], who suggested that the AON shares features with the primary sensory cortices of other

sensory modalities. Haberly split the traditional AON into two functionally distinct areas (the “anterior” and “medial” olfactory cortices), opening the door for further research examining regional differences within the structure. In light of its substantial connections with both the olfactory bulb and the piriform cortex, the AON is likely to play a central role in olfactory information processing; understanding this role will lead to a more complete understanding of vertebrate olfaction.

References

1. Brunjes PC, Illig KR, Meyer EAA (2005) A field guide to the anterior olfactory nucleus (cortex). *Brain Res Rev* 50:305–335
2. Meyer EAA, Illig KR, Brunjes PC (2006) Differences in chemo- and cytoarchitectural features within *pars principalis* of the rat anterior olfactory nucleus suggest functional specialization. *J Comp Neurol* 498:786–795
3. Haberly LB (2001) Parallel-distributed processing in olfactory cortex: New insights from physiological and morphological analysis of neuronal circuitry. *Chem Senses* 26:551–576

Anterior Parolfactory Sulcus

Synonyms

- Sulcus parolfactorius ant.

Definition

The subcallosal area is enclosed by the anterior parolfactory sulcus and posterior parolfactory sulcus.

- Telencephalon

Anterior Peduncle of Thalamus

Definition

Corticothalamic and thalamocortical fibers together form the thalamic peduncles:

- Anterior peduncle of thalamus: rostral parts of the cerebral cortex and of cingulum
- Inferior peduncle of thalamus: temporal striate cortex, retrosplenial region
- Posterior peduncle of thalamus: occipital lobe without area 17 (striate cortex)

- Superior peduncle of thalamus: precentral gyrus, postcentral gyrus, prefrontal area.

- Diencephalon

Anterior Perforated Substance

Synonyms

- Subst. perforata ant.

Definition

The anterior perforated substance has a typical, perforated appearance and lies beneath the putamen and globus pallidus, at the site where the olfactory bulb divides into the medial stria and lateral stria (olfactory trigone). It passes laterally in the direction of the limen insula and contains various nuclei of the secondary, olfactory area and limbic system.

- Telencephalon

Anterior Poliomyelitis

Definition

- Polioencephalitis

Anterior Pyramidal Tract

Definition

In the pyramidal decussation 70–90% of the fibers cross to the contralateral side forming the lateral pyramidal tract.

The remaining 10–30% continue their ipsilateral course and descend in the anterior pyramidal tract crossing, however, on entering the gray matter of the spinal cord and innervating also the motoneurons. The tract extends only as far as the cervical cord.

- Nerves

Anterior Spinocerebellar Tract

Synonyms

► Tractus spinocerebellum ant

Definition

This tract conducts proprio- and exteroceptive impulses (skin receptors, muscle spindles, tendon spindles) of the spinal cord (lumbar cord) to the cerebellum without synapsing in the lateral column. They are the only afferent fibers to enter the cerebellum via the superior cerebellar peduncle.

► Cerebellum

Anterior Thalamic Nucleus

Synonyms

► Nuclei ant. thalami; ► Anterior nuclei of thalamus

Definition

This nucleus of the lateral nuclear group is divided into three parts: anteromedial nucleus, anterodorsal nucleus, anteroventral nucleus. Afferents come from the mammillary body, lateral nucleus and the mammillary body, medial nucleus.

In addition, the nucleus has reciprocal connections with the limbic cortex of the cingulate gyrus, the retrosplenial area and the pre- and parasubiculum.

Functions in this regions are emotion, motivation and short-term memory.

► Diencephalon

Anterograde Amnesia

Definition

New memories are not formed following the incident (e.g., trauma), but events prior to the incident can be remembered.

► Amnesia

► Memory Improvement

Anterograde Degeneration

Definition

Anterograde degeneration is the breakdown of fibers (axons) that occurs distal to the point of injury of an axon i.e., away from the cell body. In contrast, retrograde changes take place toward, and can include, the cell body.

Anterograde Tracing Techniques

Definition

Neuron tracing techniques take advantage of the fact that axoplasmic transport of materials goes in both directions within the axon. Anterograde transport is away from the cell body, and has fast (400 mm/day) and slow (1–5 mm/day) components that involve the microtubules. Early studies utilized reduced silver techniques or radio autographic methods using labeled amino acids, to outline axons and/or terminals. A variety of immunocytochemical methods are now used to trace and reveal transmitters and other neuron components.

Anterolateral Column

Synonyms

► Tractus anterolat; ► Anterolateral tract

Definition

The white matter between the ventral root and dorsal root gives rise to the lateral column, containing:

1. anterolateral column with
 - anterolateral fasciculus
 - parts of the anterior spinocerebellar tract.
2. posterolateral column with
 - posterior spinocerebellar tract
 - parts of the anterior spinocerebellar tract
 - lateral pyramidal tract.

► Medulla Spinalis

Anterolateral Fasciculus

Synonyms

► Lemniscus spinalis; ► Spinal lemniscus

Definition

Somatotopically organized column of the spinal cord containing somatosensory afferents in the direction of the brain. The following tracts course in this column:

- Spinotectal tract
- Spinothalamic tract
- Spino-anular tract
- Spino-olivary tract

► Medulla Spinalis

Anterolateral Tract (Pain & Temp Pathway)

► Anterolateral column

► Tractus anterolat.

The fibers in this pathway originate from neuron cell bodies in the dorsal gray of the spinal cord, cross the midline in the anterior commissure at their level of origin, and ascend the spinal cord in its anterolateral quadrant. A portion of the tract, the spinothalamic fibers, ends in the thalamus. Many of the ascending anterolateral quadrant fibers end in the brainstem reticular formation.

Anti-aliasing Filter

Definition

A filter placed before a sampling element, designed to prevent frequency components higher than half the sampling frequency entering the sampler. Such

frequency components would be incorrectly sampled according to the Nyquist sampling theorem.

► Nyquist Sampling Theorem

► Signals and Systems

Anti-amnesic Agents

Definition

Agents that reverse or ameliorate amnesia.

► Memory Improvement

Anticipatory Motor Action

Definition

Skilled action requires that we predict the sensory consequences of our actions, since the sensory signals conveying information about the world and our body are processed too slowly to allow fast, skilled movements.

For example in rapidly reaching for an object, we estimate the distance between our hand and the object and, in an anticipatory, feed-forward manner, compute the time at which we need to activate the appropriate muscles to brake the movement at the proper point in space.

Anticipatory Postural Adjustment (APA)

Definition

A predictive motor response that acts to counter, in a preemptive manner, the postural destabilization associated with a forthcoming movement. For forward and backward stepping movements, the APA acts to propel the center of mass of the body toward the stance limb prior to the lifting of the swing foot, so as to counter the tendency of the body to fall laterally toward the unsupported side during the swing phase.

► Anticipatory Postural Responses

► Postural Strategies

Anticipatory Postural Responses

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Synonyms

Feedforward postural control; Preparatory postural adjustments

Definition

► **Anticipatory postural adjustments** are defined as the activation of postural muscles in a feedforward manner before a voluntary movement begins, in anticipation of the destabilizing forces caused by the movement.

Characteristics

Investigation of the characteristics of anticipatory postural adjustments was initiated in the 1960s, when researchers in Russia studied the way humans control posture to steady the execution of tasks. This original research showed that when a standing human is asked to raise one arm, postural (leg and trunk) muscles were activated both before and after the activation of the prime mover (arm) muscles. The first part of the postural activity was in preparation for the movement, to compensate in advance for the destabilizing effects of the movement. In this case, leg and trunk muscles were activated more than 50 ms in advance of the prime mover arm muscles. Thus, anticipatory postural adjustments are activated in a feedforward manner, in anticipation of any sensory feedback associated with potential postural instability related to the movement. In addition, the postural muscles were activated after the arm muscles in a feedback manner to stabilize the body further [1,2].

When specific muscle synergies were identified as basic units of reactive postural control, a study was performed to determine if the same muscle synergies used in feedback postural control were also used during anticipatory postural adjustments. Cordo and Nashner [3] asked subjects to perform a task that required anticipatory postural adjustments (pushing or pulling on a handle while standing in a reaction time task) and measured the muscle response organization of the postural muscles activated in advance of the arm muscles (biceps or triceps). Results showed that the very similar postural response synergies used to react to external perturbations to balance control were activated as anticipatory synergies, before the arm flexion or extension movements. Thus, when a participant pulled on the handle in front of him/her, first the gastrocnemius, hamstrings and

trunk extensor muscles were activated, followed by the prime mover the biceps.

To determine the extent to which anticipatory postural synergies adapt to the initial support conditions, researchers compared anticipatory postural responses under two conditions. In the first condition, subjects were asked to stand without additional support, as described above. In the second condition, subjects leaned forward against a horizontal bar at chest height, thus eliminating the efficacy of postural muscle activation in the legs. The research showed that anticipatory postural muscle responses in the legs were reduced or disappeared when subjects were supported. In addition, the voluntary reaction time latencies in the arm were shorter when subjects did not need anticipatory postural muscles in the legs for stability.

These data suggest that there is a preselection of an anticipatory postural muscle synergy associated with each voluntary movement task, as a function of the synergy's contribution to postural stability. This preselection or tuning of sensorimotor systems in anticipation of tasks is often described as "central set." ► **Central set** is defined as a state of the nervous system readiness that is influenced or determined by the context of a task [4]. In the experiment described above, the subject's leaning against a horizontal bar changed the context under which balance would occur during the arm movement task. As a result of the change in context, there was an associated change in central set. A different set of anticipatory postural muscles was selected in advance of the movement, based on their ability to contribute to balance under the new task conditions [5,6].

Anticipatory adjustments are usually discussed in relation to tasks in which postural muscles are activated in advance of prime mover muscles; however, anticipatory control based on central set is also used when postural adjustments to balance threats are scaled in amplitude according to the expected perturbation velocity or size. Experiments designed to test the effect of expectation on postural response characteristics used three platform perturbation contexts: (i) serial versus random conditions, (ii) expected versus unexpected conditions and (iii) practiced versus unpracticed conditions. Results showed that expectation contributed to the modulation of the amplitude of postural responses, with participants giving hypermetric responses when they expected a larger perturbation than they received and hypometric responses when they expected a smaller one. There was also a practice effect, with a reduction in postural response magnitude and in the amplitude of antagonist muscle responses with repeated trials. However, central set did not affect EMG onset latencies. The authors noted that when different perturbations were presented in random order, all scaling disappeared. Results that suggest that scaling

of postural responses is based on prediction of what is needed in a specific context [7,8].

Anticipatory postural adjustments are also used in arm movements in which one arm serves a postural role (holding an object) and the second arm is the prime mover manipulating the object. In experiments examining anticipatory postural adjustments in this context, a 1 kg weight was lifted from the subject's forearm either by the subject or the experimenter. Results indicated that when the subject actively unloaded the arm, there was preparatory biceps muscle inhibition to keep the arm from moving upward during unloading. There was also a coupling between the anticipatory reduction in the biceps EMG of the arm holding the object and the onset of contraction of the biceps of the lifting arm. This inhibition of the biceps activity was not found in the condition in which the experimenter lifted the object (passive unloading) [9].

Animal experiments have been performed to examine the neural circuitry contributing to these anticipatory adjustments [10]. Cats were trained to perform a leg-lifting task that required them to activate postural muscles simultaneously in the other three legs when they lifted the initial leg. Researchers found direct stimulation of the motor cortex or the red nucleus in the area of the forelimb flexors could also produce the leg-lifting movement. When the cortex or red nucleus was stimulated, the leg-lifting movement was accompanied by a postural adjustment in the other limbs, initiated in an anticipatory or feedforward manner. This has led to the hypothesis that postural adjustments are organized at the bulbospinal level and that the pyramidal tract activates these postural response centers as it sends descending commands to the prime mover muscles. In addition to the basic control of postural adjustments occurring at this level, there is also modulation of these responses by other neural subsystems, including the cerebellum.

References

1. Belen'kii VY, Gurfinkel VS, Paltsev YI (1967) Elements of control of voluntary movements. *Biofizika* 12:135–141
2. Chong RKY, Horak FB, Woollacott MW (2000) Parkinson's disease impairs the ability to change set quickly. *J Neurol Sci* 175:57–70
3. Cordo P, Nashner L (1982) Properties of postural adjustments associated with rapid arm movements. *J Neurophysiol* 47:287–302
4. Prochazka A (1989) Sensorimotor gain control: a basic strategy of motor systems? *Prog Neurobiol* 33:281–307
5. Horak FB (1996) Adaptation of automatic postural responses. In: Bloedel JR, Ebner TJ, Wise SP (eds) *The acquisition of motor behavior in vertebrates*. MIT, Cambridge, pp 57–85
6. Shumway-Cook A, Woollacott MH (2006) Motor control: translating research into clinical practice, 3rd edn. Lippincott Williams & Wilkins, Philadelphia
7. Hansen P, Woollacott MH, Debu B (1988) Responses to sequential postural perturbations. *Exp Brain Res* 73:627–636
8. Horak F, Dierer HC, Nashner LM (1989) Influence of central set on human postural responses. *J Neurophysiol* 62:841–853
9. Hugon M, Massion J, Wiesendanger M (1982) Anticipatory postural changes induced by active unloading and comparison with passive unloading in man. *Pflugers Arch* 393:292–296
10. Massion J (1992) Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol* 38(1):35–36

Anticonvulsants

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Synonyms

Anti-seizure medicine; Anti-epileptic medicine

Definition

Anticonvulsants are medicines used to stop seizures or prevent recurrent seizures in ►epilepsy. Currently, none of the anticonvulsants are known to actually be anti-epileptic in that they do not prevent or cure epilepsy.

Characteristics

Overview

Anticonvulsants are medicines used to stop seizures or prevent recurrent seizures in epilepsy. A single ►seizure may affect 2–4% of the entire population, while recurrent unprovoked seizures or epilepsy may affect 0.5% [1]. Seizures and epilepsy have many causes and are discussed in detail elsewhere, however particular anticonvulsants are often more suited to a particular type of epilepsy. According to the International League Against Epilepsy (<http://www.ilae-epilepsy.org/>), these types are broadly broken down into (i) localization related epilepsy (LRE), (ii) generalized epilepsy, which includes absence epilepsy (GE), (iii) undetermined focal or generalized epilepsy (UE) which includes some

forms of myoclonic epilepsy and (iv) situation-related syndromes. Seizures due to situation-related syndromes (fever, infection, etc) are treated in concert with their underlying cause. Approximately 25% of patients have medically refractory epilepsy that does not respond favorably to two or more medications. Treatment decisions, consequences of seizures, and specific management of seizures and epilepsy are addressed in numerous texts.

A variety of conditions have been treated by anticonvulsant drugs. These have included ►neuropathic pain, migraine, ►movement disorders, sleep disorders and ►mood and anxiety disorders.

Causes of Seizures and the Basis of Drug Design

Seizures are caused by imbalances between excitation and inhibition in the normal pattern of communication between neurons in the central nervous system. The imbalances lead to abnormal, repetitive discharges that are often sustained by the underlying neuronal circuitry. Typically, the circuit re-exites itself leading to the sustained, repetitive discharges that are the hallmark of seizures. Due to their innate recurrent circuitry, certain regions of the central nervous system are more prone to seizures, such as the ►hippocampus. Abnormal formation of recurrent circuitry due to developmental or other causes can also underlie seizures and epilepsy.

Neuronal communication happens through a combination of electrical and chemical signaling. Communication along a neuron is electrical while communication between neurons is mostly chemical. Neurotransmitters mediate the chemical communication between neurons and ►gap junctions mediate electrical transmission between neurons. Proteins that mediate the various means of communication are the molecular targets of anticonvulsants. The mechanisms of neuronal communication and the networks that sub-serve them are under the control of developmental as well as environmental influences. Thus, the molecular targets of anticonvulsants vary according to developmental and environmental influences. Achieving the balance of preventing abnormal and preserving normal communication is the ultimate goal of anticonvulsant drug design.

Most anticonvulsants interfere with at least one form of neuronal communication [1–3]. Electrical and chemical communication is either depolarizing or excitatory or hyperpolarizing or inhibitory. ►Voltage-gated ion channels are proteins that mediate selective ionic fluxes across the neuronal membrane. These channels open in response to the potential, changing or static, of the neuronal membrane around them. ►Neurotransmitter receptor-channels open in response to the binding of a neurotransmitter. The relative concentration of ions on either side of the membrane, the membrane potential and the relative ion selectivity (e.g., sodium, potassium, calcium, chloride, etc.) of the channel direct the

overall net flux of ions across the neuronal membrane according to the ►Goldman–Hodgkin–Katz equation. The net flux of ions through the ►ion channels can result in depolarizing or hyperpolarizing influences that in turn affect neuronal communication.

Neurotransmitter release involves many tightly linked processes. Only specialized structures and regions are involved in neurotransmitter release. Initiation involves either local voltage-gated changes or second messenger systems activated by neurotransmitters themselves. Vesicles, membranous spheres filled with neurotransmitter by pumps within the vesicular membrane, fuse with presynaptic membranes to release neurotransmitter into the ►synaptic cleft that separates the presynaptic neuron from the postsynaptic neuron. Alternatively, neurotransmitters may be directly pumped into the cleft. Neurotransmitters are either enzymatically ►degraded in the cleft or pumped back out of the cleft by ►transporters into the presynaptic terminal, postsynaptic neuron or surrounding ►glial support cells. From there it is either enzymatically broken down, recycled and shuttled across membranes, resynthesized or pumped backed into vesicles.

While each neuronal communication process (e.g., excitation, neurotransmitter release) can be thought of as “generic”, these must all be differentiated when considering the effects of anticonvulsants and rational drug development and design. Since most anticonvulsants are unable to differentiate between “good” communication and “abnormal” communication (seizures), side effects are the result. In terms of understanding the different types of seizures, epilepsy and anticonvulsants, it must be kept in mind that specific types of neurons in unique anatomical locations use specific subtypes of channels for each individual process. The few characterized genetic epilepsies occur through single gene (often ion channel) defects and therefore rational drug design should seek to directly restore, enhance or limit function (depending on loss or gain of function) of the affected ion channel. In principle, this should be considered even in cases of epilepsies caused by multiple genetic defects.

The ideal anticonvulsant, therefore, should recognize and correct not only specific ion channel dysfunction in a particular brain region, but also recognize that defects are also likely limited to unique aspects of neuronal structure. Neurons are multipolar structures, that is, they have unique compartments designed for unique functions. As part of this, unique subtypes of ion channels are segregated to unique compartments. For example, a particular type of ►voltage-gated potassium channel (hyperpolarizing) may be segregated to dendrites, while another type (also hyperpolarizing but with different voltage-dependent properties and pharmacological sensitivity) may be segregated specifically to presynaptic terminals. Neurons themselves are also

segregated as inhibitory or excitatory, depending on the type of neurotransmitter(s) they may (predominantly) release. Each class of neuron may also express a unique complement of subtyped ion channels.

Historical Perspectives of Drug Development

Up until recently, the anticonvulsant drugs in use were developed not only before the genetics of epilepsy were imagined but before the nature of neurotransmission itself was understood. As a result, most drugs were discovered through brute force trial and error in animal models. These animal models typically used injected pro-convulsants or direct electrical stimulation. As such, these often did not directly mimic human seizures or epilepsies, occasionally resulting in a mismatch between model and human efficacy. This has been somewhat improved by the use of different animal models of genetic epilepsies [1]. Effective parent compounds (e.g., carbamazepine) have been used as models for later drugs (oxcarbazepine) with better side-effect profiles.

As techniques in neuroscience have advanced, for example the development of ►patch-clamp techniques for recording currents through single ion channels in the early 1980s, the mechanisms of anticonvulsant drugs have more recently become better understood. Despite advances in molecular neuroscience, many anticonvulsants are still classed according to the general types of ion channels that are affected. ►Voltage-gated sodium channels (VGSCs) are somewhat broadly categorized while ►voltage-gated calcium channels (VGCCs) are segregated according to their biophysical properties (T, P/Q, N, and L/HVA-type) due in part to the fact that most anticonvulsant drugs do not themselves segregate the different molecular entities of ion channels.

Similarly, as more detailed descriptions of neurotransmission are presented, it has been found that anticonvulsant drugs can affect chemical neurotransmission at all stages of the process from neurotransmitter synthesis, vesicular fusion, neurotransmitter reuptake as well as neurotransmitter receptors themselves. Inhibitory transmission, primarily mediated by ►GABA-A receptors (GABARs), is often enhanced by anticonvulsants while excitatory transmission, primarily mediated by glutamate receptors, is typically reduced. The effects of anticonvulsants on glutamate receptors are pharmacologically divided into ►AMPA-type (GluRs), ►kainate-type (KARs) and ►NMDA-type (NMDARs) primarily because it is still contentious how their molecular diversity equates to their functional and pharmacological diversity. NMDARs and perhaps KARs, due to their ability to flux the second messenger calcium, hold important distinction because of their role in triggering specific forms of synaptic plasticity and thus may play a role in epileptogenesis. Another class of glutamate receptors that is directly linked to second messenger systems, the

►metabotropic glutamate receptors (mGluRs), has not been demonstrated to be a target of currently used anticonvulsant drugs.

Valproic acid has the broadest pharmacological and clinical spectrum of all of the anticonvulsant drugs [2]. Most of its anticonvulsant effects can be attributed to enhancing GABA-mediated inhibitory transmission. Additional effects, which may play a role in its use as a mood altering drug, include inhibiting excitatory transmission. Valproic acid may have antiepileptogenic effects by its effect on DNA binding proteins with subsequent alteration of gene expression.

Adrenocorticotropin and prednisone are frequently used to treat infantile spasms, a form of myoclonic/UE. The mechanisms for these agents are not entirely understood. Vigabatrin is often used to treat infantile spasms caused by ►Tuberous sclerosis; however lack of FDA approval has prevented its use in the United States (Table 1).

Rational Drug Development

At present, there are three major thrusts in anticonvulsant rational drug design [3,4]. First, the parent structures of anticonvulsants currently in use are being modified to find drugs with improved efficacy and tolerability. This rational has been used in developing many of the drugs in current use. Second, drugs with specific molecular targets that have been suggested either by discovery in the molecular genetics of epilepsy or advances in neuroscience research are being sought, developed and further modified for efficacy and tolerability. Finally, novel anticonvulsant compounds with possible antiepileptic properties are actively sought. Many potential compounds, especially those targeting NMDARs, have been pursued and subsequently abandoned due to lack of efficacy and poor tolerability. GluR antagonists, due to sedation issues, are likely to be more appropriate for ►status epilepticus. Serendipity continues to play a major role as our understanding of neuroscience, seizures, and epilepsy expands (Table 2).

Future Directions in Drug Development

The fact that 25% of all epilepsies are drug resistant with only 50% of these potentially amenable to surgical treatment (itself with significant cost and morbidity) dictates that further drug development is necessary. Animal studies have suggested several important lines for future development. Group I mGluR agonists or Group II mGluR antagonists are thought to have both anticonvulsant and antiepileptogenic potential [5]. Since these modulatory receptors do not directly participate in fast excitatory synaptic transmission, it is felt that targeting these receptors would be effective with fewer side effects compared to agents that directly modulate GluRs and NMDARs. Similarly, targeting

Anticonvulsants. Table 1 Anticonvulsant drugs currently in widespread use

Drug	Date of initiated or pubmed first citation of anticonvulsant use (date synthesized)	Mechanisms of action (in presumed order of efficacy)	LRE	GE	UE	Notes
Phenobarbital	1912 (1911)	GABAR, VGCC-HVA, GluR	+	+		
Phenytoin	1938 (1908)	VGSC	+			Phenytoin, carbamazepine and oxcarbazepine may exacerbate some generalized epilepsies
Ethosuximide	1951 (1927)	VGCC-T-type, VGSC		+		
Carbamazepine	1962 (1953)	VGSC	+			Blocks defective nicotinic acetylcholine receptors in ADNFLE
Benzodiazepines (Diazepam)	1964 (1961)	GABAR	+	+	+	
Valproic acid	1973 (1882)	↑GABA turnover, VGSC, VGCC-T-type	+	+	+	
Zonisamide	1982	VGSC, VGCC-T-type	+	+	+	
Vigabatrin	1983 (1977)	↓GABA transaminase (GABA degradation prevented)	+	+	+	Not FDA approved in the United States due to retinal damage associated with long-term use
Lamotrigine	1985	VGSC, VGCC-HVA, I_h	+	+		
Gabapentin	1987	VGCC-HVA, ↓GABA transaminase	+			
Oxcarbazepine	1987	VGSC	+			
Felbamate	1989	VSCS, GABAR, VGCC-HVA, NMDAR	+	+		Use limited by bone marrow and liver toxicity
Topiramate	1994 (1987)	VGSC, VGCC-HVA, GABAR, KAR/GluR	+	+	+	
Tiagabine	1994 (1988)	blocks GABA reuptake (transporter)	+			
Levetiracetam	1996 (1992)	VGCC-HVA, GABAR, Binds to SV2A (presynaptic vesicle protein)	+	+	+	

See text for most abbreviations. "+" indicates clinical evidence for usage. ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy. Modified from [2,3].

KARs [6], which to some extent also modulate fast excitatory transmission, holds promise, as has been shown with topiramate that antagonizes KARs [2]. Other receptor systems (amines, peptides, acetylcholine, etc.) have also been suggested as targets [2].

Targeting potassium channels with anticonvulsive agents that augment their function may be helpful, as suggested by the progression of advanced clinical trials with retigabine. Many additional potassium channels other than the KCNQ-type have been proposed. For instance, I_h , a potassium channel that modulates dendritic excitability, has been implicated in epilepsy. Long-term alteration of I_h , resulting in

reduced function of this potassium channel, has been induced by experimental models of seizures and epilepsy [7]. Thus, by attempting to reverse this process, it may be possible to obtain better seizure control as well as reverse epilepsy. It is thought that the primary anticonvulsant mechanism of lamotrigine is to augment I_h function [2]. Recently it has been shown that the ketogenic diet, used to treat medically refractory epilepsy, may augment function of another type of potassium channel that is sensitive to ATP (K-ATP channels) [8].

Agents that do not target ion channels directly but rather accessory proteins that modulate their

Anticonvulsants. Table 2 Anticonvulsants in development [4,3]

Drug	Parent structure	Mechanisms of action
Brivaracetam and selectracetam	Levetiracetam	SV2A ligand, similar to levetiracetam?
Valrocemide, valnoctamide, isovaleramide, propylisopropyl acetamide	Valproic acid	Similar to valproate?
Flurofelbamate	Felbamate	Similar to felbamate?
RWJ-333369	Carbamate	Similar to felbamate?
Licarbazepine, BIA 2-093	Oxcarbazepine	Similar to oxcarbazepine?
ELB139	Benzodiazepine	Selective benzodiazepine receptor agonist
Lacosamide	Functionalized amino acid	Unknown
Talampanel	2,3 benzodiazepine	Non-competitive GluR antagonist
NS1209		Competitive GluR antagonists, weak KAR antagonist
Ganaxolone	Neuroactive steroid	GABAR modulator
Retigabine		KCNQ (voltage-gated potassium channel) opener
ICA-27243	Benzanilide	More selective KCNQ opener
Rufinamide	Triazole	Unknown

function are also on the horizon. For instance, it has been shown that the direction of chloride flux through GABARs is developmentally regulated by the expression of specific transporters. Targeting transporters with a diuretic to maintain the “correct” direction of chloride flux has been shown in an animal model to attenuate otherwise medically refractory seizures [9]. Furthermore, aberrant expression of transporters has been found in human epileptic tissue, potentially resulting in “wrong-way” chloride fluxes [10]. Thus targeting these transporters with diuretics that can cross the blood-brain barrier would present a novel therapeutic approach. In the end, targeting either the specific enzymes capable of altering ion channel properties (for instance by ►phosphorylation or de-phosphorylation) or the genetic expression of aberrant channels and transporters are likely to be the key to anticonvulsant and antiepileptogenic drugs of the future. For example, the phosphorylation state of I_h is critical in regulating dendritic excitability and preventing this may alter the course of epilepsy. Also, targeting the selective activation of ►kinases and phosphatases that underlie the long-term alteration of excitatory synapses (►synaptic plasticity) in the early stages after a first seizure might prevent epilepsy before abnormal synaptic modifications induced by the seizure become “hard-wired”. By targeting these processes early in the course of epilepsy or just after the first seizure, the long-term consequences (of medical refractory epilepsy or learning impairment) could potentially be averted.

References

- White HS (2003) Preclinical development of antiepileptic drugs: past, present and future directions. *Epilepsia* 44 (Suppl 7):2–8
- Rogawski MA, Loscher W (2004) The neurobiology of antiepileptic drugs. *Nat Rev Neurosci* 5:553–564
- Stefan H, Feuerstein TJ (2007) Novel anticonvulsant drugs. *Pharmacol Ther* 113:165–183
- Rogawski MA (2006) Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res* 69:273–294
- Ure J, Baudry M, Perassolo M (2006) Metabotropic glutamate receptors and epilepsy. *J Neurol Sci* 247:1–9
- Vissel B, Royle GA, Christie BR, Schiffer HH, Ghetti A, Tritto T, Perez-Otano I, Radcliffe RA, Seamans J, Sejnowski T, Wehner JM, Collins AC, O’Gorman S, Heinemann SF (2001) The role of RNA editing of kainate receptors in synaptic plasticity and seizures. *Neuron* 29:217–227
- Poolos NP (2005) The h-channel: a potential channelopathy in epilepsy? *Epilepsy Behav* 7:51–56
- Ma W, Berg J, Yellen G (2007) Ketogenic diet metabolites reduce firing in central neurons by opening K_{ATP} channels. *J Neurosci* 27:3618–3625
- Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, Delpire EJ, Jensen FE, Staley KJ (2005) NKCC1 transporter facilitates seizures in the developing brain. *Nat Med* 11:1205–1213
- Munoz A, Mendez P, DeFelipe J, Alvarez-Leefmans FJ (2007) Cation-chloride cotransporters and GABAergic innervation in the human epileptic hippocampus. *Epilepsia* 48:663–673

Antidepressants

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Definition

The symptoms of unipolar depression may vary widely between individuals and may include apathy, subdued mood, sadness or sorrow, loss of libido, sleep disturbances, weight loss or gain, and in children and adolescents, irritability. A defining symptom of depression is the loss of self-esteem, for which there may be no apparent explanation. Chronic depression is a debilitating disease that sometimes leads to suicide and is more prevalent in females than in males. In the USA it is the third leading cause of death among people aged 15–24 Years. It is an expensive disease in terms of lost working capacity, increased use of social services and impairment of family and social relationships. Antidepressants are drugs that are used in the treatment of unipolar depression, although they are often used in conjunction with some form of psychological therapy. In addition, some antidepressants are used for certain subtypes of anxiety disorders, such as obsessive compulsive disorder and phobias, as well as neuropathic pain.

Characteristics

There is a genetic component to unipolar depression in many cases, with an increased incidence of the disease being reported in individuals with first degree relatives who also suffer from depression. In long-term depression, enlarged adrenal and pituitary glands have been observed, as have increased levels of cortisol in the blood, CSF and urine of patients. Elevated levels of corticotrophin releasing factor in the plasma of patients have also been observed. Taken together, these observations indicate constant elevated levels of stress and consistent with long term stress, in some patients, a reduced volume of the hippocampus has been observed.

Depression is attributed to a decreased availability of the biogenic amine neurotransmitters, noradrenaline, serotonin, and to a lesser extent, dopamine [1]. Current strategies in the treatment of depression aim to increase the available amount of these neurotransmitters. There are four main categories of antidepressant drugs: tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and an “atypical” category that includes dopamine modulating drugs.

Interestingly, the different categories of drugs all have a therapeutic lag of 2–3 weeks and a similar efficacy in treating depression. This therapeutic lag presents a problem in the initiation of antidepressant treatment, particularly in patients expressing suicidal ideations. The primary differences between the drugs are in the side effects and a patient’s acceptance of a particular drug is often side effect dependent.

Tricyclic Antidepressants

The first successful antidepressants were the tricyclic antidepressants that became widely available in the 1960s [2]. Tricyclics such as imipramine, clomipramine and amitriptyline, inhibit the reuptake of noradrenaline from the synaptic cleft with moderate selectivity. Most of the drugs in this category have a relative long plasma half-life, and some have active metabolites, that further prolong the drug’s action. This prolonged action provides stable levels of the drug in the blood plasma and reduces the occurrence of fluctuating side effects that many patients find annoying. Although newer antidepressants are slowly replacing tricyclics in clinical practice, many prescribers prefer them because their long clinical use has provided evidence for their relative safety and efficacy.

The side effects associated with tricyclics include sedation, postural hypotension and anticholinergic effects including dry mouth, blurred vision and urinary retention. The occurrence of postural hypotension is a particular problem for elderly patients and has led to the preferential prescription of SSRIs in this patient population. There are also effects on the cardiovascular system that require consideration. In addition, these drugs can be fatal in overdose and may be contraindicated in patients expressing suicidal ideations. Tricyclic antidepressants generally have interactions with a number of other drugs including alcohol and these drugs are therefore contraindicated in alcoholic patients. Tricyclic antidepressants are included in Category D of the FDA classification of potentially teratogenic drugs. This category includes drugs for which there is evidence of risk in humans, however the benefit of the drug may outweigh the potential risk.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have now overtaken tricyclic antidepressants as the most prescribed drugs for the treatment of unipolar depression [3]. Although they have similar efficacy to tricyclics, SSRIs demonstrate less acute toxicity and less risk of overdose, making them an overall safer choice for the severely depressed patient. SSRIs inhibit the reuptake of serotonin from the synaptic cleft with greater selectivity for serotonin than for noradrenaline. For most SSRIs, the selectivity for

serotonin is a factor of 10 greater than the selectivity of tricyclics for noradrenaline.

The side effects of SSRIs include nausea, insomnia, agitation and sexual dysfunction. For some patients, the experience of sexual dysfunction ultimately leads to dissatisfaction with the drug and a change to a different antidepressant. Although generally safer than tricyclics, there are two drug interactions with SSRIs that raise concern. In an effort to achieve better control of their depression, a number of patients have resorted to self-medication with the herbal remedy, St. John's Wort. St. John's Wort contains significant levels of serotonin and a life threatening "5-HT reaction" has been observed that includes muscular rigidity, hyperthermia and in the most severe cases, cardiovascular collapse. The other interaction is with cannabis, which can cause severe anxiety, panic, hypertension and muscle spasms.

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase is the enzyme in the presynaptic terminal that breaks down the aminergic neurotransmitters to allow recycling to their constituents. Inhibition of this breakdown increases the amounts of transmitter available for release into the synaptic cleft. MAOIs were discovered in the late 1950s and originally studied as drugs known to produce mania. These drugs have a number of other effects, including lowering blood pressure, and at one time were used as antihypertensives. Although MAOIs are effective treatments for depression, particularly when it is associated with anxiety and phobias, they are now used primarily when a patient has failed to respond to tricyclics and SSRIs.

There are two subtypes of monoamine oxidase, type A, that breaks down noradrenaline and serotonin, and type B, that breaks down dopamine. The early monoamine oxidase inhibitors were not specific for monoamine oxidase subtypes and, as a result, severe side effects were associated with their use. One of the most dangerous side effects associated with MAOIs was the hypertensive crisis resulting from interactions with tyramine containing foods or with other drugs. Interactions with tyramine containing foods pose the greatest problem for many patients, with banned foods including cheeses, beer, wine, yeast, chocolate and cream. Other common side effects include postural hypotension and sedation or excitation. There is also a severe interaction with tricyclic antidepressants, so that if a patient is changed from a tricyclic to an MAOI, a drug free washout period is necessary.

Newer MAOIs have been synthesized that are specific for monoamine oxidase subtypes. Moclobemide, for example, is selective for type A monoamine oxidase. Moclobemide and similar drugs have side effects similar

to tricyclics, although cautions for tyramine containing food still apply. In addition, seizures have been reported to be associated with acute overdose.

Atypical Antidepressants

This is a mixed category of drugs that has been demonstrated to be effective for the treatment of depression in some cases, and includes trazodone, nefazodone and bupropion. The neuropharmacology of these drugs is less well understood, hence the name "atypicals." One of the major advantages of drugs in this category is that they tend to be safer and better tolerated by patients with fewer, if any, cardiovascular effects. It has been suggested that because of their relative safety, atypical antidepressants should be the first choice for the treatment of unipolar depression in geriatric patients.

Of particular interest in this category is bupropion, a reuptake inhibitor for noradrenaline, serotonin and dopamine. Bupropion is generally well tolerated and in addition to its antidepressant properties, it is also useful in withdrawal from nicotine [4]. Bupropion is not suitable for individuals with seizure disorders or a susceptibility to seizures. It has also been reported to produce mania in some depressed patients.

Overview

While the immediate effect of antidepressants is to increase the availability of biogenic amines in the synaptic cleft, it is the longer term effects, developing over 2–3 weeks, that are thought to provide the antidepressant effects. The characteristic therapeutic lag associated with these drugs suggests that it is long term changes in receptors and transporters that provide the therapeutic effect. One consequence of this therapeutic lag is that antidepressants cannot be administered acutely "as required." Another consequence is that when the depression has been alleviated, the drug must be withdrawn slowly to allow the receptors or transporters to gradually adapt to a drug-free state.

In cases of severe recurrent depression, where antidepressants alone are not fully effective, administration of lithium has been reported to be an effective supplement to antidepressant treatment [5].

Bipolar Disorder (Bipolar Depression)

Bipolar disorder is a mood disorder characterized by periods of depression followed by periods of mania or hypomania. Although depression is a significant part of the disorder, treatment with antidepressant drugs is not effective in the manic phase and may indeed exacerbate it. Instead, treatment is required that will stabilize the individual's mood, preventing both the episodes of depression and the episodes of mania [6].

In 1949 lithium was introduced for the treatment of mania but it was not until the 1970s that it became accepted world wide as an effective treatment for bipolar disorder. The effectiveness of lithium in bipolar disorder is interesting because a therapeutic dose has no discernable effect in a person without bipolar disorder. This distinguishes it from other drugs, such as tricyclics, that produce sleepiness when administered to non-depressed individuals. The actions of lithium are not well understood. It is speculated that it may produce its effect by acting upon sodium channels or possibly by inhibiting the release of dopamine and noradrenaline but not serotonin [6].

Although lithium is generally well absorbed after oral administration, absorption is somewhat erratic, with peak plasma levels exceeding the threshold for adverse events. Slow release lithium prevents the early erratic plasma peaks, but may result in later accumulation of the drug resulting in gastrointestinal side effects. Overall, lithium is a difficult drug to use. It has a very low therapeutic index, meaning that the therapeutic dose is in a very narrow margin between the ineffective dose and the toxic dose. Initiation of lithium treatment requires consistent monitoring until steady state plasma levels are achieved. Often the required dose, even for the slow release preparations, is given in divided doses throughout the day to minimize the fluctuating plasma levels. Acute toxic effects of lithium include gastrointestinal disturbances, tremor and sedation. More serious side effects include severe gastrointestinal side effects, coma and even death.

Because of the numerous problems associated with lithium administration, in recent Years there has been a move towards the use of antiepileptic drugs, particularly carbamazepine and valproic acid, for the treatment of bipolar disorder.

References

1. Ruhe HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatr* 12(4):331–359
2. Gillman PK (2007) Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 151(6):737–748
3. Pae CU, Patkar AA (2007) Paroxetine: current status in psychiatry. *Expert Rev Neurother* 7(2):107–120
4. Grant KM, Kelley SS, Smith LM et al. (2007) Bupropion and nicotine patch as smoking cessation aids in alcoholics. *Alcohol* 41(5):381–391
5. Kok RM, Vink D, Heeren TJ et al. (2007) Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open randomized controlled trial. *J Clin Psychiatr* 68(8):1177–1185
6. Miklowitz DJ, Johnson SL (2006) The psychopathology and treatment of bipolar disorder. *Ann Rev Clin Psychol* 2:199–235

Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens

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Synonyms

Autoimmune disease; Inflammatory response; Self-antigen; Systemic lupus erythematosus; Glutamate receptors

Definition

Molecular mimicry refers to the similar structures shared by molecules from different genes or different proteins. In autoimmune or infectious disease, molecular mimicry also refers to shared cross reactive epitopes for B- and T-cells with the host. The concept of molecular mimicry evolved from monoclonal antibodies in which mutation analysis led to cross reactive B-cells and T-cells and now to its participation in human diseases.

Characteristics

Activation of Cross-Reactive Lymphocytes

The innate immune system, which recognizes shared determinants on microbes, together with general tissue barriers function as an effective first line defense against the world of pathogens while an adaptive immune response with memory function develops. B- and T-cells form the central components of the adaptive immune response; each expresses one of an enormously diverse repertoire of antigen receptors and each is highly selective. The frequency of T- and B-cells expressing any given receptor can increase through clonal expansion or decrease through negative selection, the process of eliminating cells with specificity for self-antigens. B-cells or T-cells that cross-react with both foreign and self antigens may escape tolerance mechanisms because the self-antigen is present in too low a concentration to mediate negative selection, or because the affinity of the antigen for the antigen receptor is below the signaling threshold. If these B-cells and T-cells are initially activated by pathogens that resemble the self antigens, they may subsequently be able to respond to both foreign and self-antigens. In autoimmune-prone individuals, despite the disappearance of the foreign pathogen and the down regulation of the immune response, some degree of

immune activation may persist, sustained by the presence of cross-reacting antigen.

Antibodies in Diseases without Antecedent Infection; Molecular Mimicry and SLE

Understanding the antigens involved in molecular mimicry also called antigenic **►cross-reactivity** is of some therapeutic importance because knowledge of either the eliciting antigen or a cross-reactive target antigen may suggest interventions that prevent immune activation or organ damage. In this brief discourse, we will discuss only the diseases of the central (CNS) and peripheral (PNS) nervous systems in which one or the other antigen is known, and refer briefly to diseases in which the antigen is suspect. Our focus on cross-reactivity of anti-DNA antibodies in **►systemic lupus erythematosus (SLE)** is derived from the observation that an antibody to phosphorylcholine (PC), the dominant epitope in the cell wall polysaccharide of *Streptococcus pneumoniae* (*pneumococcus*), could acquire a single amino acid substitution and gain reactivity to DNA [1]. This led to an analysis of antibodies produced by splenic B-cells from a patient with lupus who had just received a pneumococcal vaccination prior to splenectomy. Over half of the anti-pneumococcal antibodies cross-reacted with DNA. Similarly, over 40% of B-cells reactive with pneumococcus from mice immunized with PC coupled to a protein carrier cross-reacted with DNA. Normally these B-cells are regulated such that they do not secrete antibody and only B-cells specific for pneumococcus develop into antibody secreting plasma cells. Poor regulation of B-cells activated by microbial antigen may lead to autoantibody production. In fact, anti-DNA antibodies cross-react with many microbial and viral antigens [2]. In order to test whether protein antigens could elicit anti-DNA antibodies in SLE, we used a murine anti-DNA antibody to screen a phage peptide display library, and we found a consensus sequence, D/E W D/E Y S/G, that was bound by this antibody [3]. Immunization with a multimeric form of this consensus sequence induced an antibody response to both peptide and DNA. The peptide motif is present in pneumococcal choline kinase, and also on the extracellular ligand binding domain of the murine and human NR2A and NR2B subunits of the *N*-methyl D-aspartate receptor (NMDAR), a class of receptors activated by the amino acid glutamate.

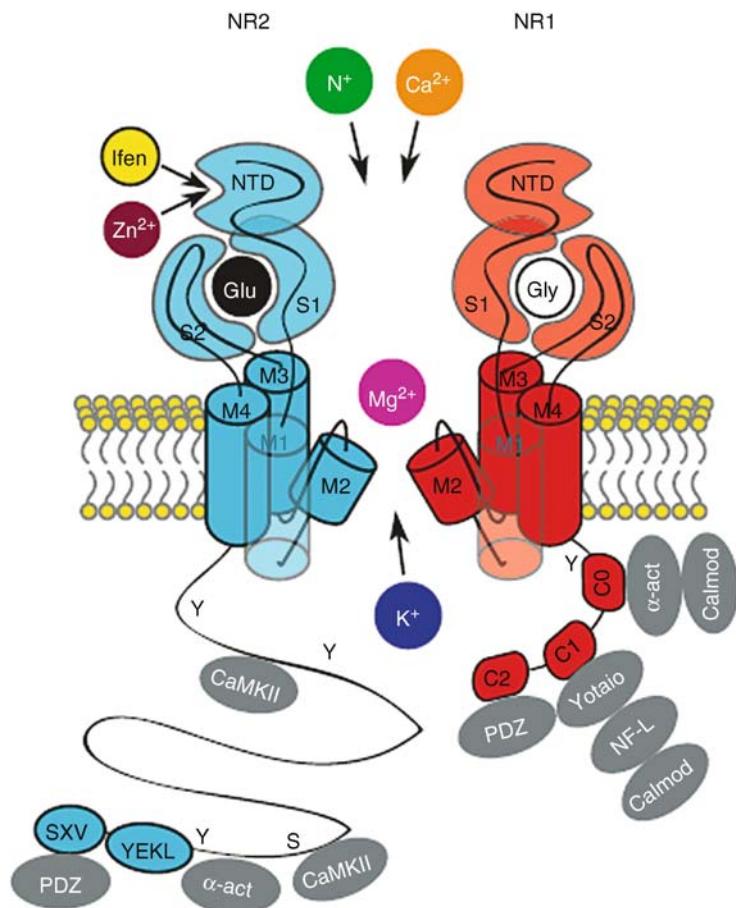
Glutamate Receptors

NMDARs are localized within the synapses of the forebrain (see **Figs. 1** and **2**) [4]. During excitatory synaptic transmission, glutamate is released from presynaptic terminals and binds to receptors on the postsynaptic membrane, resulting in rapid depolarization of the postsynaptic membrane. Growth- and

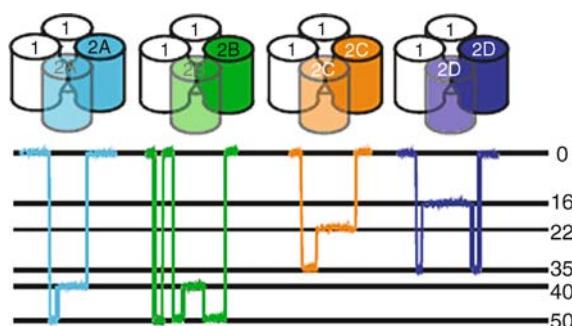
survival-promoting signals derive from synaptic NMDARs enriched with NR2A subunits, especially related to the regulatory role of mitogen-activated protein kinases, and distinct gene expression programs. Conversely, pro-death signals emerge from hypoactivity of synaptic NMDARs or extreme activity of extrasynaptic NMDARs. Pro-death signals are responsible for shutting-down cAMP response element binding protein function and triggering mitochondrial depolarization. The mechanism of cell death is believed to depend on the severity of the insult. Slow apoptotic cell death occurs after a mild (although ultimately toxic) episode of NMDAR activation. Rapid cell death occurs after acutely excessive NMDAR activation, and it is usually referred to as excitotoxicity. This condition is known to occur in several acute diseases (ischemia, trauma, and epileptic seizures).

Because lupus patients in growing numbers suffer from symptoms due to brain dysfunction – disorders of thinking and memory and mood, we tested whether a possible mechanism might depend on antibody-mediated NMDAR dysfunction. In fact, sera and cerebrospinal fluid (CSF) from SLE patients harbor antibodies to DNA that are cross-reactive with NMDARs, and these antibodies can cause apoptosis of neurons [5]. **►Anti-NMDAR antibodies** are present in 30–50% of patients with SLE, and may present more frequently in those with cognitive complaints [6]. Furthermore, cross-reactive antibodies are found in the CSF of lupus patients where their presence correlates with symptoms of neuropsychiatric SLE. In one study, the symptoms of brain dysfunction in patients with SLE were improved commensurate with a decrease in the NMDAR antibody in CSF [6]. In mice immunized with multimeric peptide so that there is a high titer of NMDAR antibody that is also DNA reactive, there is no neurological damage unless the blood-brain barrier is breached [7]. Once the antibodies have access to brain, they mediate neuronal death leading to a cognitive or behavioral disturbance depending on the agent used to breach the blood-brain barrier and the site of the neuronal damage [7,8]. The presence in serum and CSF of autoantibody to a defined cell surface antigen that is known to function in neurocognitive processes which are disturbed in clinical disease strongly suggests that NMDAR antibodies may play a role in neuropsychiatric SLE. The development of an animal model in which anti-NMDAR antibodies actually mediate disease increases the potential validity of this mechanism.

As much as animal models can ever mimic human disease, these murine studies demonstrate histopathological and behavioral outcomes consistent with the cognitive and behavioral disorders that occur in SLE. Recently in human post mortem specimen, we were able to identify IgG localized to NMDARs on neurons in the hippocampus. Furthermore, IgG eluted from the



Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens. **Figure 1** (from [4]) The NMDA receptor has conserved domains (S1 and S2) to form the binding site for glutamate (NR2) and for glycine (NR1). The extracellular region can contain modulatory sites that bind Zn^{++} or ifenprodil. The channel lining region, M2, enters the membrane from the intracellular membrane. The ion channel is permeable to Na^+ , K^+ , Ca^{++} . Extracellular Mg^{++} binds deep in the pore and causes voltage-sensitive block. The C-terminal tail of each subunit binds to kinases and structural proteins.



Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens. **Figure 2** The NMDA receptor is formed as a tetramer of pairs of NR1 with NR2A, NR2B, NR2C, or NR2D. Each sub-type produces distinct receptor-channel properties. NMDA receptor with NR2A and NR2B subunits produce high conductance states, and those with NR2C and NR2D produce low conductance.

brain of a lupus patient demonstrated neuronal toxicity [9]. Finally, the mechanism of the observed neuron death in peptide immunized mice exposed to blood-brain barrier breaching agents suggests direct antibody toxicity. Preliminary electrophysiological analysis demonstrates that the antibody can act at the NMDAR as a partial agonist. It is noteworthy that there is precedent for antibodies to affect the electrophysiology of neurons without cytotoxicity. Patients with human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy (also called tropical spastic paraparesis) develop antibodies to heterogeneous nuclear ribonuclear protein-A1 that cross-reacts with HTLV-1-tax (a viral regulatory protein). These antibodies functionally inhibit the firing and amplitude of dopamine and pyramidal neurons in a dose dependent manner [10]. Whether differential binding characteristics of anti-NMDAR antibodies will lead to alternate behavioral and cognitive outcomes, and whether some are more

likely to moderate neuronal function and less likely to mediate toxicity remains to be investigated; nevertheless, this class of NMDAR antibodies may mediate aspects of brain dysfunction in patients with SLE.

Antibodies in Autoimmune Diseases Lacking Antecedent Infection; Molecular Mimicry and Neuromuscular Disease, Paraneoplastic Syndromes and Encephalitis

The isolation and measurement of antibodies to acetylcholine receptor (AchR) from the serum of patients with myasthenia gravis (MG), led to the detailed description of anti-AchR antibodies, and the identification of antigenic epitopes on each of the two alpha subunits of the receptor and distinct from the acetylcholine binding site. The pathogenic activity of these antibodies has been demonstrated in studies in which adoptive transfer leads to weakness in recipient animals, and studies in which animals immunized with peptide fragments of the human extracellular domain of the alpha-AchR become weak. In MG there is no apparent antecedent infection and the auto-antibodies are currently thought to arise directly in response to the epitopes on the AchR. It is possible that antigen from a possible microbial source activates cross-reactive antibodies. It is even possible that the cross-reactive antibodies are not pathogenic, but that a process called epitope spreading in which a response to one determinant of an antigen (in this case the AchR) spreads to multiple determinants, and stimulates the generation of antibodies that cause the disease.

Other neurological diseases in which there is no antecedent infection or, at best, obscure or controversial prior inflammations include multiple sclerosis and the paraneoplastic disorders. In the paraneoplastic syndrome characterized by cerebellar dysfunction and associated with breast or ovarian cancer, the tumor expresses a protein termed cdr2 antigen that is routinely expressed in Purkinje neurons. The immune response generated against the tumor can also target brain, once the antibody or antigen-specific T- or B-cells traverse the blood-brain barrier to contact brain.

Small cell lung tumors express voltage gated calcium channels; if the immune system makes antibodies that down-regulate these calcium channels and reduce acetylcholine release, the patient develops severe muscle weakness. In yet another paraneoplastic syndrome, small cell lung and breast tumors stimulate the production of antibodies to amphiphysin, a synaptic vesicle associated protein, which result in aching, stiff axial muscles associated with painful spasms. A related antibody-mediated disease that also induces severe muscle stiffness occurs with ►autoantibodies to glutamic acid decarboxylase (GAD), the rate limiting enzyme in the synthesis of the neurotransmitter gamma amino butyric acid. While paraneoplastic syndromes may improve

when the tumor load is decreased, the anti-GAD antibody syndrome responds to immunomodulation.

Finally, Rasmussen's encephalitis that causes intractable epilepsy and is often preceded by febrile seizures, although a particular infection has not been identified, appears to be caused by auto-antibodies to the amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) which mediate fast excitation, through the influx of sodium into the postsynaptic cell, resulting in rapid depolarization of the postsynaptic membrane. Immunosuppression was shown to be an effective therapy to avoid neurosurgical approaches to epilepsy control, supporting the pathogenic function of the autoantibodies. There is controversy whether the anti-AMPAR antibodies are specific for this disease or are widely present in other forms of epilepsy.

Antibodies in Autoimmune Diseases With Antecedent Infection; Campylobacter and Autoimmune Polyneuropathy

The Guillain-Barre syndrome is the prototypical post-infectious autoimmune inflammatory polyneuropathy, with or without axon sparing, caused by antibody and complement deposited on Schwann cells and myelin membranes. This disease depends on molecular mimicry between epitopes on bacteria and gangliosides on neurons. It is preceded by an often trivial infection, most commonly a Campylobacter infection, which can last for approximately a month and leaves variable neurological impairment that correlates with the location of antibody deposition and complement-mediated destruction. Prompted by earlier studies of specific T-and B-cell related responses to myelin (the so-called experimental allergic neuritis model), investigators have identified antigenic epitopes in axonal glycolipids specifically recognized by anti-ganglioside antibodies. Gangliosides are enriched in the synapses of neural tissues and bear structural similarities among these and the lipo-oligosaccharides of the *Campylobacter jejuni* and *Hemophilus influenzae*. When antibody to ganglioside Q1b is abundant, the cranial nerves are involved in the demyelination process (the so-called Miller Fisher variant), thereby providing support for the hypothesis that toxic antibodies cross the blood brain barrier and produce destruction in the central nervous system, as well as the histopathologically verified damage to the peripheral nervous system.

Antibodies in Autoimmune Diseases With Antecedent Infection; Group A Streptococcus and Movement Disorders

Another infectious agent that stimulates the immune system to generate cross-reactive antibodies is Group A Streptococcus-pyogenes. Antibodies to Streptococcus binding both the streptococcal M protein and cardiac myosin have been implicated in rheumatic heart disease. Cross-reactive antibodies now also appear responsible

for the neurological manifestations. The precipitating infection occurs a week to 6 months prior to the neurological sequela which include the classic movement disorder, chorea, but also include dystonias, tics, hemiballismus, and myoclonus. Recently, antibody derived from a human hybridoma generated from B-cells of a patient who developed chorea after a strep infection was demonstrated to cross-react with mammalian lysoganglioside and *N*-acetyl β -D-glucosamine (GlcNAc), which is the dominant epitope of the group A streptococcal carbohydrate. The monoclonal hybridoma derived antibody, as well as acute sera from patients with chorea, induced Ca/calmodulin-dependent protein (CaM) kinase II activation in a human neuroblastoma cell line, and recognized cell surface antigen in a neuroblastoma line and caudate-putamen *in vivo*. On further analysis, the chorea associated antibodies from sera and CSF were demonstrated to cross-react with lysoganglioside GM1 and GLcNAc. Similar to the molecular mimicry that occurs in SLE; antibody-mediated neuron signaling may underlie the pathophysiology of the post-streptococcal neurological disorders.

Molecular mimicry between epitopes on the basal ganglia and Group A Streptococcus-pyogenes carbohydrate has fueled interest in the pediatric clinical disorders in which children have tics or dystonias associated with psychiatric maladies like obsessive compulsive disorder, the so called pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections. The possibility that there is a pathogenic autoantibody was supported by the felicitous effect of plasma exchange in early studies, but larger trials have been disappointing.

Recently it has been suggested that Parkinsonism, and possibly encephalitis lethargica as well as a wide spectrum of neuropsychiatric syndromes can also be provoked by a prior strep infection. It is not determined whether any of these disorders are caused by antibodies.

Conclusion

Molecular mimicry is a phenomenon in which antibodies or T-cells cross-react with identical or highly homologous epitopes that are present on both foreign and self-molecules. A “two-hit” model for disease, autoantibody plus breach in blood-brain barrier integrity suggest that to consider a mechanistic role for antibodies in disease requires: a cell surface antigen relevant to disease symptoms; antibodies in serum, and spinal fluid, and target nervous system tissue; the transmission of the disease to animals by human serum; successful treatment of the disease through immunomodulation.

References

1. Diamond B, Scharff MD (1984) Somatic mutation of the T15 heavy chain gives rise to an antibody with autoantibody specificity. Proc Natl Acad Sci USA 81:5841–5844
2. McClain MT, Heinlen LD, Dennis GJ, Roebuck J, Harley JB, James JA (2005) Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry. Nat Med 11:85–89
3. Gaynor B, Puterman C, Valadon P, Spatz L, Scharff MD, Diamond B (1997) Peptide inhibition of glomerular deposition of an anti-DNA antibody. Proc Natl Acad Sci USA 94:1955–1960
4. Cull-Candy SG, Leszkiewicz DN (2004) Role of distinct NMDA receptor subtypes at central synapses. Sci STKE 2004:re16
5. DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B (2001) A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 7:1189–1193
6. Yoshio T, Onda K, Nara H, Minota S (2006) Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 54:675–678
7. Kowal C, DeGiorgio LA, Nakao T, Hetherington H, Huerta PT, Diamond B, Volpe BT (2004) Cognition and immunity; antibody impairs memory. Immunity 21:179–188
8. Huerta PT, Kowal C, DeGiorgio LA, Volpe BT, Diamond B (2006) Immunity and behavior: antibodies alter emotion. Proc Natl Acad Sci USA 103:678–683
9. Kowal C, DeGiorgio LA, Lee JY, Edgar MA, Huerta PT, Volpe BT, Diamond B (2006) Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proc Natl Acad Sci USA 103:19854–19859
10. Kalume F, Lee SM, Morcos Y, Callaway JC, Levin MC (2004) Molecular mimicry: cross-reactive antibodies from patients with immune-mediated neurologic disease inhibit neuronal firing. J Neurosci Res 77:82–89

Antidromic

Definition

Propagation of action potentials in the direction opposite to the naturally occurring direction.

► Action Potential Propagation

Antidromic Activation

Definition

A method for identifying the axon projection target of a single neuron which can also be functionally studied.

An electrode passes a brief current directly activating an axon and resulting in an action potential that

travels “backward” to the cell body. There, it can be recorded using standard extracellular electrophysiological techniques.

The stimulating electrode can be moved to follow the path of the axon and a map of this pathway can be generated. Additional information about the response properties of the recorded neuron can be obtained by applying the appropriate stimuli to the receptive field.

- Extracellular Recording
- Receptive Field

Anti-epileptic Medicine

- Anticonvulsants

Antigen Presentation

Definition

Antigen presentation is a process of antigen peptide fragments bound to MHC molecules on the surface of cells being specifically recognized by T cell surface receptors expressed by T lymphocytes. CD8⁺ T lymphocytes recognize antigen peptides bound to MHC class I molecules on nucleated cells, while CD4⁺ T lymphocytes recognize antigen peptides bound to MHC class II molecules on professional antigen presenting cells, such as dendritic cells, B lymphocytes, macrophages and microglia.

- Immune System and Pain

Antigen-presenting Cell

Definition

Antigen-presenting cells first take up antigen by pinocytosis or phagocytosis. The antigenic proteins are processed into antigenic peptides and presented on the major histocompatibility complex (MHC) to T cells.

T helper cells recognize antigens presented on MHC II and cytotoxic T cells recognize antigens presented on MHC I respectively.

Anti-GQ1b Antibody

Definition

IgG binding to GQ1b ganglioside characteristic for clinical syndromes manifested by brainstem and cranial nerve involvement.

Anti-Motion Sickness Drugs

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Synonyms

Anti-sea sickness; Car sickness; Air sickness; Space motion sickness; Space adaptation syndrome drugs

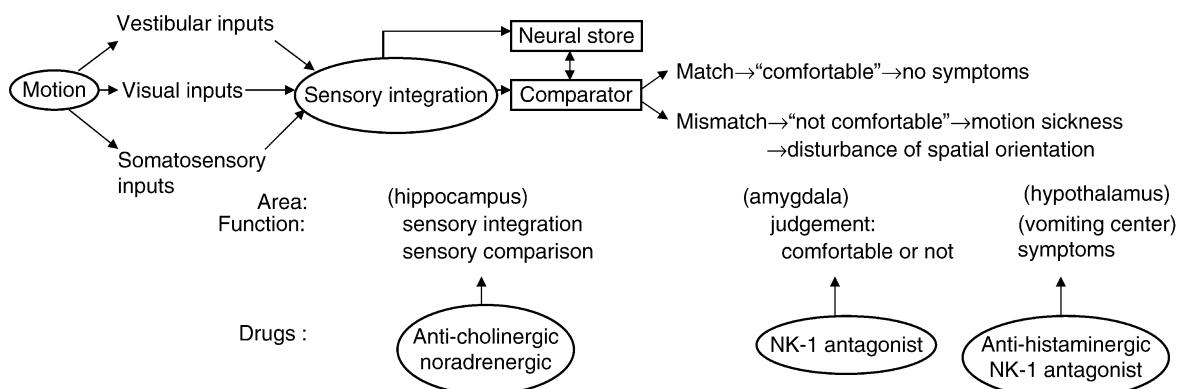
Definition

Motion sickness is a disorder characterized by nausea, vomiting, pallor, cold sweating, and increased salivation, which occur when exposed to certain types of real or apparent motion. It usually occurs during passive motion stimuli by vehicles, ships, airplanes, however, apparent motion by a simulator or virtual reality can cause the similar symptoms. Anti-motion sickness drugs are used for prevention of motion sickness. There are three types of drugs used for motion sickness: Anti-histaminergic drugs, anti-cholinergic drugs, and adrenergic drugs. Recently, other types of drugs such as anti-neurokinin1 (NK-1) receptor blockers, anti-arginine vasopressin 1 (AVP1) receptor blockers and serotonin (5-HT1A) receptor agonists have been tested for their effectiveness on motion sickness in animals.

Characteristics

Neural Mechanisms of Motion Sickness

Neural mismatch theories for motion sickness are widely accepted [1,2]. According to this theory, ►spatial orientation is disturbed by a conflict between sensory inputs during ongoing motion and the expected pattern of sensory signals established by earlier



Anti-Motion Sickness Drugs. Figure 1 Neural mechanisms of motion sickness and possible effective sites of anti-motion sickness drugs.

experience. Disturbance of spatial orientation finally causes motion sickness symptoms as a warning signal to withdraw the body from unfamiliar stimulus situations. Main sensory information involving sensory integration and maintenance of spatial orientation are the inputs from vestibular, visual, and somatosensory systems. It should be noted that deafened (and perhaps with no normal vestibular function) patients do but rarely experience motion sickness, probably because there arises fewer mismatch signals from fewer sensory modalities. Fig.1 shows the scheme of neural mechanisms of motion sickness and possible effective sites of anti-motion sickness drugs.

Classification of Anti-Motion Sickness Drugs by Neural Mismatch Theories

According to the neural mismatch theories of motion sickness, there are three steps from motion perception to motion sickness symptoms: (i) perception of sensory information during motion stimuli, (ii) integration of new sensory information and comparison with stored sensory patterns, and (iii) final development of motion sickness symptoms. Takeda et al. postulated that anti-motion sickness drugs could be also divided into three classes [2]: Class A drug, reduces neural mismatch signals by a blockade of sensory inputs; Class B drug, facilitates the acquisition of habituation to a new pattern of sensory inputs; Class C drug, blocks the development of symptoms. Although each of these drugs could be effective in preventing motion sickness, their effects on habituation to motion stimuli would differ as follows: Class A drugs would retard the acquisition of habituation, because there are no longer new sensory inputs; Class B drugs would accelerate the habituation to motion stimuli; Class C drugs would not affect the habituation. Based on precise studies using a rat animal model of motion sickness, Takeda et al. demonstrated that cholinergic muscarinic receptor blockers and histamine H1 receptor blockers are the Class B and Class C

drugs, respectively [2]. Glutamate receptor blockers might be Class A drugs, however, it would be difficult to use Class A drugs in practice, because glutamate receptors are involved in most excitatory synaptic transmission in the brain.

Central Activation and Inhibition by Peripheral Vestibular Stimulation and Its Relation to Motion Sickness

It has been reported that vestibular information is processed not only in the short brainstem and cerebellar circuits but also in higher center levels in the brain such as the hypothalamus, amygdala and hippocampus. Recent progress in this area could provide further information on neural substrates for motion sickness.

Histaminergic Neurons

Histamine is well known as a chemical mediator of Type I allergy in the peripheral tissue, however, it also acts as a neurotransmitter in the central nervous system. Histaminergic neurons are known to have important roles in arousal, feeding, thermo regulations, circadian rhythms and other autonomic functions. In vivo release of hypothalamic histamine measured by a microdialysis technique was increased by electrical/caloric vestibular stimulation [3] or 2G-hyper gravity stimulation in rats. Histamine H1 blockers are clinically effective in the prevention of motion sickness and it is also demonstrated that H1 blockers prevented the final development of motion sickness symptoms without affecting the habituation process in the rat model of motion sickness (Class C drugs) [2]. The hypothalamus, which contains the histaminergic cell bodies, is the center of autonomic function and the histaminergic neurons project their nerve fibers to brainstem ►vomiting center. Therefore, it is postulated that the histaminergic neurons, which are activated by the vestibular inputs and provocative motion stimuli, would be involved in the final development of motion sickness symptoms.

Cholinergic Neurons

Several lines of evidence suggest an important role of hippocampal cholinergic neurons in the central processing of vestibular information. For instance, spontaneous firings of neurons in the CA1 area of hippocampus are increased by the electrical stimulation of the vestibular nuclei and firing properties of place cells in the rat hippocampus, which fire only when an animal locates at a specific area in the space, was disturbed in rats that received bilateral vestibular deafferentation. The hippocampus is an area with many converging sensory inputs and therefore it would suit the hypothesis that the hippocampus acts as a neural store and a comparator in the neural mismatch model of motion sickness. Moreover, acetylcholine release from the hippocampus was increased by vestibular stimulation in rats [4] and anti-muscarinic drugs facilitated the habituation to motion in the rat animal model of motion sickness (Class B drugs) [2]. All these findings suggest that the integrated sensory signals would be compared with the stored patterns of sensory signals in the hippocampus and muscarinic blockers would facilitate the adaptation to the new sensory signals.

Noradrenergic Neurons

Catecholamine releasers such as amphetamine and ephedrine are effective in preventing motion sickness, although addiction is a big problem for their clinical use. It is well known that a high degree of emotional or physical stress, which activates the noradrenergic neuron system, can prevent motion sickness. Therefore, these drugs would increase an arousal state and thus prevent motion sickness. In turn, it is reported that caloric vestibular stimulation decreases the spontaneous firing of Locus Coeruleus (LC) neurons, which is the largest nucleus of noradrenergic neurons. This might account for the drowsiness seen in motion sickness.

Serotonergic Neurons

Serotonin 5-HT1A agonists are used clinically for anxiety disorders and have also been shown to prevent motion sickness in animals [5,6], although their effects have not been tested on humans. 5-HT1A receptors are located on both the pre-synaptic and post-synaptic sites. Pre-synaptic 5-HT1A receptors are the autoreceptors, whose activation decreases the release of serotonin from nerve terminals. Although the precise mechanisms of 5-HT1A agonists in preventing motion sickness are not clear, depletion of serotonin by the serotonin synthesis inhibitor parachlorophenylalanine was not effective against motion sickness, suggesting that active sites for 5-HT1A agonists for motion sickness may not be the pre-synaptic autoreceptors. A 5-HT1A agonist would affect any post-synaptic receptors among the neural circuit responsible for motion sickness. For

instance, the firing of vestibular nuclei neurons was negatively regulated by a 5-HT1A agonist [7]. Serotonin 5-HT3 receptor blockers are used for emesis induced by anti-cancer drugs, however, they are not effective for emesis associated with motion sickness.

Substance P Neurons

Substance P and its receptor neurokinin-1 (NK-1) function not only in peripheral tissue but also in the central nervous system. NK-1 receptor blockers were developed as anti-depressants and as anti-emetic drugs. Animal studies demonstrated their efficacy in the prevention of motion sickness [8]. Because these drugs are effective on emesis induced by both motion stimuli and emetic chemical agents, their effective site would be the brainstem vomiting center, which is the final common structure responsible for the emetic reflex. We reported that substance P mRNA was increased by 2G hypergravity stimulation in the amygdala and NK-1 receptor blockers were effective in preventing motion sickness in rats [9]. The Amygdala substance P neuron system is important for the judgment of whether the situation is “comfortable” or not. We hypothesized that neural mismatch signals from hippocampus might be sent to the amygdala and are then judged as to whether they are comfortable or not. If the signals are not “comfortable” for the body, they are sent to areas relating to the expression of motion sickness symptoms, working as warming signals. NK-1 receptor blockers may affect both the brainstem vomiting center and the amygdala.

Vasopressin Neurons

Vasopressin is a pituitary hormone which has an anti-diuretic effect. Intra venous application of vasopressin induces emesis and arginine vasopressin 1 (AVP-1) blockers are effective in the prevention of motion sickness. Moreover, plasma vasopressin levels were increased by electrical/caloric vestibular stimulation in rats [10]. Therefore, AVP-1 blockers are expected to be effective on motion sickness and have been tested by several researchers. However, the effects of AVP-1 receptor blockers on motion sickness are different between species [6].

References

1. Reason JT (1978) Motion sickness adaptation: a neural mismatch model. *J Roy Soc Med* 71:819–829
2. Takeda N, Morita M, Hasegawa S, Horii A, Kubo T, Matsunaga T (1993) Neuropharmacology of motion sickness and emesis. A review. *Acta Otolaryngol Suppl* 501:10–15
3. Horii A, Takeda N, Matsunaga T, Yamatodani A, Mochizuki T, Okaura-Mochizuki K, Wada H (1993) Effect of unilateral vestibular stimulation on histamine release from the hypothalamus of rats in vivo. *J Neurophysiol* 70:1822–1826

4. Horii A, Takeda N, Mochizuki T, Okakura-Mochizuki K, Yamamoto Y, Yamatodani A (1994) Effects of vestibular stimulation on acetylcholine release from rat hippocampus: an in vivo microdialysis study. *J Neurophysiol* 72:605–611
5. Lucot JB, Crampton GH (1989) 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine. *Pharmacol Biochem Behav* 33:627–631
6. Yates BJ, Miller AD, Lucot JB (1999) Physiological basis and pharmacology of motion sickness: an update. *Brain Res Bull* 47:395–406
7. Johnston AR, Murnion B, McQueen DS, Dutia MB (1993) Excitation and inhibition of rat medial vestibular nucleus neurones by 5-hydroxytryptamine. *Exp Brain Res* 93:293–298
8. Rudd JA, Ngan MP, Wai MK (1999) Inhibition of emesis by tachykinin NK1 receptor antagonists in *Suncus murinus* (house musk shrew). *Eur J Pharmacol* 366:243–252
9. Uno A, Nakagawa A, Horii A, Mitani K, Takeda N, Kubo T (2004) Effect of an NK1 receptor antagonist on motion sickness in rats and its putative site of action. *J Vestib Res* 14:155
10. Horii A, Koike K, Uno A, Uno Y, Kubo T (2001) Vestibular modulation of plasma vasopressin levels in rats. *Brain Res* 914:179–184

Anti-NMDAR Antibodies

Definition

NMDA (N-methyl D-aspartate) receptor (NMDAR) antibodies. Antibodies to a protein molecule on the neuronal surface that bind to glutamate, a neurotransmitter that participates in excitatory neurotransmission.

Activation of NMDARs is important for learning and memory; overactivation of NMDARs injures the cell.

- NMDA Receptors

Antinociception

- Analgesia

Antinodes

Definition

A point, line, or surface of a standing wave in which some characteristic of the wave field is maximal.

- Acoustics

Antiporter

Definition

- Chloride Channels and Transporters
- Ion Transport

Antipsychotic Drugs

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Synonyms

Neuroleptic drug; Major tranquilizer; Ataractic drug

Definition

Antipsychotic drugs are medications used to treat the state of mental turmoil called “►psychosis”.

Characteristics

History

Antipsychotic drugs were discovered in 1952. A drug-development program by the French pharmaceutical company Rhône-Poulenc, primarily aimed at finding medications to alleviate post-operative shock, produced the agent chlorpromazine (“Largactil”). This was found to produce a remarkable calming effect on patients to whom it was given, and it was suggested that it be used to “tranquillize” disturbed patients in psychiatric hospitals. It was found to be effective in reducing symptoms of psychosis. However, right from its earliest use, it was found also to produce major motor side effects, reminiscent of symptoms of ►Parkinson’s disease. Further pharmaceutical research soon produced a variety of other medications with similar effects. The combination of their two effects (antipsychotic main effects and motor side effects) led to this group of drugs being called “►neuroleptic drugs”.

Antipsychotic Drugs and the Dopamine Hypothesis of Psychosis

Research in the early 1960s led to the proposal by Carlsson that the common property of antipsychotic drugs was that they are antagonists of the forebrain neurotransmitter dopamine, a deficit of which had also recently been found to underlie many of the symptoms of Parkinson’s disease. This led to formulation of the so-called “►dopamine hypothesis of ►schizophrenia”.

However, this was always a misnomer: The phrase “dopamine hypothesis of psychosis” would have been more accurate, since the neuroleptic drugs do not alleviate many of the non-psychotic symptoms of schizophrenia. Even some of the distinctive apparently-psychotic symptoms of schizophrenia (auditory verbal ▶hallucinations, and the group of symptoms described by Kurt Schneider [see “▶passivity experience”]) can often persist despite otherwise effective antipsychotic drug treatment.

The birth of the “dopamine hypothesis” has led to many attempts to reveal directly an overactivity of dopamine in the forebrain of persons in active psychotic states. One line of enquiry has sought an excess of dopamine receptors associated with schizophrenia. Although much evidence for such an excess has been obtained, it has been difficult to show that this is really a feature of the illness, rather than a by-product of antipsychotic drug treatment, and there is no precedent for any illness caused by a primary excess of any receptor type. The other possibility is that there is excess release of the transmitter itself in these states. Starting with Reith et al [1], using a method based on ▶Positron Emission Tomography, several studies have now shown such an excess.

Prediction of Antipsychotic Effects

Pharmaceutical research in the 1960s revealed a variety of behavioral effects of neuroleptic drugs in animal tests, which could be used to predict whether a new compound would have antipsychotic activity. Some of these tests were based on production of syndromes equivalent to the motor side effects seen in humans. However, the most reliable animal behavioral tests for determining the antipsychotic potency of new compounds were based on antagonism of simple ▶instrumental conditioning tasks (such as avoidance responding).

Receptors Targeted by Antipsychotic Drugs

In the mid-1970s radio-ligands became available specific for the pharmacological receptors by which dopamine produces its effects. This provided independent verification of the thesis that the common property of neuroleptic drugs was their ability to block dopamine receptors. It was found that the affinity of a variety of antipsychotic drugs for the relevant ▶dopamine receptor varied in parallel with their clinical potency as antipsychotic agents. By the early 1980s, when ligands for different dopamine receptors became available, it was clear that the dopamine receptor type which showed this close relation to clinical effects was the so-called “▶dopamine D2” receptor. From this evidence, it became widely believed that the D2 receptor was the essential target of antipsychotic

drugs, and that this single receptor mediated both the therapeutic effects and the motor side effects of antipsychotic drugs.

More recently, several bodies of evidence have appeared which challenge this view. *First*, not all antipsychotic drugs are “neuroleptic”, in the sense of also producing motor side effects. This was known in the 1970s, when some the clinical properties of the antipsychotic drug clozapine were defined. More recently a wider range of medications has been developed with antipsychotic potency, but with a low tendency to produce motor side effects, at doses which are effective against psychosis. These are the “second generation” or “▶atypical” antipsychotic drugs. *Second*, the role of dopamine in instrumental conditioning depends on its actions as a psychological reinforcing signal in the brain, a role now generally believed to be independent of its role in motor performance [2]. Psychopharmacological experiments have generally shown the reinforcing role of dopamine to be based on its actions at the so-called “▶D1” dopamine receptor, and recent studies of the processes of synaptic plasticity in the striatum, upon which instrumental conditioning depends, support this [3]. Part of the mechanism underlying such dopamine-dependent synaptic plasticity is the increased production of the intracellular messenger ▶cyclic-Adenosine-Monophosphate (cAMP). As mentioned, blockade of instrumental conditioning is the best predictor of antipsychotic potency, and tests of this in animals recognize clozapine and similar drugs as antipsychotic agents when production of motor side effects in animals by these drugs does not [2]. This is paradoxical if it is assumed that the D2 dopamine receptor is the only essential target of antipsychotic drugs. *Thirdly*, in the 1990s methods became available to determine the percentage “occupancy” of dopamine receptors by antipsychotic drugs needed to produce therapeutic effects. For most antipsychotic drugs occupancy of 70–80% was needed. For clozapine, a substantially lower occupancy would suffice [4]. This suggests that receptors in addition to the dopamine D2 receptor are influential in antipsychotic drug therapy.

Theory of Antipsychotic Drug Action

Starting in the mid-1970s, the author of this article has developed a theory to resolve these paradoxes [5]. A central fact in this work is that the full therapeutic effect of antipsychotic drugs is not achieved until long after the relevant receptors are blocked [2,6]. This applies particularly to ▶delusions (Symptom of Psychosis), which are the symptom which responds most slowly during antipsychotic drug therapy. The extended time course of antipsychotic drug therapy is still debated by some, but was clearly revealed in clinical trials in the 1960s, is mentioned explicitly in some “first-person” accounts of psychosis, and was

referred to in a recent symposium on antipsychotic drug treatment [6]. For patients whose psychotic state has remained untreated for a long period, it may take many months of drug treatment before resolution of symptoms is complete. This central fact was explained as follows: Active psychosis occurs when dopamine release is excessive, and this leads to an exaggeration of a process of dopaminergic reinforcement. In humans, this reinforcement is directed mainly at distinctively human cognitive information, whose representation in cerebral processes then becomes exaggerated and distorted. Many of the details of psychotic psychology can be explained on this basis (for instance the production of delusions, “incurable” by any amount of reasoning or contrary empirical evidence) (see reference [5], chapter 9). Administration of antipsychotic drugs halts the production of such exaggerated and distorted material, but does not immediately abolish that which has already been laid down in memory. However, by reducing the overall “pressure” on cognitive processes it becomes possible for a patient to gradually “work through” the conflicts of belief set up during the period of psychosis, and thus to work out which beliefs were symptoms of an illness, and which are more trustworthy. This process inevitably takes time.

The paradox about the dopamine receptor type involved in antipsychotic therapy is then accounted for by the proposal that D2-blocking neuroleptic drugs act indirectly, the ultimate target being either a reduction of activation at the dopamine D1 receptor (which mediates psychological reinforcement), or an attenuation of intracellular processes “downstream” to, and usually controlled by, this receptor type. At present, the most likely mechanism for this indirect action [5] is as follows: In the striatum, which has the highest concentration of dopamine, one class of neuron (about 2% of the total neuron count there) are the cholinergic interneurons. Dopamine, acting at D2 receptors inhibits the firing of these interneurons [7]. It is then expected that D2-blocking neuroleptic drugs would release these neurons from inhibition, leading to a sustained increase in acetylcholine release in the striatum. The principal neurons in the striatum bear cholinergic receptors of various types. Of importance are the so-called M4 receptors which reduce production of cyclic-AMP when the receptors are activated by acetyl choline [8]. Thus, D2 blockade would indirectly reduce cAMP production, an effect similar to that produced more directly by D1 blockade, and which would attenuate the dopaminergic reinforcement process.

Adverse Effects of Long-Term Treatment

Antipsychotic drugs have been controversial. In the past this has been because of the unpleasant nature of the motor side effects, a drawback which is less important

with the advent of the atypical antipsychotic drugs. An additional hazard of the traditional neuroleptic drugs, recognized as early as the late-1950s, was that they were a contributory cause of a more persistent motor abnormality, referred to as ►**tardive dyskinesia**. In this syndrome, abnormal involuntary movements occur, especially of tongue, mouth and face. The atypical antipsychotic drugs have a lesser tendency to cause this syndrome, but since tardive dyskinesia, once established, is often quite persistent and difficult to treat, there is still a legacy of disability due to past use of first-generation neuroleptic drugs, especially when they were used in large doses. The persistence of these abnormal movements suggests that they arise due to permanent cell loss in the brain. In 1993 [9] it was suggested that during neuroleptic treatment, the prolonged overactivity of the striatal cholinergic neurones might be so intense that it led to damage and destruction of these cells, this being the necessary cause of tardive dyskinesia. Animal experiments support the view that prolonged regimes of neuroleptic drugs can lead to loss of striatal cholinergic interneurons. Loss of such cells has also recently been documented in post-mortem brains of human schizophrenia patients treated with neuroleptic drugs (review in reference [5], chapter 10).

Psychotic states are not always alleviated by antipsychotic drugs. However, it is well established that clozapine is often an effective treatment when other antipsychotic medications have failed [10]. In addition, it has been suggested that prolonged treatment with traditional neuroleptic drugs, especially in high doses leads gradually to the re-emergence of psychotic symptoms despite drug treatment, and eventually to psychosis resistant to conventional treatment, though often still responsive to clozapine (“neuroleptic-induced supersensitivity psychosis”; review in reference [5], chapter 10). The parallel between this course of development, and the emergence of tardive dyskinesia during neuroleptic treatment, led to the suggestion that they are parallel pathologies, due in both cases to loss of striatal cholinergic interneurons, but in different parts of the striatum. The special effectiveness of clozapine then suggests that this drug acts more directly than typical neuroleptic drugs, by-passing the link through striatal cholinergic interneurons. Its direct action could be by either of two mechanisms, a direct blockade of D1 receptors (supported by the fact that clozapine has somewhat higher relative affinity for D1 versus D2 receptors than other antipsychotic drugs in clinical use), or by direct stimulation of M4 cholinergic receptors (for which clozapine may have an affinity, probably as an agonist). Either of these mechanisms would reduce cAMP formation, and attenuate the dopaminergic reinforcement process even when the normal mechanism for this, dependent on transmitter release from intact cholinergic interneurons, is no longer possible.

References

1. Reith J, Benkelfat C, Sherwin A, et al. (1994) Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc Natl Acad Sci USA* 91:11651–11654
2. Miller R (1987) The time course of neuroleptic action for psychosis: role of learning processes and implications for concepts of psychotic illness. *Psychopharmacology (Berl)* 92:405–415 (A review)
3. Farde L, Nordstrom AL (1992) PET analysis indicates atypical central dopamine receptor occupancy in clozapine-treated patients. *Br J Psychiatry Suppl* 17:30–33
4. Kerr JN, Wickens JR (2001) Dopamine D-1/D-5 receptor activation is required for long-term potentiation in the rat neostriatum *in vitro*. *J Neurophysiol* 85:117–124
5. Miller R (2007) A theory of the basal ganglia and their disorders (especially chapters 9 and 10). Conceptual advances in brain research series. CRC Press, Boca Raton
6. Marder SR, Essock SM, Miller AL, Buchanan RW et al. (2002) The Mount Sinai conference on the pharmacotherapy of schizophrenia. *Schizophrenia Bull* 28:5–16
7. Lehmann J, Lange SZ (1983) The striatal cholinergic interneuron: synaptic target of dopaminergic terminals? *Neuroscience* 4:1105–1120
8. Olianas MC, Adem A, Karlsson E, Onali P (1996) Rat striatal muscarinic receptors coupled to the inhibition of adenylyl cyclase activity: potent block by the selective M4 ligand muscarinic toxin 3 (MT3). *Br J Pharmacol* 118:283–288
9. Miller R, Chouinard G (1993) Loss of striatal cholinergic neurons as a basis for tardive and L-Dopa-induced dyskinésias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. *Biol Psychiatry* 34:713–738
10. Kane JM, Honifeld G, Singer J, Meltzer H (1988) Clozapine for the treatment-resistant schizophrenic: a double blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45:789–796

Antiretrovirals (ARVs)

Definition

These are the agents active against retroviruses, and act at one or more sites. These inhibit reverse transcriptase, protease or integrase of the retroviruses or inhibit fusion of the virus with the host cells. Highly Active Anti-Retroviral Therapy (HAART) is a combination of the highly active anti-retrovirals with different mechanisms of action, and is used to prolong the life of a patient suffering from Acquired Immune Deficiency Syndrome (AIDS).

- Central Nervous System Disease – Natural Neuro-protective Agents as Therapeutics

Anti-Saccade

Definition

A saccade triggered by the appearance of an eccentric target but directed away from that target into the opposite, empty visual hemifield. Antisaccades are not a natural behavior but generally only obtained upon instruction. To generate an antisaccade, first the reflexive saccade toward the new target (often called prosaccade in this context) must be suppressed, a task requiring considerable attentional effort and imparting the antisaccade a long reaction time. The antisaccade task is of considerable practical interest as an elevated frequency of errors (inability to suppress prosaccades) is suggestive of frontal dysfunction.

- Oculomotor Control (Theory)
- Saccade, Saccadic Eye Movement

Anti-Saccade Task

Definition

At the beginning of a trial, a visual target is presented, and the subject (human or monkey) is required to fixate it. At the end of the fixation period, this target is extinguished at the same time that a second target comes on. The subject must then make a gaze shift to the location that is equal to the target in eccentricity, but opposite in direction.

- SC-Saccade Related Burst Neurons
- SC – Sensory Maps
- Superior Colliculus – Quasi-Visual Neurons
- Superior Colliculus – Role in Eye Movements

Anti-schizophrenic Drugs

Definition

Drugs that reduce schizophrenic and manic symptoms. Their therapeutic efficacy correlates with their ability to block competitively dopamine-2 receptors in the limbic system.

- Antipsychotic Drugs
- Schizophrenia

Anti-sea Sickness

- Anti-Motion Sickness Drugs

Anti-seizure Medicine

- Anticonvulsants

Antisense RNA

Definition

Antisense RNA is a single-stranded RNA copy that is complementary to the sequence of nucleotides found in an mRNA. Antisense RNA can be introduced into a cell to block translation of mRNA.

Anti-SSA (Anti-Ro)/Anti-SSB (Anti-La) Antibodies

Definition

Antinuclear antibodies that typically occur in pSS.

Anti-SSB (Anti-La) antibodies are more specific to pSS, whereas anti-SSA (Anti-Ro) antibodies are also commonly associated with other autoimmune diseases, such as subtypes of systemic lupus erythematosus.

- Central Nervous System Disease in Primary Sjögren's Syndrome

Anurans

Definition

Anuran amphibians are one of three orders of living amphibians (order Anura). They are commonly referred to as frogs or toads. These are in many ways highly specialized vertebrates quite unlike ancestral amphibians.

Their visual systems are expanded and have specialized features related to visual prey capture. Their auditory systems are likewise enlarged with processing specializations reflecting the use of vocal signals in

reproductive social communication. The characteristic body shape of frogs and toads reflects the specialized mode of salutatory, or jumping, locomotion seen in many anuran species. There are no doubt motor system functional specializations related to this and to the vocal production common in this amphibian group. Anurans have by far been the subject of most neuroanatomical and neurophysiological studies of the amphibians.

- Evolution of the Brain: Amphibians

Anxiety Disorder

Definition

A blanket term covering several different forms of pathological anxiety, fear, phobias and nervous conditions that may impair or prevent the pursuit of normal daily routines.

- Learning and Extinction
- Neuroendocrinology of Psychiatric Disorders
- Hypothalamo-Pituitary-Adrenal Axis, Stress and Depression

Anxiolytic Agents

Definition

Anxiolytic agents such as benzodiazepines are capable of reducing anxiety. As a side-effect, they cause anterograde amnesia.

- Anterograde Amnesia
- Memory Improvement

Anxiolytic and Hypnotic Drugs Acting on Ionotropic GABA Receptors

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Definition

Anxiolytic and ►hypnotic drugs are used in the treatment of anxiety disorders and sleep disturbances

to reduce anxiety and promote sleep. These drugs encompass a number of different classes of compounds, including the ►benzodiazepines. Most of the currently used anxiolytic and hypnotic drugs act on ►ionotropic receptors for ►GABA, the major inhibitory neurotransmitter in the brain. This reflects the importance of GABAergic systems for anxiety and sleep related behaviours [1].

The focus of this essay is on compounds acting at ionotropic GABA receptors and the development of new anxiolytic and hypnotic drugs. There is great diversity in these receptors and of particular interest are compounds that show selectivity for specific subtypes of ionotropic GABA receptors.

Characteristics

Ionotropic GABA Receptors

Ionotropic GABA receptors comprise the GABA_A and ►GABA_C receptors, whereas GABA_B receptors are metabotropic [2]. Ionotropic GABA receptors are ►ligand-gated ion channels that are formed from five protein subunits surrounding a chloride channel, thus controlling the flow of chloride ions into nerve cells. To date, fifteen GABA_A receptor subunits ($\alpha 1-6$, $\beta 1-3$, $\gamma 1-3$, δ , ϵ , θ) and three GABA_C receptor subunits ($\rho 1-3$) have been cloned from the mammalian brain. ►GABA_A receptors are heteromeric (►Heteromeric receptors), while GABA_C receptors are known to be homomeric (►Homomeric receptors). The majority of GABA_A receptors are assembled from two α , two β and one γ subunit with the arrangement $\alpha\beta\alpha\beta\gamma$. The most commonly occurring GABA_A receptors are $\alpha 1\beta 2\gamma 2$ receptors, $\alpha 2$, $\beta 2/3$, $\gamma 2$ and $\alpha 3$, βn , $\gamma 2/3$ heteromers. GABA_A and GABA_C receptors differ significantly in their molecular biology, pharmacology and physiology [2]. GABA_A receptors are present on most, if not all, neurones in the brain, whereas GABA_C receptors have a much more restricted distribution. GABA_C receptors are considered to play an important role in vision, memory and sleep [3].

Anxiolytic Drugs Acting on Ionotropic GABA Receptors

Benzodiazepines are the most well known class of ►anxiolytic drugs. Examples of widely used benzodiazepines include diazepam, oxazepam, nitrazepam, flunitrazepam and temazepam. Benzodiazepines act as allosteric ►modulators of many subtypes of GABA_A receptors, enhancing the action of GABA at these receptors. In the presence of GABA, benzodiazepines increase the frequency of chloride channel opening without increasing the maximal response to GABA. Benzodiazepines are considered to be relatively safe and effective, however their main drawbacks are associated with dependence, ataxia and amnesia [4].

In addition to their anxiolytic effect, the classical benzodiazepines are also sedative (►sedative drugs),

►hypnotic (sleep inducers), anticonvulsant and myorelaxant. This is due to the fact that they act at all GABA_A receptors containing $\alpha 1$, $\alpha 2$, $\alpha 3$ or $\alpha 5$ subunits, coupled with a $\gamma 2$ subunit. Benzodiazepines bind to the interface between α and $\gamma 2$ subunits. The $\gamma 2$ subunit is essential for high affinity benzodiazepine binding, while the α subunit predicts benzodiazepine ►efficacy.

Studies using knock-in point mutations at the $\alpha 1$, $\alpha 2$, $\alpha 3$ and $\alpha 5$ benzodiazepine binding site that render the subunit insensitive to benzodiazepines, show that the different α subunits mediate different actions of benzodiazepines [5]. We now know that the $\alpha 1$ subunits mediate the sedative/hypnotic and anticonvulsant actions of benzodiazepines, the $\alpha 2$ subunits contribute to the anxiolytic action, and the $\alpha 3$ and $\alpha 5$ subunits partly mediate the myorelaxant effect. That $\alpha 2$ subunit-containing ►GABA_A receptors contribute to the anxiolytic effects of benzodiazepines is consistent with localization of these subunits in the central nucleus of the amygdala, a key area in the brain for control of emotions and fear. There is also evidence that $\alpha 3$ subunit-containing GABA_A receptors contribute to the anxiolytic effects of benzodiazepines.

Anxiolytics Specific for Subtypes of GABA_A Receptors

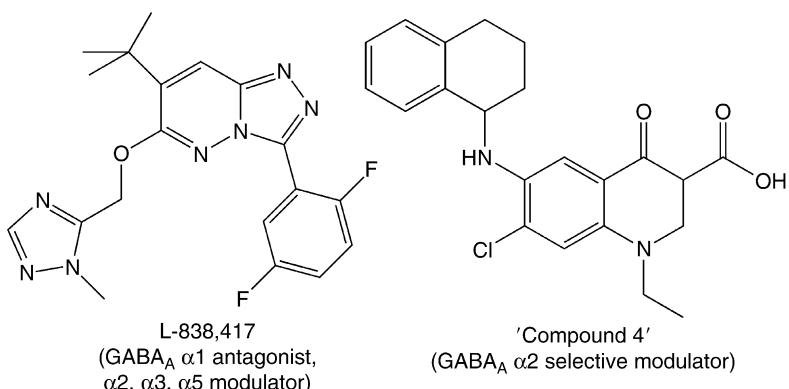
On the basis of this knowledge, subtype selective benzodiazepines have been developed. L-838,417 (Fig. 1) is one of a series of novel site ligands, selective for $\alpha 2$ and $\alpha 3$ subunits and which block $\alpha 1$ subunits, that have recently been described. Such agents produce anxiolysis and myorelaxation without associated sedation [4]. New benzodiazepine-site ligands with selectivity for $\alpha 2$ or $\alpha 3$ over $\alpha 1$ GABA_A receptors are being developed but have yet to reach the clinic [2,4].

Patients taking fluoroquinolone antibiotics such as norfloxacin are known to show a low incidence of anxiety and convulsions. Chemical modification of norfloxacin has led to "compound 4" (Fig. 1) that shows $\alpha 2$ subunit selectivity as a GABA_A receptor modulator. It is a non-sedating anxiolytic whose action is independent of classical benzodiazepine receptors [2].

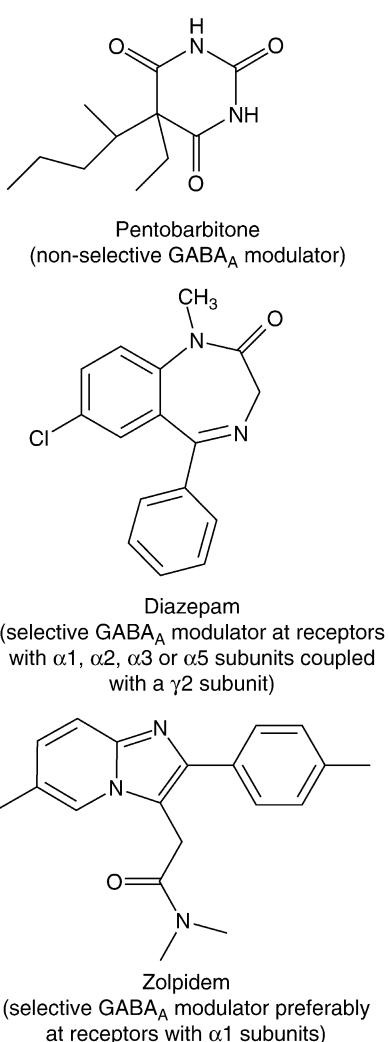
Hypnotics and Ionotropic GABA Receptors

GABA mechanisms play an important role in the sleep-wake cycle and it is well established that activation of GABA_A receptors favours sleep [6]. This is the mechanistic basis of the action of three generations of hypnotics (Fig. 2) with increasing GABA_A receptor subtype selectivity leading to more selective actions.

Barbiturates (such as pentobarbitone) enhance the activation of most, if not all, GABA_A receptors by GABA. Benzodiazepines (such as diazepam) have a more specialised action, as noted above, acting only on subsets of GABA_A receptors containing $\alpha 1$, $\alpha 2$, $\alpha 3$ or $\alpha 5$ subunits, coupled with a $\gamma 2$ subunit. The third



Anxiolytic and Hypnotic Drugs Acting on Ionotropic GABA Receptors. Figure 1 Agents acting selectively on subtypes of GABA receptors.



Anxiolytic and Hypnotic Drugs Acting on Ionotropic GABA Receptors. Figure 2 Therapeutic agents acting on ionotropic GABA receptors.

generation of hypnotics (so-called “non-benzodiazepines” such as zolpidem, zolpiclone and indiplon) act on still more specialised subsets of GABA_A receptors, acting preferentially on GABA_A receptors that contain α1 subunits [7].

The development of new hypnotics is necessary due to significant problems associated with currently available agents. Barbiturates, in addition to their induction of liver enzymes and potential for lethal overdose, are far from ideal hypnotics as they massively extend the “intermediate stage” of sleep between slow-wave sleep and paradoxical sleep at the expense of the latter [6]. In the 1970s barbiturates were largely replaced as hypnotics by benzodiazepines; these were far safer drugs that enhanced slow-wave sleep. However, their use as hypnotics was associated with residual daytime sleepiness, anterograde amnesia and significant potential for dependence [7]. The third generation hypnotics showed significant improvement over the classical benzodiazepine hypnotics producing sedation without ataxia, but significant adverse effects have been reported with some of these agents. Indeed, zolpidem has been linked to bizarre compulsive activity including sleep walking and binge eating.

The sedative action of diazepam is abolished in mice in which the $\alpha 1$ GABA_A receptor subunit has been made insensitive to diazepam by a point mutation [1]. This appears to be consistent with the hypnotic action of $\alpha 1$ -preferring ligands such as zolpidem. However, changes in sleep patterns induced by diazepam are strongly attenuated in mice lacking a diazepam-sensitive $\alpha 2$ GABA_A receptor subunit. This indicates that the sedative and hypnotic effects of diazepam are not equivalent and that more than one α -subunit type contributes to the overall effects of diazepam on sleep. While the third generation hypnotics are classified as $\alpha 1$ -preferring agents they do show some activity at $\alpha 2$ and $\alpha 3$ -subunits. Thus the situation regarding the relative importance of specific α -subunits to the hypnotic actions

of these agents is nowhere near as clear cut as originally thought. We need agents with significantly increased subunit selectivity to sort this out.

Future Generations of Hypnotics Acting on Ionotropic GABA Receptors

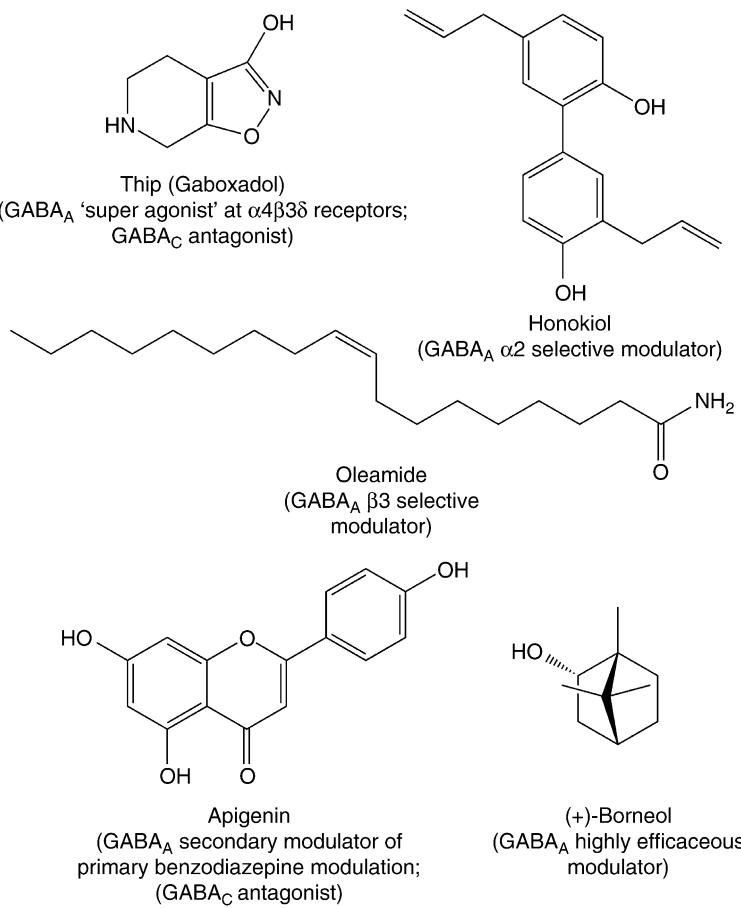
It has been suggested that the development of newer GABAergic hypnotics might be targeted to producing changes in EEG patterns that correspond to those during physiological sleep [1]. A promising approach appears to be to move away from benzodiazepine-like modulation altogether and to target sites on ▶ionotropic GABA receptors that are insensitive to the classical effects of benzodiazepines [3].

Oleamide (Fig. 3) is an endogenous cannabinoid that promotes sleep (see Chapter on Cannabinoids). It acts as a modulator at GABA_A receptors that contain β3 subunits, being inactive in β3 knockout mice. Its action is flumazenil insensitive and thus independent of classical benzodiazepine sites. Interestingly, a patient with chronic insomnia is known to have a β3 GABA_A receptor subunit mutation. Oleamide represents a lead

for the development of new hypnotics based on modulation of β3 containing GABA_A receptors [2].

There is considerable interest in extrasynaptic δ subunit-containing GABA_A receptors on thalamocortical neurones as molecular targets for future generations of hypnotics [8]. Such receptors are more sensitive to GABA than most GABA_A receptors and appear to be involved in tonic inhibition, regulating neuronal excitability. They are insensitive to benzodiazepines and are potently modulated by ethanol.

THIP (Gaboxadol, Fig. 3) is an important lead compound in the development of new types of hypnotics. THIP was originally developed as a novel GABA agonist of restricted conformation. It was found to be a potent analgesic, but unwanted sedative effects curtailed its clinical development. The sedative effects led to its investigation as a hypnotic [9]. THIP was found to produce high quality sleep characterised by increased non-rapid eye movement sleep and decreased awakenings. Studies with healthy elderly volunteers indicated that THIP reverses typical age-related changes in sleep by improving sleep efficiency and by boosting



Anxiolytic and Hypnotic Drugs Acting on Ionotropic GABA Receptors. Figure 3 Chemically diverse natural and synthetic agents acting on ionotropic GABA receptors.

slow wave sleep, which declines with age [7,9]. Studies in animals indicated that the hypnotic effects of THIP were not potentiated by benzodiazepines or ethanol. THIP is known to act as a “super agonist” at $\alpha 4\beta 3\delta$ GABA_A receptors, i.e. it produces a greater activation of these receptors than does GABA. The activation by THIP of these receptors in the thalamus is thought to produce a firing pattern that promotes restful, slow-wave sleep. THIP went into clinical trials in 2004, but it was withdrawn during stage three trials early in 2007 because the overall clinical profile for THIP in insomnia did not support further development.

THIP is almost as potent at GABA_C receptors, where it acts as an antagonist, as it is as an agonist at $\alpha 4\beta 3\delta$ GABA_A receptors [3]. It is possible that an action on GABA_C receptors may confound the hypnotic properties of THIP as other studies have shown that GABA_C receptors that are insensitive to benzodiazepines and barbiturates are targets for the development of novel hypnotics [3,6]. Studies using TPMPA, a specific GABA_C receptor antagonist that decreases slow wave sleep, show that these receptors are involved in sleep-waking regulation. GABA_C receptor agonists and modulators, as distinct from antagonists, may be suitable for development as novel hypnotics [6].

Herbal Preparations for Anxiety and Sleep Disorders

Many herbal preparations that have long been used for their anxiolytic and sleep promoting properties are now known to contain compounds that modulate ionotropic GABA receptors [10]. These preparations include valerian, chamomile and green tea, and their active constituents (Fig. 3) include flavonoids (e.g. apigenin), terpenoids (e.g. (+)-borneol) and polyphenolic compounds (e.g. honokiol). The rich chemical diversity of these GABA receptor modulating compounds and their effects on brain function provide a rational basis for the anxiolytic and hypnotic properties of the herbal preparations from which they are derived and may lead to the development of new therapeutic agents.

Plant flavonoids have long been known to interact with benzodiazepine binding sites on GABA_A receptors and have served as lead compounds for the development of synthetic flavonoids that have anxiolytic and sedative properties. Two flavonoids, apigenin (from chamomile, Fig. 3) and epigallocatechin gallate (from green tea), have shown to have unique additional effects at GABA_A receptors, enhancing the modulatory effects of benzodiazepines [10], and thus being the first known secondary modulators of GABA_A receptors. In concentrations at which they have no direct effects on GABA_A receptors they act as secondary modulators of primary modulation by benzodiazepines. This action is restricted to enhancing the modulation by benzodiazepines and is not seen with barbiturate or neurosteroid

modulation. These compounds are anxiolytic in animal models of anxiety suggesting that they are modulating an endogenous benzodiazepine-like modulation. Furthermore, the action of these flavonoids offers the opportunity of reducing the dose of benzodiazepine needed, possibly reducing side effects and dependence liability of benzodiazepines.

The terpenoid (+)-borneol (Fig. 3), an active constituent of valerian (*Valeriana officinalis*), acts with high efficacy at GABA_A receptors, enhancing GABA action through a benzodiazepine-insensitive mechanism [10].

Honokiol, a polyphenolic compound from *Magnolia* species (Fig. 3), is an anxiolytic in animal models of anxiety without causing sedation, and this effect can be blocked by the benzodiazepine antagonist flumazenil [10]. It is thought that this compound acts preferentially at $\alpha 2$ subunit-containing GABA_A receptors, consistent with its non-sedating anxiolytic properties.

Conclusion

Site-directed mutagenesis and the availability of increasingly subtype selective compounds acting at GABA_A receptors has led to a greater understanding of the molecular basis of anxiolytic and hypnotic drug effects. This understanding, coupled with the availability of a diverse range of compounds from herbal preparations and lead development will result in new and better agents to treat anxiety and sleep disorders.

References

1. Möhler H (2006) GABA_A receptors in central nervous system disease: anxiety, epilepsy, and insomnia. *J Recept Signal Transduct* 26:731–740
2. Johnston GAR (2005) GABA_A receptor channel pharmacology. *Current Pharm Des* 11:159–164
3. Chebib M, Hanrahan JR, Mewett KN, Duke RK, Johnston GAR (2004) Ionotropic GABA receptors as therapeutic targets for memory and sleep disorders. *Annu Rev Med Chem* 39:13–23
4. Rudolph U, Möhler H (2004) Analysis of GABA_A receptor function and dissection of the pharmacology of benzodiazepines and general anaesthetics through mouse genetics. *Annu Rev Pharmacol Toxicol* 44:475–498
5. Dawson GR, Collinson N, Atack JR (2007) Development of subtype selective GABA_A modulators. *CNS Spectr* 10:21–27
6. Gottesmann C (2002) GABA mechanisms and sleep. *Neuroscience* 111:231–239
7. Ebert B, Wafford KA, Deacon S (2006) Treating insomnia: current and investigational pharmacological approaches. *Pharmacol Ther* 112:612–629
8. Belelli D, Peden DR, Rosahl TW, Wafford KA, Lambert JJ (2005) Extrasynaptic GABA_A receptors of thalamocortical neurons: a molecular target for hypnotics. *J Neurosci* 25:11513–11520

9. Lancel M, Wetter TC, Steiger A, Mathias S (2001) Effect of the GABA_A agonist gaboxadol on nocturnal sleep and hormone secretion in healthy elderly subjects. *Am J Physiol Endocrinol Metab* 281:E130–E137
10. Johnston GAR, Hanrahan JR, Chebib M, Duke RK, Mewett KN (2006) Modulation of ionotropic GABA receptors by natural products of plant origin. *Adv Pharmacol* 54:285–316

AOS

Definition

► Accessory Optic System

► Nerves

AP2 α

Definition

AP2 α is a member of transcription factor AP-2 gene family that consists of three different genes. AP-2 is shown to have important functions in differentiation of neural crest-derived cell lineage. AP2 α is thought to be required for a number of morphogenetic events including aspects of craniofacial development and midline fusion.

► Neural Crest
► Neural Development

APC (Adenomatosis Polyposis Coli)

Definition

A protein involved in mobility of the growth cone through microtubule plus-end capping. GSK-3 β phosphorylates.

APC, preventing microtubule plus-end capping, thereby reducing stability and decreasing motility. Neurotrophin binding (TrkA activation) allows microtubule plus-end capping by APC, through inhibition of glycogen synthase kinase 3 β (GSK-3 β).

► Neurotrophic Factors in Nerve Regeneration

Aperture Problem

Definition

The aperture problem refers to the fact that the motion of a one-dimensional spatial structure, such as a bar or edge, cannot be determined unambiguously if it is viewed through a small aperture such that the ends of the stimulus are not visible. In the context of visual motion processing, the aperture problem is faced by individual neurons with receptive fields that sample only a spatially restricted region of the retinal image.

► Visual Motion Processing

Aphasia

Definition

Inability to produce and/or understand language that results from damage to portions of the brain that are responsible for language. Depending on which portion is affected, the language disability changes. Damage to the frontal lobe tends to cause a more expressive aphasia (the patient may understand what people say but cannot produce words), while damage to the temporal/parietal, i.e., auditory areas tends to cause more of a receptive aphasia: the patient speaks fluently but makes no sense nor understands other people talking. The damage is always on the dominant side of the brain which, in 95% of people, is the left.

► Ischemic Stroke
► Stroke

Aplysia

Definition

An invertebrate, a sea slug, which features in a number of important neurophysiological investigations of memory.

Apnea

Definition

Period of time during which breathing stops or is markedly reduced.

- Development of the Respiratory Network

differentiation which it involves a cascade of complex biochemical events leading to characteristic changes in cell morphology prior to death. The main feature of apoptosis is that events, including chromatin condensation and DNA fragmentation, are accomplished in such a way to dispose of cellular debris without inducing an inflammatory response.

- Development and Regeneration

Apneusis

Definition

Apneusis is characterized by a marked prolongation of inspiration and a plateau inspiratory discharge of respiration-related brainstem neurons regardless of length of expiration.

- Pontine Control of Respiration
- Respiratory Neurotransmitters and Neuromodulators

Apparent Motion

Definition

Apparent motion is an illusion of motion that can be produced by presentation of a sequence of discrete “snapshots” rather than a continuously changing image signal. For example, the motion in movies is apparent rather than real as it involves the rapid presentation of a series of static images.

- Visual Motion Processing

Apodans

Definition

- Evolution of the Brain: Amphibians
- Gymnophiones

Appetite Regulation

- Neuropeptides in Energy Balance

Aponeurosis

- Tendon

Appetitive Behavior

Definition

Explorative or goal-directed behavior.

Apoptosis

Definition

A type of programmed cell death in response to stress, oxidants and genetic aberrations. It may also be a controlled process during development and cell

Appetitive Conditioning

Definition

Conditioning with a rewarding unconditioned stimulus (US).

- Operant Conditioning

Appetitive Response

Definition

A class of conditioned Pavlovian responses that occurs to a stimulus predictive of the subsequent delivery of a reward (usually food or water). Increased salivation, licking, increased pupil dilation, and approach behavior can all be elicited in such appetitive situations.

- ▶ Value-based Learning

APP/Secretase

Definition

APP/secretase – an enzyme which cleaves inside the $\beta/A4$ portion of the amyloid precursor protein (APP); abnormal processing of APP occurs in AD brains.

- ▶ GAL4/UAS

Apraxia

Definition

Non-paralytic disorder of learned movements in the absence of sensory loss, weakness, incoordination, or the inability to understand commands. There are different forms of apraxia, related to different body parts and functions: buccofacial apraxia, truncal apraxia, limb apraxia, apraxia of eyelid opening, apraxia of speech. For example, in limb apraxia, patients may make simple movements but not perform complex motor acts with sequences of movements, such as combing their hair, shaving, toothbrushing. Ideomotor apraxia is characterized by disturbances of performing communicative gestures, e.g., waving the hand for goodbye, or imitative or requested tool-use gestures, such as using a hammer or other tool.

Aprosodias

Definition

Disturbances in recognizing or producing prosody (musical intonation) of language, which is an expression of affective components of speech. Aprosodia is

associated with lesions of the right hemisphere. Damage to anterior regions produces a prosodic, emotionless, flat tone of voice; damage to posterior regions entails incomprehension of affective components in other people's speech.

Aquaporins

Definition

A family of 7 members of molecules that form the water pores in the cell membrane.

- ▶ Drinking Disorders and Osmoregulation

Aqueduct of Sylvius

Definition

This is the cerebral aqueduct. It is a channel located in the midbrain that connects the third and fourth ventricles. It is filled with cerebrospinal fluid, and if constricted can cause hydrocephalus.

2-Arachidonoyl Glycerol (2-AG)

Definition

2-Arachidonoyl glycerol (2-AG) is an endogenous cannabinoid neurotransmitter first isolated from canine gut. It is an ester formed from arachidonic acid and glycerol. Compared to anandamide, 2-AG is present at relatively high levels in the central nervous system.

- ▶ Cannabinoids
- ▶ Hallucinogens

Arboviral Infection

Definition

Pertaining to arthropod-borne viruses causing infection of the central nervous system.

- ▶ Central Nervous System Infections: Humoral Immunity in Arboviral Infections

Arbovirus

Definition

Arbovirus denotes any virus in vertebrates biologically transmitted by infected hematophagous arthropods.

► Arboviral Infection

► Central Nervous System Infections: Humoral Immunity in Arboviral Infections

Archaic Species

Definition

Species of animals that are members of a presently extinct order of vertebrates.

► Evolution and Brain-Body Allometry

Archosauria

Definition

Diapsid reptile clade incorporating crocodiles, dinosaurs, pterosaurs and birds.

► The Phylogeny and Evolution of Amniotes

Arcuate Fasciculus

Synonyms

► *Fasciculus longitudinalis sup.*; ► Superior longitudinal fasciculus

Definition

With its two branches (anterior brachium and posterior brachium), the superior longitudinal fasciculus establishes connections between virtually all cortical areas. The part of the fasciculus connecting the motor (Broca's) speech center with the sensory (Wernicke's) speech center is called the arcuate fasciculus.

► Telencephalon

► Broca's Aphasia

► Wernicke's Aphasia

Arcuate Nucleus (Hypothalamus)

Definition

This nucleus (also called the infundibular nucleus) is located in the floor of the hypothalamus adjacent to the ventralmost part of the third ventricle. Its axons project to the pituitary portal vessels at the median eminence of the hypothalamus. Its neuroendocrine cells contain various neuropeptides involved in the control of the anterior pituitary gland.

Arcuate Nucleus (Medulla)

Definition

The arcuate nucleus in the medulla is ventral to the pyramid that is continuous with the pontine gray. It projects to the contralateral cerebellum as mossy fibers via ventral external arcuate fibers.

Are Humans Sensitive to Pheromones?

Definition

Anatomically, there is clear evidence that the vomeronasal organ of human adult exists. However, there are serious doubts about its functionality. In the human genome, only five orthologs of the V1R genes are still functional, all the others are pseudogenes and, to date, no intact human V2R gene has been reported, suggesting that humans have a very limited number of functional vomeronasal receptors. In addition, the other members of the signal transduction cascade (PLC β 2, TRPC2 channel) existing in vomeronasal cells of rodents, are pseudogenes. No ligand is known for any of the human vomeronasal receptors. There are various behavioral studies that implicate putative pheromones in regulating endocrine dependent behavior such as menstruation, but the detailed mechanisms of actions are unknown so far.

► Olfactory Sense

► Vomeronasal Organ (Jacobson's Organ)

Area 4

Definition

Primary motor cortex (MI, M1, F1).

- Visual Space Representation for Reaching

Area 7b

- Visual Space Representation for Reaching

Area Centralis

Definition

The area centralis or central area is a small region, typically located in temporal retina, where neuron density peaks and neurons are smallest. It is the region of highest visual acuity and is used for the fixation of objects. Some animals (e.g. rabbit) have a horizontally elongated area centralis, which is termed a visual streak. The extent of the area centralis is somewhat arbitrarily defined by a ganglion cell density threshold or in some species by the presence of more than one tier of ganglion cell somata in the ganglion cell layer.

- Inherited Retinal Degenerations
- Retinal Ganglion Cells
- Visual Acuity, Hyperacuity

Area F4

- Visual Space Representation for Reaching

Area F5

- Visual Space Representation for Reaching

Area F6

- Visual Space Representation for Reaching

Area F7

- Visual Space Representation for Reaching

Area 7m

- Visual Space Representation for Reaching

Area F2

- Visual Space Representation for Reaching

Area MIP

- Visual Space Representation for Reaching

Area F3

- Visual Space Representation for Reaching

Area PE

- Visual Space Representation for Reaching

Area PEA

- ▶ Visual Space Representation for Reaching

Area PEc

- ▶ Visual Space Representation for Reaching

Area PFG

- ▶ Visual Space Representation for Reaching

Area Postrema (AP)

Definition

Belongs to circumventricular organs and is located dorsal to the nucleus tractus solitarii (NTS) on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle, where it forms an about 1 mm long, but rather narrow elevation. The postremal area is strongly vascularized, during the second half of one's life degenerated, and rich in cells and fibra with different transmitters. Since blood vessels do not have a blood-brain-barrier here, substances with compulsory barriers reach the nervous tissue as well, which are analyzed here. The AP is the "vomiting center" of the brain, though is also plays an important part in vegetative processes, such as food intake, drinking and cardiovascular regulation. AP projects heavily to the adjacent NTS and dorsal motor nucleus of the vagus (DMV) using acetylcholine as the main neurotransmitter.

If intracranial pressure increases, the ensuing concomitant stimulation of the area postrema can elicit emesis.

To curtail elicitation of emesis, dopamine antagonists, inter alia, are used, to act upon the dopamine receptors of the AP, thus suppressing their activating effect.

- ▶ Autonomic Reflexes
- ▶ Myelencephalon
- ▶ Dorsal motor nucleus of the vagus (DMV)
- ▶ Nucleus Tractus Solitarii (NTS)

Area SII

Definition

In the lower portion of the postcentral gyrus is situated a cytoarchitectonically slightly modified zone which reaches as far as the lateral sulcus and features a complete representation of the contralateral body half. This area is called the secondary somatosensory cortex, abbreviated SII.

- ▶ Telencephalon

Area V1

- ▶ Striate Cortex Functions

Area V6

- ▶ Visual Space Representation for Reaching

Area V6A

- ▶ Visual Space Representation for Reaching

Areflexia

Definition

Loss of tendon reflexes and may be genetic or due to a number of neurological diseases.

Arginine Vasopressin

Definition

A peptide hormone synthesized by neurons in the hypothalamus and released from the posterior pituitary.

- ▶ Motion Sickness

Argument

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Synonyms

Reasoning; Inference

Definition

An **argument** is a piece of text or speech that can be put forward in order to support a thesis. An argument in standard form is a finite sequence of meaningful sentences

$$\begin{array}{l} P_1 \\ \dots \\ P_n \\ \therefore C. \end{array}$$

P_1, \dots, P_n are the **premises**, C is the **conclusion**, which is typically the thesis to be supported. Putting forward an argument normally involves three claims: firstly, that all premises are in fact **true**; secondly, that all premises are **justified** or warranted independently of justification or warrant for C ; thirdly, that the conclusion **follows from** the premises, or at least that the premises together strongly **support** the conclusion. An argument is **valid** just in case this third claim is true. An invalid argument is called a **fallacy**. An argument may also be presented with the third claim only, just to see where certain assumptions would lead. Or it may be presented together with the claim that the conclusion is already established as false so that it provides reason to give up at least one of the premises (**reductio ad absurdum**).

Characteristics

Good, Valid and Sound Arguments

A large part of what may be called the theory of human rationality is concerned with criteria for distinguishing **good** arguments from bad ones. An argument as it is normally put forward is good just in case all three claims indicated above are true. The standard distinction is between valid and sound arguments: an argument is valid just in case the conclusion does indeed follow from or is strongly supported by the conclusion. It is **sound** just in case in addition to being valid it has only true premises. Consequently, there are two steps in checking an argument. The first step is to find out whether it is valid or not. If it is valid, the second step is to find out whether all premises are true or not. Establishing the truth of the premises is a matter of particular empirical or formal research.

Critical reflection on arguments as such primarily concerns their validity.

An argument in standard form is valid if and only if acceptance of all premises makes it rational also to accept the conclusion, or at least to attribute a high probability to the conclusion's being true. A special case of extraordinary importance is **deductive validity**. In a deductively valid argument the conclusion is a **consequence** of the set of premises, i.e. it follows from this set. So acceptance of the premises of a deductively valid argument makes it rational to accept the conclusion, because the truth of the premises **excludes** the falsity of the conclusion and so **guarantees** its truth: it is **impossible** that the conclusion is false while all premises are true.

This suggests an intuitive test for deductive validity: try to describe a consistent scenario that would render all premises true but the conclusion false. The scenario can be far-fetched and highly improbable. It can, for instance, involve science fiction elements such as beaming. The consistency of the scenario suffices to show that the argument is deductively invalid.

Deductive Logical Validity: Conditional Premises

The kind of deductive validity that has by far been studied best is validity according to deductive logic [1]. An argument is **logically valid** (in the sense of deductive logic) just in case the truth of its premises excludes the falsity of the conclusion for *logical* reasons rather than for reasons that concern the descriptive content of the sentences involved. This can be explained by means of an important kind of arguments that are subject to deductive logic, namely arguments with **conditional** premises. Suppose that prior medical examination has established the conditional premise "If test T is positive, the patient has illness I." Now the positive test result is submitted. The premise "Test T is positive" is added and the conclusion "The patient has illness I" is inferred. The whole argument is an instance of a certain logical schema:

Argument	Logical schema
If test T is positive, the patient has illness I	If A then B
Test T is positive	A

In the schema, only the connective "if – then" is retained, which may plausibly be dubbed a **logical expression**. The connected sentences are replaced by the place-holders "*A*" and "*B*." It is impossible to find an argument of the same logical schema all premises of which are true, while the conclusion is false (i.e. not true). The meaning of the logical expression "if – then"

excludes the falsity of the conclusion given that all premises are true. It is hence by logical reasons alone that it is excluded that all premises are true while the conclusion is false. The argument is logically valid.

This can be generalized. A ►logical schema only contains logical expressions and place-holders for descriptive expressions. Descriptive expressions can be sentences, but also sub-sentential expressions such as names like “Peter” or predicates like “is happy.” A particular argument is an ►instance of a logical schema just in case it can be obtained from the schema by replacing all occurrences of a certain place-holder by the same descriptive expression. An argument is a ►counter-instance to a logical schema just in case it is an instance of the schema and its conclusion is false, while all its premises are true. A ►logical schema is logically valid if and only if there is no possible counter-instance to it. A particular ►argument is logically valid if it is an instance of a logically valid schema. The general idea is that if an argument is an instance of a schema that has no counter-instance, the meanings of the logical expressions in the argument and the way they are connected to descriptive expressions alone guarantee the truth of the conclusion if all premises are true. It is by logical reasons alone that it is excluded that all premises are true but the conclusion is false. The argument is logically valid.

It is hard and perhaps impossible to systematically capture the exact logical behavior of ordinary conditional sentences. But in many cases asserting an indicative conditional can be understood as excluding the possibility (for whatever reason) that the antecedent *A* of the conditional is true but its consequent *B* false. Thus, when a person argues from a premise “If *A* then *B*” in the indicative we may often understand her as arguing from the premise “It is not the case that it is true that *A*, but false that *B*.” Let us abbreviate this latter sentence schema as “*A* → *B*,” which we will read for convenience as “If *A*, then *B*.” Its instances are called ►material or ►truth-functional conditionals.

The two most important logically valid logical schemata with conditional premises are (1) and (2). They can be contrasted with the two invalid schemata (1*) and (2*):

(1) Modus ponens	(2) Modus tollens	(1*) Invalid	(2*) Invalid
$A \rightarrow B$	$A \rightarrow B$	$A \rightarrow B$	$A \rightarrow B$
A	non- B	B	non- A

Here “non-...” is short for “It is not the case that” In both (1*) and (2*), substituting a false sentence for *A* and a true sentence for *B* yields the counter-instance.

Further important valid schemata are (3) and (4):

(3) Contraposition	(4) Conditional transitivity
$A \rightarrow B$	$A \rightarrow B$
$\therefore \text{non-}B \rightarrow \text{non-}A$	$B \rightarrow C$

A good part of the logical behavior of ordinary conditional sentences can be retained by standard translations by means of the material conditional “→”:

Ordinary sentence schema	Translation
If <i>A</i> , then <i>B</i>	$A \rightarrow B$
<i>A</i> is sufficient for <i>B</i>	$A \rightarrow B$
Only if <i>A</i> , <i>B</i>	$B \rightarrow A$
<i>A</i> is necessary for <i>B</i>	$B \rightarrow A$

Deductive Logical Validity: General Premises

So far we have been concerned with argument schemata with place-holders for complete sentences only. But there are important logically valid schemata with premises and conclusions of one of the so-called categorical forms:

	Affirmative	Negative
General	All <i>F</i> s are <i>G</i> s	No <i>F</i> is (a) <i>G</i>

“*F*” “*G*” and “*H*” are place-holders for English predicates such as “is an animal” rather than for sentences. Here is an instance of a famous valid schema called ►modus Barbara:

Argument	Schema (modus Barbara)
All men are animals	All <i>F</i> s are <i>G</i> s
All animals are mortal	All <i>G</i> s are <i>H</i> s

A convenient way of looking for counter-instances to such schemata makes use of naive set-theoretical predicates such as “is a member of the set {1, 2,}.” A perspicuous counter-instance to an invalid schema can be formulated as follows:

Invalid schema	Counter-instance
All <i>F</i> s are <i>G</i> s	All members of {1, 2} are members of {1, 2, 3, 4}
Some <i>G</i> s are <i>H</i> s	Some members of {1, 2, 3, 4} are members of {3, 4}

Notice that if an argument is an instance of an invalid logical schema, it can still be valid because it is an instance of a more subtle schema that is valid.

Deductive arguments in scientific practice often involve sentences that contain relational predicates such as “is greater than” and iterations of means of quantification such as “all” and “some” or “there is.” An example from arithmetics is “For every natural number there is a greater number.” This should be construed as an instance of the schema “For every individual x there is an individual y such that y stands in relation R to x .” The inference from this to “There is an individual y such that every individual x is such that y stands in R to x ” is invalid. For every number there is a greater one, but there is no number that is greater than all numbers. If one fails to see through the fallacy from “For every – there is” to “There is – for every,” one can “prove” the existence of a necessary being:

P_1	Ex nihilo nihil fit
P_2	There exists something now
C_1	∴ There was no time at which nothing existed. (from P_1 and P_2)
C_2	∴ But then there is something that has existed at all times. (from C_1)
P_3	But no contingent being exists at all times

The invalid step is from (C_1) to (C_2).

Non-logical Deductive Validity and Implicit Premises

The following argument appears to be valid, though the corresponding schema is invalid:

Argument	Schema
Peter is a bachelor	a is F

The argument’s validity rests on the meanings of the descriptive expressions. Consequently we cannot apply the testing method of trying to find counter-instances to a logical argument schema. Often the intuitive test suffices: if a consistent scenario can be depicted that would render all premises true but the conclusion false the argument is deductively invalid. But in order to make one’s arguments perspicuous one should turn non-logically valid deductive arguments into logically valid inferences. In the example, just add as a premise the analytic truth “All bachelors are unmarried.” The relation between the meanings of the descriptive terms “bachelor” and “unmarried” on which the validity rests is thereby made explicit.

Arguments in science and philosophy are seldom in standard form, and very often they are incomplete [2,3]. Even when spelled out in an explicit sequence of sentences they rely on hidden premises that are not just uncontested explications of meanings. For example, nothing of scientific interest does directly follow from an experimental result formulated in a premise of the form “Activity in brain area B occurs whenever a subject performs cognitive task T .” A huge amount of substantial background assumptions is required for correctly deducing a conclusion to the effect that there is a typical process in area B that *is* or *realizes* the achievement of T . In many cases the background assumptions are scientific common ground. But the more general and substantial the conclusions become the more they draw on profound theoretical or even metaphysical assumptions that can reasonably be contested. A researcher is seldom explicitly aware of the way her scientific convictions or prejudices enter into her reasoning. So although scientists rarely spell out their scientific inferences in detail, knowledge of what a full-fledged deductively valid argument would look like can help them to keep a check on themselves and to deal reasonably with their disagreement.

Reductio ad absurdum and Paradox

“From your hypothesis it follows that C is the case, which is absurd; so your hypothesis is false.” This popular mode of critique of another person’s hypothesis or theory is called reductio ad absurdum. However, usually the alleged absurdity C follows from a hypothesis H only if certain background assumptions $P_1 \dots P_n$ are made. Moreover, the alleged refutation of H requires the assumption that C is false. A complete reductio ad absurdum is of the following form:

P_1	The critic’s background assumptions
...	
P_n	
H	Assumption of the hypothesis for the sake of argument
$\therefore C$	Conclusion inferred from $P_1 \dots P_n$ and H
non- C	Assumption of the negation of C as the main premise

From $P_1 \dots P_n$ and H the critic infers C , which contradicts her main premise non- C . She thereby shows that at least one of the premises $P_1 \dots P_n$, non- C and H must be false. Insisting on her own claims $P_1 \dots P_n$ and non- C she infers non- H . In order to evade this rebuttal all the proponent of H has to do is to reject ►one among the critic’s premises $P_1 \dots P_n$ and non- C . Often this is easy to do, as the background assumptions tend to involve

fundamental but contested convictions of the critic's which the proponent need not share. Given the proponent's background theory even conclusion *C* may be acceptable.

There is a famous case in the history of science in which an attempted ►reductio backfired [4]: Poisson showed that the wave theory of light implied that a bright spot had to occur at the center of the shadow of a disk (conclusion *C*). Making the common sense assumption that this is false (his main premise non-*C*) he took the wave theory to be refuted. But in careful experiments the spot was in fact observed. Unwillingly Poisson had contributed to an impressive confirmation of the wave theory.

►Paradoxes are particularly fascinating philosophical arguments [5]. A paradox is a seemingly valid deduction of a seemingly unacceptable conclusion from seemingly inevitable premises. Skeptical arguments with conclusions such as "We do not know anything about the external world (or: the past, other minds, the laws of nature)" are paradoxes. Different reactions are possible: that the conclusion is in fact true and only *appears* to be false; that one of the premises is in fact false; or that the deduction rests on a logical or meaning explicating principle that should be rejected.

References

1. Salmon W (1984) Logic, 3rd edn. Prentice Hall, Englewood Cliffs, NJ
2. Groarke L (2007) Informal logic, <http://plato.stanford.edu/entries/logic-informal/>
3. Irvine A, Walton D, Woods J (2004) Argument: critical thinking, logic and the fallacies, Prentice Hall, Toronto
4. Brittan G, Lambert K (1987) An introduction to the philosophy of science, 3rd edn. Ridgeview, Atascadero
5. Sainsbury M (1995) Paradoxes, 2nd edn. Cambridge University Press, Cambridge

Argyll-Robertson Pupil

Definition

A condition characterized by loss of light reflex but normal pupil constriction during accommodation. This is indicative of a lesion in brainstem neurons mediating the pupillary light reflex, and is characteristic of neurosyphilis.

- Neural Regulation of the Pupil
- Neurosyphilis
- Pupillary Light Reflexes

Arm Trajectory Formation

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Definition

Arm ►trajectory formation refers to the principles and laws that invariantly govern the selection, planning and generation processes of multi-joint movements, as well as to the factors that dictate their kinematics, namely geometrical and temporal features.

Characteristics

The repertoire of human and animal goal-directed actions is broad and diverse, ranging from relatively simple single-joint movements to complex interactions among several limb segments or even among different limbs. These movements may follow various motion ►paths with numerous ►speed profiles along each ►path, resulting in countless possible trajectories. Nonetheless, focusing here specifically on arm movements, there seem to be some stereotypical trajectories that the central nervous system (CNS) chooses for the arm to perform. Although many questions still remain open, some underlying principles behind the selection, planning and execution of these trajectories have emerged from the combination of behavioral and computational studies of trajectory formation.

Computational Problems Associated with Trajectory Formation

The motor system transforms neural signals into contractile forces in muscles, which produce motion and enable us to act upon our environment. Some prominent research questions that have received great attention in recent years are as follows:

1. What are the geometric and temporal characteristics of simple and complex movements?
2. What coordinates or reference frames are used in movement representation and generation?
3. What are the interactions between CNS-based planning, body mechanics and physical laws and constraints in dictating the emerging movements? How do these aspects influence trajectory planning?
4. How does the nervous system resolve kinematic redundancies, especially those associated with the planning and execution of multi-joint arm movements?

5. To what extent are the produced behaviors constructed from a limited set of motion primitives, i.e., basic building blocks? What syntactic rules are used in constructing complex and/or sequential movements from such simpler elements?
6. Is the motor system hierarchically organized? Does trajectory formation and generation occur at different levels of representation?

Some attempts at answering these questions are presented below.

In robotics, the problem of trajectory formation is usually composed of two separate problems: trajectory planning and trajectory tracking. The first deals with the selection and planning phase. The second refers to the execution of the planned trajectory and to feedback control, guaranteeing minimal deviation from the desired trajectory. When investigating how disjoint these two problems might be in human movement generation, some analogy can be made with the question of whether there is a clear separation in the motor hierarchy between kinematics and dynamics in biological trajectory formation. Some recent load adaptation studies provided evidence that human arm trajectories tend to obey the same kinematic plan independently of the external force conditions [1]. These, among others, support the notion that the desired behavior is independent of movement dynamics. However, although there is some evidence that the kinematic and dynamic aspects of motion constitute two distinct levels of the motor hierarchy, this is neither sufficient nor conclusive enough to unequivocally decide the matter (this matter is also discussed in the “Internal models” article).

Coordinate Frames for Trajectory Formation

When reaching for a cup of coffee, the hand can theoretically follow a wide variety of paths, each with numerous speed profiles. These hand trajectories could further result from different sets of joint rotations. Understanding how the motor system plans and executes motion under redundancy, or in the presence of an excess number of degrees of freedom (DOF), beyond those required to carry out a motor task, is paramount (the redundancy problem, or Bernstein problem, is also discussed in the articles “Equilibrium point control” and “Coordination”).

Numerous studies have demonstrated that during point-to-point movements in the horizontal plane the hand tends to follow rather straight hand paths (see Fig. 1a). This has prompted the suggestion that arm trajectories are planned in hand rather than in joint coordinates. By contrast, during unconstrained three-dimensional movements, or during movements in the vertical plane, the hand paths are likely to become considerably more curved [3] (see Fig. 2). This may be

due to the presence of gravity or the lack of a continuous visual tracking of the movements.

Optimality and Trajectory Formation

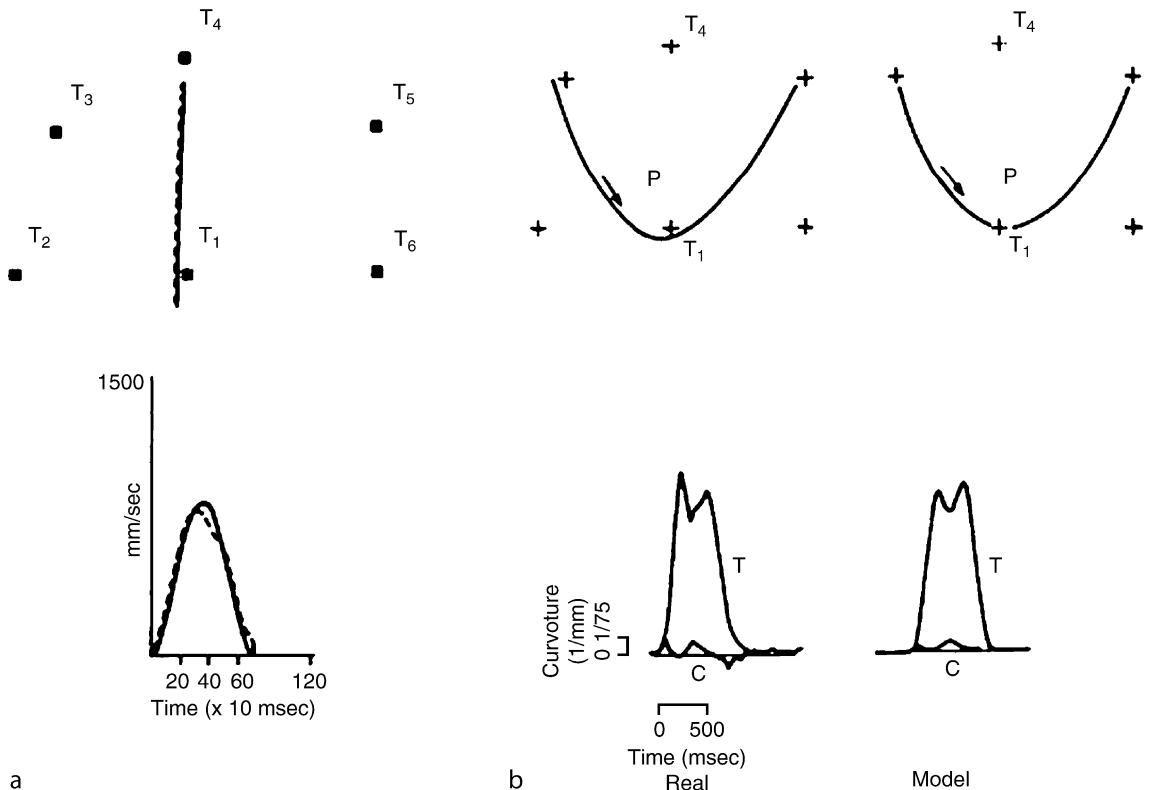
Many studies have attempted to account for the observed characteristics of arm movements based on optimization theory [2]. Optimization theory is an important venue for discovering what organizing principles govern the generation of goal-directed motor behavior. It provides a convenient way to formulate a coarse-grained model of the underlying neural computation, without requiring specific details of the way those computations are carried out. Generally speaking, this approach consists of defining a quantitative objective function that defines the optimum (i.e., best) performance. Optimization tools are then applied in order to identify the specific behavior that achieves that optimum. Quantitative hypotheses regarding the goals of motor actions and their relation to observable behavior must therefore be explicitly stated.

Not all motor behaviors are necessarily optimal. Nevertheless, attempts to identify optimization principles can be useful for developing a taxonomy of motor behavior and for gaining insight into the neural processes that produce motor behavior. In particular, several different optimization principles were hypothesized in the context of reaching movements. These included smoothness maximization, expressed through the minimization of hand ▶jerk [2], the rate of change of joint torques [4], the minimization of movement variance [5] and optimal feedback control [6].

While in the minimum-jerk model the ▶cost function is kinematic in nature, some of the other models’ ▶cost functions depend on dynamic variables such as torque change, muscle-tension or motor-command. A critical difference between the kinematics- and dynamics-based models is the separability of planning and execution. Kinematic models, which specify the hand trajectory in external or in joint coordinates, require separate movement execution processes to delineate the joint torques or muscle forces and eventually the motor commands that are needed in order to realize the desired trajectory. In contrast, the solutions to dynamic models are the joint torques, muscle forces and possibly also the motor commands (depending on the definition of the cost function) required to achieve the movement; and therefore planning and execution are no longer separated.

Laws of Motion and Motor Invariants

A basic notion in current thinking about trajectory formation is that the motor memory does not store a huge collection of “motor tapes,” each encoding the neural commands specifying the generation of an individual movement. Rather, based on evidence from



Arm Trajectory Formation. **Figure 1** An example of hand trajectories in the horizontal plane. (a) The experimental data are depicted by a *dashed line*, and the minimum-jerk model prediction is portrayed by a *solid line*. A point-to-point reaching movement is characterized by a *straight line* path (top panel), with a bell-shaped speed profile (bottom panel). (b) Reaching from one point to another through an intermediate via-point. The experimental data are given on the top left and the minimum-jerk prediction is on the top right. This time the path is curved and the speed profile shows a slowdown in the movement around the region of maximal curvature (bottom panel; T is movement speed and C movement curvature). As is apparent, there is good correspondence between the experimental data and the model predictions in both cases. Adapted from [2].

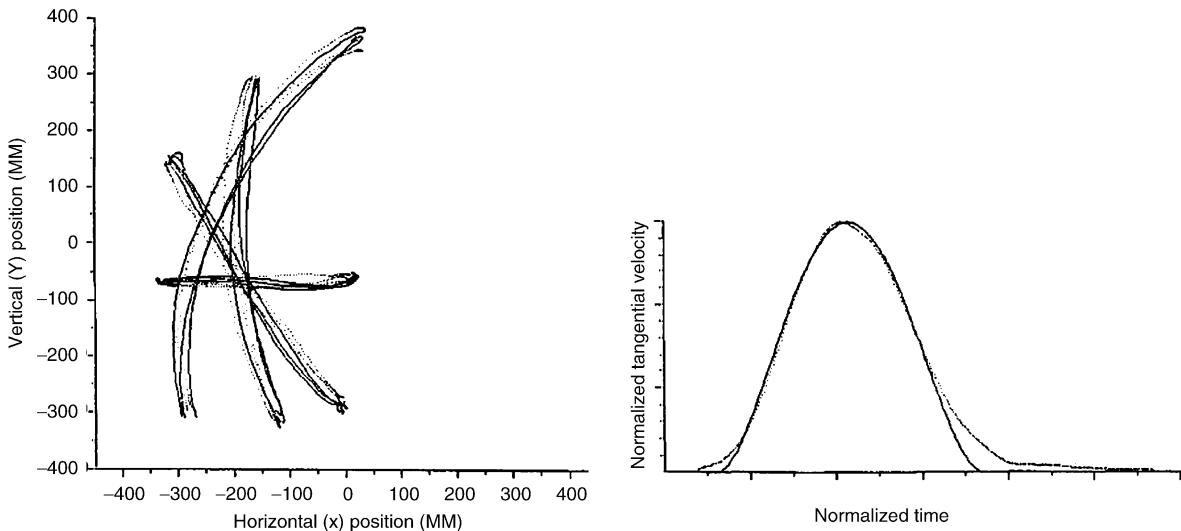
both behavioral observations and accurate kinematic analysis of movements, it is argued that motor memory stores more general plans, or programs. These dictate all the movements belonging to a particular class, which share similar geometric, kinematic and temporal characteristics.

A central problem in motor control research is therefore one of taxonomy, namely classifying and grouping all possible movements into different classes. This critically depends on our ability to define metrics that can be used to evaluate the similarity between different movements and motor behaviors. Another possibly more scrupulous method of classifying movements is by searching for differences among the principles that underlie the planning of different movements. Both schemes are based on the identification of ►motor invariants.

Several kinematic and temporal invariants have been observed in human arm movements. For example, point-to-point reaching movements in the horizontal

plane tend to follow straight paths with single-peaked bell-shaped speed profiles (see Fig. 1a). For more curved motions, as when reaching through a via-point, the movements slow down around the point of highest ►curvature (see Fig. 1b). Both behaviors are predicted by the minimum-jerk model [2], but also by the minimum torque-change and minimum variance models. In three-dimensional movements and movements in the vertical plane, the hand paths are more curved, though they still vary in a consistent manner across the workspace, while the speed remains more or less bell-shaped [3] (see Fig. 2). Studies that examined the symmetry of the speed profiles, found them to range from highly symmetrical profiles to ones which are more skewed or contain additional speed peaks. This may possibly indicate multiple corrections, as observed when subjects are instructed to be highly accurate.

One persistent temporal invariant is that of isochrony [7]. Global isochrony refers to the observation that



Arm Trajectory Formation. **Figure 2** Point-to-point reaching movements in the vertical plane. The left panel shows the superimposed paths of four different typical reaching movements. Upward movements (and leftwards movements, for the horizontal movement) are *dotted lines*, where downward (and rightwards movements, for the horizontal case) movements are *solid lines*. While the horizontal movement is rather straight, the other hand paths tend to be much more curved for both upward and downward movements. The right panel shows a typical experimental speed profile as the *dotted line*, with the minimum-jerk model prediction as the *solid line*. Adapted from [3].

the average speed of movements increases with the path length, thereby maintaining movement duration nearly constant. Local isochrony is the tendency to carry out motion subunits of unequal lengths in roughly equal times. For example, if subjects trace out a figure eight in which the two lobes are of unequal size, they are traversed with approximately equal durations. This second type of isochrony becomes an emergent property of the maximization of movement smoothness, i.e., the minimization of jerk [7] as well as other costs [4–6].

In addition to characterizing the path and ►speed profile separately, many studies have examined the dependency of the speed on the path geometry. Although there is no a priori reason for it, coupling between the geometrical form of the path and the hand speed have been repeatedly observed. When drawing simple forms like ellipses, this relationship takes the form of

$$V = K C^{-\beta}, \quad (1)$$

where V is the tangential speed, K is constant and C is the curvature. Expressing the same law in terms of angular speed, we get

$$A = K C^{1-\beta} \quad (2)$$

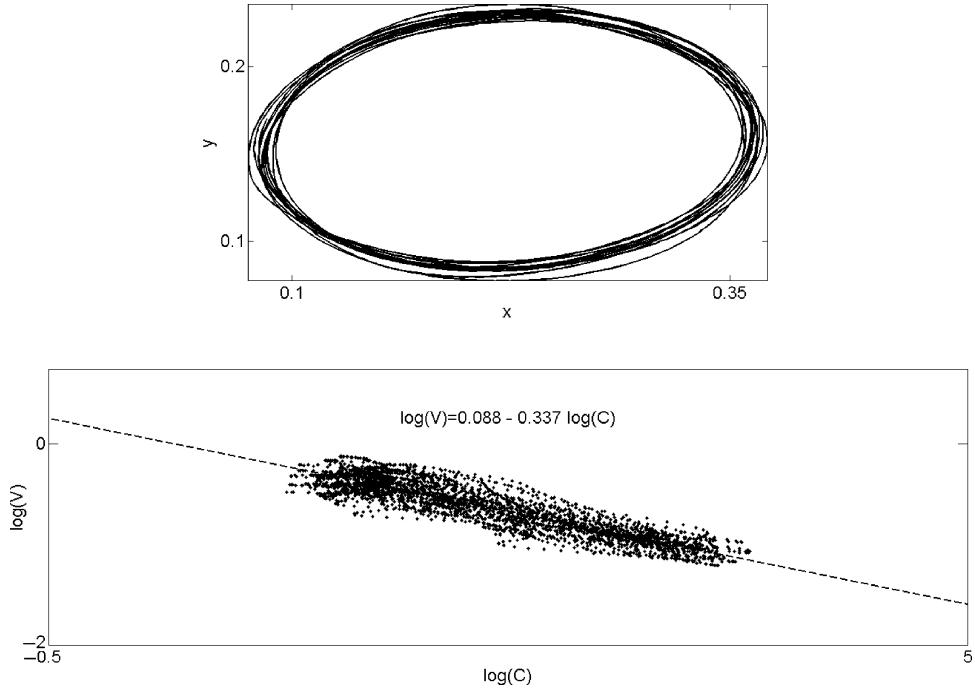
where A is now the angular speed. Originally the power β was found to be close to 1/3, and the second formulation lent it the name “the two-thirds power law”

[8] (see Fig. 3). Nonetheless, in other non-elliptic paths the exponent was found to range between 0.2 and 0.4.

The Notion of Motor Primitives

There is evidence that suggests that the brain may store a limited set of motor templates, and that it possesses mechanisms that generate our rich motor repertoire by applying some basic operations or transformations onto those elementary primitives, joining simple movements into more complicated behavior. This organization provides a parsimonious representation of our huge motor repertoire and eases learning of new behavior.

Some recent studies of the characteristics of hand trajectories that emerge following a period of extensive practice, suggest the emergence of purely geometric sub-movements from which the learned goal-directed movements are composed. Yet these sub-movements may not encompass the most elementary level in the plausible hierarchy of movement construction based on motor primitives. If we associate this hierarchy to that of an alphabet from which words are composed, which in turn are combined to yield complete sentences, the geometric primitives might correspond to words, not to letters. It remains to be seen, however, whether it is possible to identify a limited set of universal building blocks from which a wide variety of diverse movements are constructed. Nevertheless, the notion of the compositionality of complex movements via



Arm Trajectory Formation. Figure 3 A demonstration of the two-thirds power law. Top panel: an ellipse traced continuously and repetitively in the horizontal plane. Bottom panel: taking the logarithm of both sides of the power-law formulation, we get: $\log(V) = \log(K) - \beta \log(C)$. Therefore, plotting $\log(V)$ versus $\log(C)$ results in a roughly straight curve with a slope of about $-1/3$, in good agreement with the power law (1).

sequencing and superposition of sensory-motor primitives proved useful in robotic applications, such as robot humanoids learning from imitation.

Three-Dimensional Trajectory Planning

The realm of three-dimensional (3D) arm movement was significantly less studied than that of planar arm movements. Movements that are restricted to the horizontal plane were, in turn, extensively studied. Moreover, the invariants of horizontal planar motion do not all scale up to 3D movement. The bell-shaped speed profiles of point-to-point reaching movements seem to be conserved. Yet the paths in 3D are much more curved, possibly suggesting motion planning in terms of joint coordinates. The two-thirds power-law describes 3D arm motion considerably less well than for horizontal planar movements. However, non-trivial mathematical considerations have led to a new power-law of 3D motion, which captures 3D drawing data quite well, namely:

$$V = K C^{-\beta} T^{-\gamma}, \quad (3)$$

where T designates the path's **torsion** (all other symbols are as above). Here β is about $1/3$ and γ about $1/6$, although their exact values depend on path geometry, both global and local. We name this the “curvature-torsion power-law” [9].

The redundancy problem, mentioned above, is especially problematic for 3D arm movements. For horizontal plane motion, humans tend to utilize only two of their four DOF at the shoulder and elbow to produce the two DOF of the hand motion within the horizontal plane. Yet, in unconstrained 3D motion, all four DOF are utilized, while only three DOF are needed to specify hand position and movement in 3D space, resulting in the excess of one DOF. Transforming hand into joint coordinates, termed the inverse kinematics problem, does not have a unique solution and therefore it is ill-posed, making its solution far from being trivial.

Another reason for this complexity is that rotations are not commutative, meaning that an object’s orientation after rotations along two non-co-linear axes depends on their order. This has severe implications for joints with three DOF (e.g. the shoulder). It implies that, if no constraints are imposed, a limb’s orientation would depend on previous joint rotations. Some recent studies investigated the idea of intrinsic constraints, which restrict the number of DOF at the wrist, elbow and shoulder joints during hand-motion, thus resolving the kinematic redundancies [10]. These intrinsic constraints include kinematic ones such as Donders’ and Listing’s laws, which were originally developed in order to account for the observed 3D end-point eye orientation (Donder’s law), and angular rotations

(Listing's law) during human saccadic eye movements. Examining whether these laws are also pertinent to 3D human arm movements, it was shown that while these constraints do account for certain aspects of the observed behavior, they cannot fully account for the entire spectrum of kinematic features of 3D arm reaching and pointing movements [10].

As is apparent from the material reviewed above, studies carried out in the last 20–30 years have made considerable contributions to our understanding of the principles underlying human arm trajectory formation. New models were conceived and old ones were refined and improved or discarded in view of new empirical observations. Yet there is still much work ahead, before we can claim to fully understand the complicated processes of arm trajectory formation during goal-directed motor behavior.

References

- Shadmehr R, Mussa-Ivaldi FA (1994) Adaptive representation of dynamics during learning of a motor task. *J Neurosci* 14:3208–3224
- Flash T, Hogan N (1985) The coordination of arm movements: an experimentally confirmed mathematical model. *J Neurosci* 5:1688–1703
- Atkeson CG, Hollerbach JM (1985) Kinematic features of unrestrained vertical arm movements. *J Neurosci* 5:2318–2330
- Uno Y, Kawato M, Suzuki R (1989) Formation and control of optimal trajectory in human multi-joint arm movement. *Biol Cybern* 61:89–101
- Harris CM, Wolpert DM (1998) Signal-dependent noise determines motor planning. *Nature* 394:780–784
- Todorov E (2002) Optimal feedback control as a theory of motor coordination. *Nat Neurosci* 5:1226–1235
- Viviani P, Flash T (1995) Minimum-jerk, two-thirds power law, and isochrony: converging approaches to movement planning. *J Exp Psychol Hum Percept Perform* 21:233–242
- Lacquaniti F, Terzuolo C, Viviani P (1983) The law relating the kinematic and figural aspects of drawing movements. *Acta Psychol (Amst)* 54:115–130
- Pollick F, Maoz U, Handzel A, Giblin P, Sapiro G and Flash T (2008) Three-dimensional arm movements at constant equi-affine speed. *Cortex* In Press
- Soechting JF, Flanders M (1997) Flexibility and repeatability of finger movements during typing: analysis of multiple degrees of freedom. *J Comput Neurosci* 4:29–46

Aroma

Definition

“Aroma”, like “odor” refers to a mixture of chemical molecules that are perceived by the sense of smell.

While the term “odor” by itself is neutral in judgment, “aroma” refers frequently to odors of pleasant nature and is associated with the smell of consumables like food and coffee. Commercial interest in chemical aroma compounds derives from the food industry. Only 5% of the ~8,000 odor molecules identified in food are present above detection thresholds that result in odor perception.

These so called key-food odorants determine the aroma of consumables. The aroma of roasted coffee for example is encoded by 27 key-food odorants out of 400 different compounds identified. Methyl-pyrazines are typical examples for key-food odorants that are formed during roasting of coffee, cocoa beans, and fried food.

► Odor

Arousal

Definition

Central nervous system stimulation driven by the ascending neuromodulatory projections, nervous system, and/or neuroendocrine systems resulting in heightened sensory sensitivity and readiness to respond. Arousal is involved in wakefulness, alertness, attention, cognition, awareness, motivation, sexual activity, emotion, and stress. The Yerkes-Dodson Law states that there is a U-shaped relationship between arousal and cognitive performance – either too little arousal (e.g., due to sleepiness from sleep deprivation) or too much arousal (e.g., from excessive caffeine consumption) has an adverse effect on performance.

Arousal can also be observed during sleep, where it may cause a transition to a lighter sleep stage or result in awakening.

► Alertness Level

Arousal Threshold

Definition

A measure of central nervous system response to external stimuli.

► Sleep States

Arrhythmicity/Rhythmicity

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Synonyms

Aperiodicity/periodicity; Arrhythmic/rhythmic; Irregularity/regularity

Definition

Refers to characteristics of cellular, physiological or behavioral variables that fail to display a rhythm or regularity (arrhythmicity) or that show such rhythm or regularity (rhythmicity).

Types of Rhythms

Most biological variables display cyclic changes in their basal levels. These cyclical changes are called biological rhythms. Rhythmicity is expressed at the level of the whole organism (i.e., rhythms in behavior) all the way down to the molecular and genetic levels (i.e., rhythms in gene expression). The length of these cycles is extremely varied and can be classified based on the intrinsic period of the biological oscillation. Rhythms can be grossly classified into three non-overlapping categories.

Circadian Rhythms

From the Latin *circa*: “around” and *dies*: “day.” Biological rhythms occurring with a frequency of one cycle per day (period of approximately 24 h in length). Examples of circadian rhythms include the ►rest-activity cycle, daily oscillations in core body temperature or blood pressure.

Ultradian Rhythms

Biological rhythms occurring with a frequency of more than one cycle per day (period significantly shorter than circadian rhythms). Examples of ultradian rhythms include the 90 min Rapid-Eye Movement (REM) cycle during sleep, heart rate (72 beat/min, in humans), or the rhythm of human growth hormone secretion (3 h).

Infradian Rhythms

Biological rhythms occurring with a frequency of less than one cycle per day (period significantly longer than circadian rhythms). Examples of infradian rhythms include the menstrual cycle (28–30 days in humans), seasonal migration cycles, and reproduction cycles. Infradian rhythms can be further sub-classified based on

their period length. For example, ►circannual (about 1 year), circatidal (about 12 h, associated with ocean’s tides), and circalunar (about 30 days, associated with cycles of the moon) can be used to further characterize ►infradian rhythms.

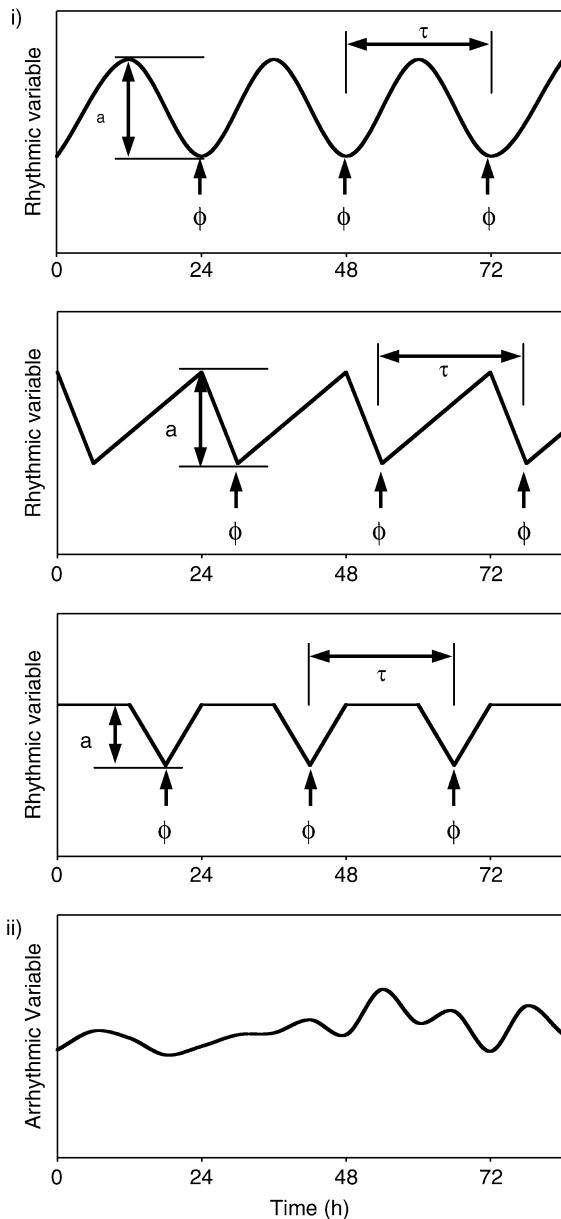
The present encyclopedic entry will focus on circadian rhythms.

Characteristics

Circadian rhythms evolved as a need to adapt to the daily transitions between days and nights. This imposed day/night cycle shaped behavioral and physiological processes and led to the emergence of circadian clocks that generate biological oscillations with a period of approximately 24 h. This ensures that each organism is optimally tuned to its environmental niche (►nocturnal vs. diurnal), and capable of anticipating the transitions between days and nights. The ability to display circadian rhythms is endogenous and widely expressed across a very wide range of living organisms [1]. Naturally occurring, complete absence of rhythms in physiology and behavior (arrhythmicity), is uncommon.

The circadian fluctuations in a physiological variable can be plotted, in a simplistic manner, as a function with a period of approximately 24 h (Fig. 1 i). Note that the shape of circadian oscillations may vary greatly and will be determined by the physiological variable being measured. From this function, several measurements can be made. The phase of the circadian rhythm, (represented by the Greek letter *phi*, ϕ) is a point of the function that can be reliably be measured over successive cycles. This phase marker is useful in determining other parameters of the circadian oscillation (or, in fact, any oscillation). The frequency of the circadian oscillation, or ►period of the rhythm (represented by the Greek letter *tau*, τ), can be measured between two or more consecutive stable phase markers on the curve. The amplitude (represented by the letter *a*), is defined as the difference between the maximum (acrophase or peak) and minimum (bathyphase or trough) values of the physiological variable measured. Of special interest to circadian ►oscillators is the fact that these parameters (phase, period, and amplitude) are endogenous, self sustaining, and relatively constant through time when the organism is kept in ►constant conditions. In contrast, during circadian arrhythmicity, none of the above parameters are constant (Fig. 1 ii). No reliable period can be extracted, the amplitude varies greatly through time, and a reliable phase marker is absent.

Figure 2 shows a representative behavioral ►actogram for a rhythmic (i) and an arrhythmic (ii) rat. In addition, Chi-square (X^2) periodograms are also displayed for both animals (iii). Both will be described in detail below.



Arrhythmicity/Rhythmicity. Figure 1 The circadian oscillation.

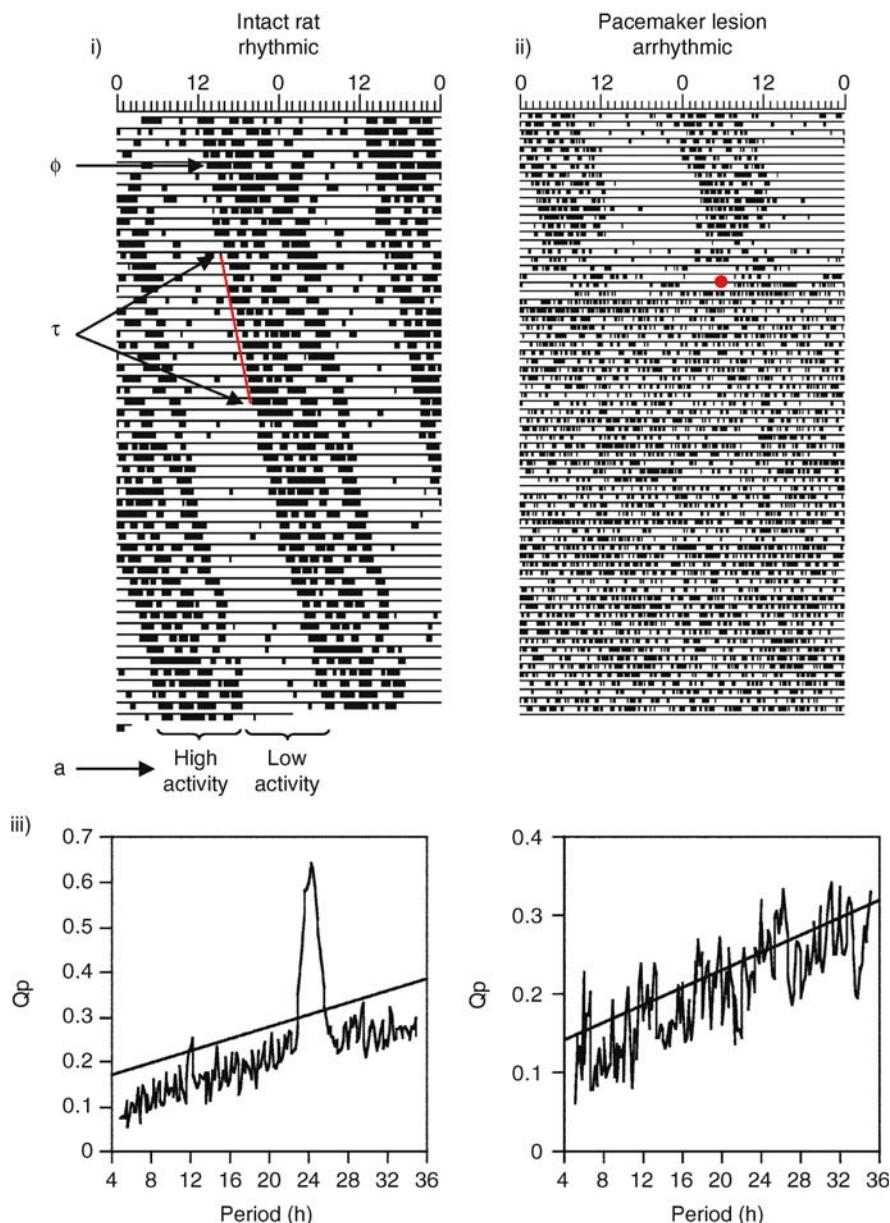
The preferred graphical representation for circadian rhythms is the actogram (Fig. 2 i, 2 ii). Actograms display time of day on the abscissa, and consecutive days on the ordinate. Activity counts are usually summed into 6 or 10 min intervals, or activity bins, and are represented as black ticks along the abscissa. Double-plotted actograms display 48 h of circadian activity on each line, facilitating the visualization of the rhythm. Although actograms were originally designed to graphically represent the locomotor activity rhythm of an organism, they can be used to plot

other physiological variables such as temperature, pupal eclosion, cell firing, or gene expression. The actogram on the left shows running wheel activity of a rat housed in complete darkness (Fig. 2 i). From this actogram, one can easily determine the phase of the rhythm: in this case (and by convention) locomotor activity onset; the period of the rhythm (the slope of the eye-fitted line of best fit that passes through successive activity onsets); and the amplitude of the rhythm (high activity at subjective nighttime (►subjective day/night), low activity at subjective daytime). In contrast, the actogram on the right shows arrhythmicity in a rat following a lesion of the central ►circadian pacemaker (Fig. 2 ii). Following the lesion (red dot on the actogram), no clear phase, period, or amplitude of the rhythms can be measured.

The Chi-square periodogram (Fig. 2 iii) is a statistical test that is commonly used to extract the presence, and compute the value, of circadian periods within a given time series data set. This procedure was first developed by Enright [2] and later refined by Sokolove & Bushnell [3]. Typically, a minimum of 10 consecutive days of activity data is required for the accurate computation of circadian periods using the Chi-square periodogram. Significant periods present in the sample are observed as peaks above the significance level of the Chi-square statistic. As can be seen in the periodogram in Fig. 2 iii, there is one significant and dominant period very close to 24 h in the rhythmic animal (Fig. 2 i) and a multitude of different periods in the arrhythmic animal (Fig. 2 ii). The Chi-square periodogram has the advantage of reducing experimenter bias in the computation of the period of circadian rhythms compared to the eye-fitted regression line used in the actogram. However, the precision of the Chi-square periodogram is affected by the size of the bins used to collect the activity data, and by very short data sets.

Dependence on the Circadian Clock

Circadian rhythmicity in all organisms is driven by a small set of ►putative clock genes that are interlinked into one or more transcription-translation ►feedback loops [4]. These genes are expressed in various cell types, tissues, organs and organisms [1]. In animals with a central nervous system, a central pacemaker is responsible for the generation of circadian rhythms. For example, in mammals, the primary circadian pacemaker is localized within the hypothalamic ►suprachiasmatic nucleus (SCN). In *Drosophila melanogaster*, a small set of lateral neurons (LN) in the fly brain are responsible for circadian rhythmicity. Lesion of the mammalian SCN or the *Drosophila* LN will abolish rhythmicity. Mutations in the molecular mechanism driving the circadian oscillation will also lead to altered rhythmicity and/or arrhythmicity. For example, the ►tau



Arrhythmicity/Rhythmicity. **Figure 2** The actogram and periodogram as ways to analyze rhythmicity and arrhythmicity.

mutation in hamsters, which affects a key regulatory enzyme, leads to a circadian period of about 20 h [5]. The genes *cryptochromes*, *period*, and *bmal1* in mammals are considered essential components of the molecular clock and mutating or knocking-out these genes will lead to drastic changes in period and arrhythmicity [4]. In flies, the *timeless* gene is an essential component of the circadian machinery and its absence leads to arrhythmicity [6]. In *Neurospora*, the circadian oscillation relies on the expression of the *frequency* and *white-collar* genes [7].

Environmental Causes for Arrhythmicity

Circadian arrhythmicity can occur through several ways. As described previously, destruction of the central pacemaker or mutations in key genetic elements will lead to immediate loss of circadian rhythmicity at the behavioral and physiological levels (see Fig. 2 ii). However, environmental signals can cause arrhythmicity as well. The best known exogenous stimulus that will severely affect circadian rhythmicity and often lead to arrhythmicity is light. Constant bright light exposure will initially affect the period of the circadian oscillation

(see ►Aschoff's Rules). Over time, constant light will lead to disruptions of circadian rhythms. ►Splitting, the fragmentation of the ►activity phase into two components 180° out of phase, occurs in mice and hamsters housed in constant bright light. Constant light can eventually lead to complete arrhythmicity, similar to what can be observed after destruction of the central pacemaker (Fig. 2 ii). Interestingly, the disruptive effects of constant light are slow to appear and typically necessitate weeks or months of constant exposure. The effects of constant light are also intensity-dependent. Constant light of low intensity is less disruptive than high intensity constant light. Importantly, the effects of constant light on rhythmicity cannot be attributed to a destruction of the pacemaker, because rhythmicity is restored upon transfer to complete darkness or a light/dark cycle.

References

1. Dunlap JC (1999) Molecular bases for circadian clocks. *Cell* 96:271–290
2. Enright JT (1965) The search for rhythmicity in biological time-series. *J Theor Biol* 8:426–468
3. Sokolove PG, Bushell WN (1978) The chi square periodogram: its utility for analysis of circadian rhythms. *J Theor Biol* 72:131–160
4. Wager-Smith K, Kay SA (2000) Circadian rhythm genetics: from flies to mice to humans. *Nat Genet* 26:23–27
5. Ralph MR, Menaker M (1988) A mutation of the circadian system in golden hamsters. *Science* 241:1225–1227
6. Sehgal A, Price JL, Man B, Young MW (1994) Loss of circadian behavioral rhythms and per RNA oscillations in the *Drosophila* mutant timeless. *Science* 263:1603–1606
7. Dunlap JC, Loros JJ (2004) The neurospora circadian system. *J Biol Rhythms* 19:414–424

Artemin

Definition

A member of the glial cell line-derived neurotrophic factor (GDNF) family of neurotrophic factors that also includes neuroturin and persephin. GDNF family members use a receptor complex that consists of the common receptor tyrosine kinase signaling component.

Ret and one of the GPI-linked receptors (GFR α 1 to 4) that regulate ligand binding specificity. GFR α 3 is the preferred receptor for artemin.

- Glia Cell Line-derived Neurotrophic Factor (GDNF)
- Neurotrophic Factors in Nerve Regeneration
- Neuroturin
- Persephin

Arterially Perfused Brainstem

- Central Integration of Cardiovascular and Respiratory Activity Studied In Situ

Arthralgia

Definition

Joint pain.

- Joints

Arthritis

Definition

Joint inflammation.

- Joints

Arthropathy

Definition

Painful, dysfunctional joint.

- Joints

Arthroplasty

Definition

Orthopedic surgery to rebuild or replace a joint.

- Joints

Articular Cartilage

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Definition

Articular cartilage is a thin layer of fibrous connective tissue on the articular surfaces of bones in synovial joints (Fig. 1).

It consists of cells (2–15% in terms of volumetric fraction) and an intercellular **matrix** (85–98%) that is made up of 65–80% water.

Characteristics

Function

The major functions of articular cartilage are to transfer forces between articulating bones, to distribute forces in joints and to provide a nearly frictionless surface for joint movement.

Description of the Structure

Articular cartilage is heterogeneous and its material properties change as a function of depth. Although these changes are continuous, articular cartilage is typically divided into four zones (Fig. 2).

- Superficial zone
- Middle (or transitional) zone
- Deep (or radial) zone
- Calcified zone

The superficial zone is the thinnest, most superficial region that provides the gliding surface for joints. It

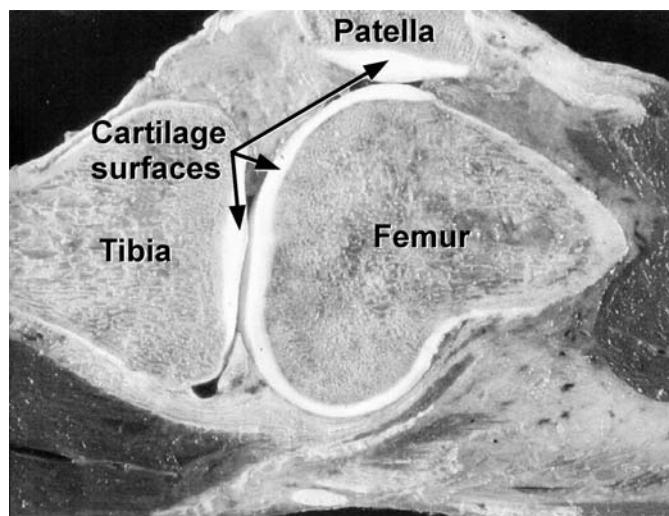
contains a superficial layer (**lamina splendens**) of about 2 μm thickness that is made up of randomly aligned **collagen** fibrils and a deep layer of collagen fibrils aligned parallel to the cartilage surface following the so-called “split line” pattern [1], which follows the direction of normal joint movement.

The collagen fibrils of the superficial zone show a wave-like pattern referred to as **crimp**. The deep layer of the superficial zone contains articular cartilage cells (**chondrocytes**) that are flat and metabolically relatively inactive [2], contains little proteoglycan, but has the highest water concentration of all zones (about 80%) [3].

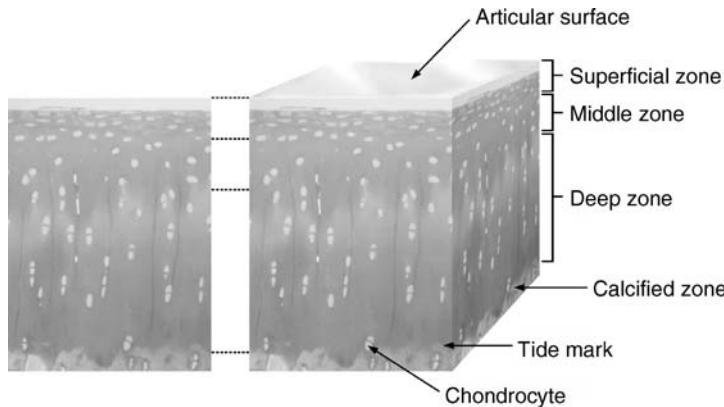
The middle (or transitional) zone is typically thicker than the superficial zone. Collagen fibrils have a greater diameter in this zone than in the superficial zone and are oriented randomly. The proteoglycan content is greater and aggregate complexes are larger than in the superficial zone. The chondrocytes are nearly spherical and are thought to be metabolically more active than those in the superficial zone.

The deep (or radial) zone contains the largest diameter collagen fibrils. They are oriented perpendicularly to the subchondral bone and the cartilage surface. The chondrocytes tend to be aligned in radial columns and are thought to be metabolically highly active.

The calcified zone provides the mechanical transition that separates the relatively soft cartilage tissue from the stiff subchondral bone. It is characterized by hydroxyapatite, an inorganic constituent of the bone matrix. The calcified zone is separated from the deep (radial) zone by the **tidemark**, an undulating line of a few micrometers thickness. Collagen fibers from the deep zone penetrate the tidemark and anchor the calcified zone, thereby adhering cartilage to bone. The calcified zone contains metabolically active



Articular Cartilage. Figure 1 Sagittal plane section through a human knee showing the femur, tibia, and patella and associated articular cartilage.



Articular Cartilage. Figure 2 The four zones of articular cartilage. The superficial zone provides the sliding surface of joints with collagen fibrils aligned parallel to the surface and flat, relatively metabolically inactive cells. The middle (or transitional) zone contains collagen fibrils that are oriented randomly, and cells that are nearly spherical. The deep (or radial) zone contains collagen fibrils that are oriented perpendicular to the subchondral bone (and articular surface) and the cells are typically aligned in radial columns. The calcified zone provides a mechanical transition that separates the relatively soft cartilage tissue from the stiff subchondral bone.

chondrocytes, serves for structural integration and is considered important for nutrition and cartilage repair arising from the underlying bone [4].

Composition

Articular cartilage consists mostly (85–98%) of *matrix* and a sparse population of cells (2–15%). It is avascular, aneural and alymphatic.

Chondrocytes are metabolically active cells in articular cartilage that are responsible for the synthesis and degradation of the matrix. They are isolated, lie in lacunae and receive nourishment through diffusion of substrates. The volumetric fraction, shape and metabolic activity of chondrocytes vary as a function of cartilage depth. Chondrocytes are soft compared to the surrounding matrix, but they are surrounded by a protective cover that consists of a pericellular matrix and capsule, called a ► *chondron*.

The *intercellular matrix* consists of structural macromolecules and fluid. Fluid comprises the greatest part of the extracellular matrix and its volume fraction decreases from the superficial (80%) to the deep zone (65%). Macromolecules, which are produced by the chondrocytes, comprise the remaining 20–35% of the matrix. Of the macromolecules, collagens are the most abundant (50%), while ► *proteoglycans* make up about 20–35%, and non-collagenous proteins/glycoproteins contribute 15–20% to the tissue dry weight [5].

There are at least 18 different types of *collagen*. However, in articular cartilage, type II collagen is by far the most abundant (about 80–85% of all collagens). Other types of collagen (V, VI, IX, X and XI) are also found in articular cartilage and have been associated

with specific functional roles [6, 7]. Collagen molecules are comprised of three α -chains that are interwoven in a helical configuration. Each chain has a high hydroxylysine content and covalently bound carbohydrates that make it readily adhere to proteoglycans.

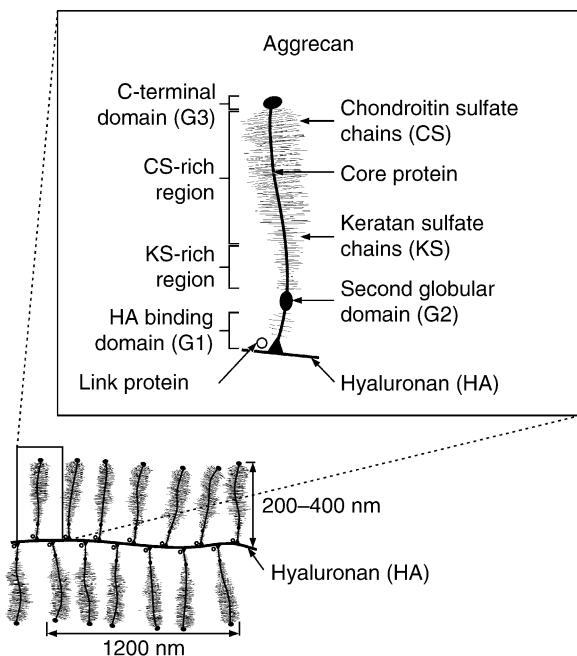
Collagens form a structural network that gives cartilage its tensile strength. Because of the characteristic orientation of the fibrillar network, collagens are associated with providing resistance to compressive loading through their coupling with fluid pressurization. Collagens are cross-linked for further strength [8] and are connected to proteoglycans via molecular chains arising from glycosaminoglycans and polysaccharides. Thus, collagens are intimately connected to other macromolecules and so make up a tough tissue that can withstand high repetitive loading effectively.

Proteoglycans are large molecules composed of a central core protein with glycosaminoglycan side chains covalently attached. The side chains contain sugars with a negative charge. When cartilage is loaded, proteoglycans are compressed and the repulsive forces from the negatively charged side chains are increased compared to the natural pre-tensed state.

Articular cartilage contains large aggregating proteoglycans (aggrecan and versican) and small interstitial proteoglycans (biglycan, decorin, fibromodulin and lumican). Aggrecan is the major proteoglycan. It consists of a core protein and up to 150 chondroitin and keratin sulfate chains (Fig. 3).

The core protein's N-terminal G1 domain interacts with link proteins and hyaluronan and these components form stable macromolecular complexes.

Changes in proteoglycan structure and decreased density often accompany articular cartilage degeneration



Articular Cartilage. Figure 3 Macromolecular aggregate formed by aggrecan molecules (*inset-blown up*) binding to a chain of hyaluronan through a link protein. The aggrecan molecule consists of a core protein with several domains: hyaluronan binding G1 domain, G2 domain, keratin sulfate-rich region, chondroitin sulfate-rich region and C-terminal domain, G3.

and aging [9, 10]. These changes are associated with increases in water content, decreased stiffness and reduced resistance to withstand mechanical loading. They are often the first signs of ▶osteoarthritis.

Non-collagenous proteins play a role in the assembly and integrity of the extracellular matrix. They form links between chondrocytes and matrix. Non-collagenous proteins include adhesive glycoproteins such as fibronectin, thrombospondin, chondroadherin and other matrix proteins such as the link protein, cartilage matrix oligomeric protein, cartilage matrix protein and proline/arginine-rich and leucine-rich repeat proteins.

Articular cartilage tissue *fluid* consists of water and dissolved gas, small proteins and metabolites. Loading of the articular cartilage produces fluid pressurization and movement. The tissue fluid is closely associated with the ▶synovial fluid of the joint, which is essential for virtually frictionless movement of the articulating surfaces.

Osteoarthritis

Osteoarthritis is a joint degenerative disease that affects about 50% of all people above the age of 60 in North

America. It is associated with a thinning and local loss of articular cartilage from the joint surfaces, osteophyte formation at the joint margins, swelling of the joint and pain. The causes for osteoarthritis are not well understood, although it is agreed that they are multi-factorial. Acknowledged risk factors include age, injury, weakness and obesity.

References

1. Hultkrantz W (1898) Über die spaltrichtungen der gelenkknorpel. Verh Anat Ges 12:248–256
2. Wong M, Wuethrich P, Egeli P, Hunziker E (1996) Zone-specific cell biosynthetic activity in mature bovine articular cartilage: a new method using confocal microscopic stereology and quantitative autoradiography. J Orthop Res 14(3):424–432
3. Maroudas A (1975) Biophysical chemistry of cartilaginous tissues with special reference to solute and fluid transport. Biorheology 12:233–248
4. Hunziker E (1992) Articular cartilage structure in humans and experimental animals. In: Peyron KE, Schleyerbach JG, Hascall VC (eds) Articular cartilage and osteoarthritis. Raven, New York, pp 183–199
5. Buckwalter JA, Hunziker EB, Rosenberg LC, Coutts R, Adams M, Eyre D (1991) Articular cartilage: composition and structure. In: Woo SL-Y, Buckwalter JA (eds) Injury and repair of the musculoskeletal soft tissues. American Academy Orthopaedic Surgeons, Park Ridge, pp 405–425
6. Hasler EM, Herzog W, Wu JZ, Muller W, Wyss U (1999) Articular cartilage biomechanics: theoretical models, material properties, and biosynthetic response. Crit Rev Biomed Eng 27(6):415–488
7. Thomas JT, Ayad S, Grant ME (1994) Cartilage collagens: strategies for the study of their organisation and expression in the extracellular matrix. Ann Rheum Dis 53:488–496
8. Pins GD, Christiansen DL, Patel R, Silver FH (1997) Self-assembly of collagen fibers. Influence of fibrillar alignment and decorin on mechanical properties. Biophys J 73:2164–2172
9. Buckwalter JA, Kuettner KE, Thonar EJ (1985) Age-related changes in articular cartilage proteoglycans: electron microscopic studies. J Orthop Res 3:251–257
10. Lark MW, Bayne EK, Flanagan J, Harper CF, Hoerrner LA, Hutchinson NI, Singer II, Donatelli SA, Weidner JR, Williams HR, Mumford RA, Lohmander LS (1997) Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. J Clin Invest 100:93–106

Articular Pain

▶Joint Pain

Articulation

Definition

The act or manner of producing a speech sound using the vocal tract (oral and nasal tracts).

- ▶ Speech Perception

Artificial Intelligence

Definition

The view that mental processes can be simulated or replicated in computers, at least in principle; that is, artificial systems can realize mental processes.

- ▶ Reductionism (Anti-Reductionism, Reductive Explanation)

Artificial Life

Definition

The study of life and life-like processes through simulation and synthesis.

- ▶ Emergence

Artificial Neural Networks

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Definition

Neural network modeling is a powerful research tool based on the combination of theoretical methods, including mathematical analyses and computer simulations, and is complementary to experimental techniques in neuroscience research. Neural networks are used to

understand how actual neuronal networks in a particular brain area represent and process information, and how they perform specific computations such as planning and execution of movements.

Description of the Theory

General Frameworks

The relationship between theory and experiment plays an important role in neural network modeling and creates a wide spectrum of approaches [1–3]. Some models are heavily based on the anatomical and electrophysiological properties of the actual neuronal networks involved. Studies along this line usually proceed from the detailed description of single cells to the behavior of the network. This approach is most useful when accurate experimental data at the morphological and physiological levels are available, the function of the neuronal network is already known, and the network itself is relatively small. Such models can determine whether existing data are sufficient to explain observed network behavior, and intend to pinpoint drawbacks and missing components in the model. The alternative to this *data-driven/bottom-up* approach is a *theory-driven/top-down* approach. Here, the emphasis shifts to descriptions of higher-level functions such as a perceptual ability. Based on the theoretical analysis, an algorithm that performs the desired function is developed first and then embedded into a simplified network while imposing known biological constraints. This kind of approach tends to be more loosely bound to particular experimental data. However, by sacrificing specificity, the theory-driven approach attempts to address fundamental and puzzling questions, and can help in formulating and testing what kind of computational algorithms the brain is using in different tasks. In the long run, this approach is expected to suggest new experiments and research directions.

Whereas the data-driven and theory-driven approaches represent two opposite extremes, there are varieties of other approaches that combine different proportions of the “abstract” and “realistic” components of the modeling and fill in the gap between these two extremes. Anyhow, biologically plausible models must not contain all the known features of the target system; they need to include only those features that are necessary to accurately simulate a particular phenomenon under study.

In this essay, only basic concepts relevant to the modeling of large-scale neural networks are considered. For further readings on the theory-driven approaches, see the book by Hertz et al. [4] and the review by Ermentrout [5] that focus not so much on biological modeling as on general theoretical approaches and algorithms. In contrast, the monograph by Anderson [6] and the textbook by Dayan and Abbott [7] consider neural networks from a broad neuroscience perspective, with an emphasis on the biology behind the assumptions of

models, as well as on for what the models might be used. Finally, the link between the theoretical studies and experimental approaches is the main concern of the book by Koch and Segev [2]. It has an excellent collection of papers for those interested in biophysical mechanisms of computation in neurons and networks.

Network Architecture and Operation

Units and Connections

Depending on the complexity of a target neuronal system and the desired level of realism, each unit of the model network may simulate either a single neuron or a set of similar neurons with coherent functional properties. The communication of activity from one neuron to another is modeled by means of a connection between a corresponding pair of units. The entire set of units and the pattern of connections between them define the architecture of the network. The realistic design of architecture requires knowledge of the underlying neural structure from neuroanatomical studies. When such data are not available, which is often the case, an educated guess based on other indirect studies could be useful.

Types of Units

Each unit can be classified as input, output, or hidden depending on the role that it plays in the operation of the network. ►Input units receive external signals that may represent sensory signals, signals from other networks, or some events in the external environment of an organism. The stimulation of input units may then change the activities of ►hidden units to which they are connected. This perturbation may further propagate across the whole network through connections to other hidden units and ultimately reach the ►output units.

The role of the latter is to provide an input to another network or simulate events at the behavioral level, for example, a motor action. Depending on the network architecture and its interpretation, the input, hidden, and output units may overlap partially or completely.

Types of Architecture

There are two prevailing network architectures in neural networks. Fig. 1a shows an example of layered ►feed-forward network. The role of the input units is to feed external signals to the rest of the network.

All connections are feed-forward. There are no connections between units in the same layer. Units in the intermediate layers are considered as hidden units, whereas the last layer represents the output units.

Networks that are not strictly feed-forward but include feedback connections are called recurrent networks. An example of a fully ►recurrent network is presented in Fig. 1b. Unlike the feed-forward architecture, there is no explicit distinction between input, hidden and output units.

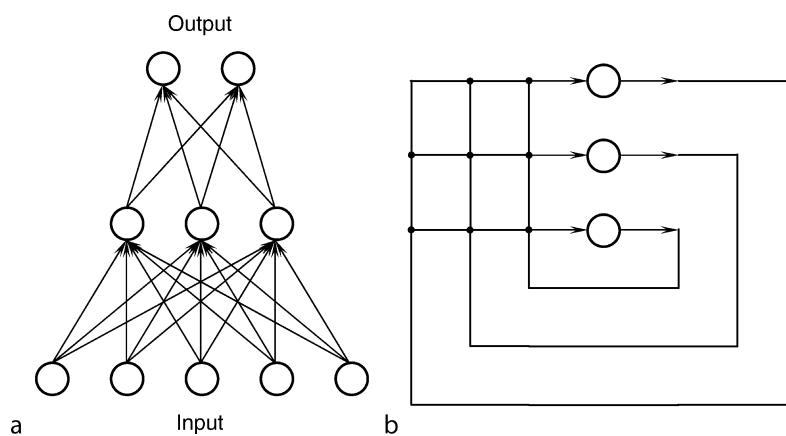
Dynamical Rules

The specification of architecture is necessary but not sufficient for the complete definition of network operation. One also needs to define the dynamical rules that stipulate how and when the state of each neuron is updated. Once the network is fully specified its operation is to transform the input signals into output ones.

Single Neuron Models and Synaptic Interactions

Integrate-and-Fire Model

A simple single-neuron model that generates action potentials is known as ►integrate-and-fire neuron. The basic idea is to divide the operation of a neuron i into



Artificial Neural Networks. Figure 1 (a) Network architecture. Circles represent units, whereas lines show connections between them. Arrows indicate the directions of connections. (a) Feed-forward network with one hidden layer. (b) Fully recurrent network with three units.

two qualitatively different modes. In the first mode, the neuron builds up its membrane potential starting from a specific value u_i^{rst} , called the reset potential, by temporally integrating its inputs. During this mode, the membrane potential $u_i(t)$ at an instant of time t obeys the dynamical rule given by a resistor-capacitor circuit charging equation:

$$\tau_i \frac{du_i}{dt} = -u_i(t) + R_i I_i(t). \quad (1)$$

Here, the time constant $\tau_i = R_i C_i$ depends on the resistance, R_i , and capacitance, C_i , properties of the cell membrane; the term $-u_i(t)$ is the trans-membrane leakage, whereas $I_i(t)$ is the total synaptic current charging the spike emitting part of the cell, soma. Once the potential $u_i(t)$ reaches a specific threshold value u_i^{thr} , the neuron enters into its second mode of operation by instantaneously firing a spike and resetting the potential to u_i^{rst} . After an absolute refractory period, during which the cell cannot emit spikes, the neuron restarts its operation in the first mode. Thus, the outcome of the model is the alteration of the prolonged period of integration and instantaneous firing.

In the framework of integrate-and-fire model, the effective synaptic current $I_i(t)$ charging the soma can be modeled in several ways. The dynamics of $I_i(t)$ depends on a set of synaptic time constants $\{\tau_{ij}^{\text{syn}}\}$. Each τ_{ij}^{syn} characterizes the temporal variation of the synaptic conductance of neuron i invoked by arriving spikes fired by neuron j . In the approximation $\tau_{ij}^{\text{syn}} \ll \tau_i$, i.e. when the characteristic time of the synaptic current changes is much shorter than that of the charging of the soma, the effective total current $I_i(t)$ is represented by a sum of elementary contributions made at the time of arrival of individual spikes [8]:

$$I_i(t) = \tau_i \sum_j w_{ij} \sum_k \delta(t - t_j^k - \Delta_{ij}), \quad (2)$$

where t_j^k is the time when neuron j emitted the k -th spike, Δ_{ij} is the delay in the arriving time at synapse i of spikes fired by neuron j , and $\delta(x)$ is the Dirac delta function. The synaptic efficacy, w_{ij} , is expressed in units of the current.

Conductance-Based Models

A more realistic approach to representing the effective charging current $I_i(t)$ utilizes a ►conductance-based model that accounts for a variety of transmembrane ionic currents. In this framework, (1) is usually given in the following form:

$$C_i \frac{du_i}{dt} + I_i^{\text{ion}}(t) = 0. \quad (3)$$

Here, $I_i^{\text{ion}}(t)$ designates the net transmembrane ionic current, including the leakage. It is assumed that all ionic

current flow occurs through membrane channels, and the instantaneous voltage-current relationship obeys Ohm's law. The ionic current through channels of a particular type chn is then given by a linear expression:

$$I_i^{chn}(t) = g^{chn}(u_i(t) - E^{chn}), \quad (4)$$

whereas the net ionic current $I_i^{\text{ion}}(t)$ is a simple sum of the currents through different types of channels: $I_i^{\text{ion}}(t) = \sum_{chn} I_i^{chn}(t)$. Here, g^{chn} is the conductance associated with the specific type of channel chn . The sign of the expression in (4), which indicates whether the current is outward or inward, depends on whether the membrane potential $u_i(t)$ is above or below the channel reversal potential E^{chn} . It is usually assumed that E^{chn} does not explicitly depend on time or potential. The known ion channels can be divided into three distinct types: passive or leak, synaptic, and active. Depending on the type of the channel, the corresponding conductance g^{chn} may have a mathematical description that ranges from very simple to very complex. For example, the passive channels are represented by a constant (time- and voltage-independent) conductance. Other channels, such as those located at synapses, change their conductance to certain ions when the appropriate chemical agents (e.g. neurotransmitters or second messengers) bind to their receptors. As the release of chemical agents is triggered by a presynaptic action potential, the conductance of the synaptic channels is modeled as a time-dependent but voltage-independent function that has a sharp peak at the spike arrival time. The active channels have conductances that are both voltage- and time-dependent. The model neuron that incorporates these types of nonlinear channels may produce responses that mimic not only a subthreshold mode but also the generation of action potentials. Unlike the integrate-and-fire model, in which spikes are discontinuous in time, here the spike generation occurs in a continuous-time fashion. Therefore, the model neuron of this type, often referred to as Hodgkin and Huxley [9] or biophysical model, may produce action potentials that have a shape similar to those observed in experiments.

Compartmental Approach and Realistic Modeling

The models considered so far are *single-point models* that disregard the underlying spatial structure of the neuron. The application of cable theory to nerve axons and dendrites, as well as the introduction of a ►compartmental approach, made it possible to develop increasingly realistic models of a single neuron. Advanced biophysical models of this kind, which are trying to incorporate as much morphological and physiological data as possible, represent a neuron as a set of electrically coupled isopotential compartments. The basic assumption is that the continuously distributed system can be divided into small segments,

called compartments. The geometry of compartments is modeled as an ellipsoid (soma) or cylinder (dendritic or axonal branch) of various sizes. Electrically, each compartment is modeled as a resistance-capacitance pair. Adjacent compartments are connected by series resistances. One must be aware, however, that detailed biophysical models incorporate a vast number of adjustable parameters. While these models are adequate for studying the behavior of a single neuron or a neuronal circuitry composed from a few cells, their application to large-scale networks may be inappropriate.

Learning and Generalization

The performance of a neural network, which is the relationship between the input signals and the output units' activities produced by the network in response, depends on several factors such as the connectivity pattern, number of neurons, synaptic interactions, etc. Traditionally, the network performance is adjusted by varying only a set of parameters w that, in the framework of the underlying model, effectively control the strengths of synaptic connections (e.g. synaptic efficacies in integrate-and-fire model, or synaptic conductances in conductance-based models). Such an approach is consonant to numerous experimental observations, indicating that during relatively short time periods the key mechanism, by which neuronal networks change their behavior, is the modification of the conductivity of pre-existing synapses (i.e. modification of the strength of connections) rather than the variation of the number of neurons or formation of new connections between them (i.e. modification of the network size and the connectivity pattern, respectively). For the sake of certainty, we shall refer to the parameters w as the connection weights.

A fixed set of w corresponds to a specific input-output transformation task implemented by the network. As the values of individual weights change, the same signals acting on the input units generate different activities of the output units. Therefore, by varying w , one can force the network to implement different transformation tasks. This also means that the network memorizes the task that it implements in the set of connection weights w . A key question in the theory of neural networks concerns the problem of *learning*: "How do we choose the connection weights so the network implements a specific task of interest?" The systematic adjustment of the connection weights, the goal of which is to find such a set w that implements the desired task, is called training or learning and is described by a corresponding ▶learning algorithm.

The common approach to network learning is formulated as follows. The known examples (i.e. input-output pairs) of a particular transformation task to be learned are divided into two subsets: the training set and the

testing set. The former is used to train the network to produce an appropriate output for each input in the set by applying a specific learning algorithm. It is expected that after training, the network will generate correct (or nearly correct) responses for all examples in the training set. Next, one would like to check whether the network indeed has learned the transformation task or whether it has simply memorized examples in the training set. For that purpose, examples from the testing set are presented to the network. If the responses to the novel examples of the same task are correct, then it is said that a *generalization* has taken place. If, however, the number of correct responses is at a chance level then there is no generalization.

Types of Learning Paradigms

Two types of learning paradigms are generally distinguished: supervised and unsupervised. ▶Supervised learning requires the knowledge of correct output responses for all examples in the training set. In this approach, which is also known as learning with a teacher, a direct comparison of the produced outputs against the correct responses provides a feedback to the network about its performance. The comparison is done in terms of the error function $E(w)$ that is, as a rule, a simple quadratic form of differences between the produced and correct outputs. The learning algorithm is an iterative procedure that adjusts the connection weights based on the feedback error $E(w)$. Its ultimate goal is to find such a set of the connections w that minimizes the error function. Thus, supervised learning, in essence, is an optimization problem. ▶Back propagation and ▶simulated annealing (see [4,6]) are two examples of supervised learning algorithms commonly used in neural networks.

Unlike supervised learning, in ▶unsupervised learning there is no teacher and corresponding algorithms do not require any feedback about the performance. Therefore, unsupervised learning can be used when correct responses to the inputs in the examples are not known, or the learning goal at the neural level is not explicitly defined. In the course of unsupervised learning, the network is expected to detect features and regularities in the input signals by itself, and represent them in the output in some appropriate way. In the framework of this approach, during the presentation of an example in the training phase, the modification of an individual connection weight is influenced only by the states (activities) of the two units that it is linked to and by its own state (value). Thus, in unsupervised learning, changes in connection weights are affected only by local events whereas in supervised learning, due to the global character of the feedback error, those changes are affected by remote events (i.e. activities of the output units). In contrast to supervised learning, the unsupervised learning paradigm could

therefore provide a suitable framework for studying biological mechanisms of learning. A well-known example of unsupervised learning is ►Hebbian learning rule, which stipulates that concurrent firing in the pre- and post-synaptic neurons strengthens the synaptic connection.

References

1. Abeles M (1991) *Corticonics: neural circuits of the cerebral cortex*. Cambridge University Press, Cambridge, New York
2. Koch C, Segev I (1998) *Methods in neuronal modeling: from ions to networks*. MIT Press, Cambridge, London
3. Marder E, Kopell N, Sigvardt K (1997) How computation aids in understanding biological networks. In: Stein PSG, Grillner S, Selverston AI, Stuart DG (eds) *Neurons, networks, and motor behavior*. MIT Press, Cambridge, London, pp 139–149
4. Hertz J, Krogh A, Palmer RG (1991) *Introduction to the theory of neural computation*. Addison-Wesley, Redwood City
5. Ermentrout GB (1998) Neural networks as spatio-temporal pattern-forming systems. *Rep Prog Phys* 61:353–430
6. Anderson JA (1995) *An introduction to neural networks*. MIT Press, Cambridge, London
7. Dayan P, Abbott LF (2001) *Theoretical neuroscience: computational and mathematical modeling of neural systems*. MIT Press, Cambridge, London
8. Amit DJ, Tsodyks MV (1991) Quantitative study of attractor neural network retrieving at low spike rates I: substrate – spikes, rates and neuronal gain. *Network Comput Neural Syst* 2:259–273
9. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol Lond* 117:500–544

Artificial Neural Networks

► Connectionism

Ascending Conjunctive Brachium

Definition

►Cerebellum

►Superior Cerebral Pedunculus, ►Ascending Branch

Ascending Neuromodulatory Projections

Definition

This collective term is used to describe a number of varyingly loosely aggregated collections of neurons occupying the brainstem or basal forebrain that are characterized by long projections that ascend to innervate, usually diffusely, the cerebral cortex and certain of the deep telencephalic nuclei. Such projections are further characterized on the basis of their major neurotransmitters, among which are included epinephrine, norepinephrine, dopamine, serotonin, histamine, orexin and acetylcholine. Consistent with the typically neuromodulatory effects of such projection systems on telencephalic functions, they have also been referred to as “state-setting projections.”

Ascending Nociceptive Pathways

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Synonyms

Anterolateral pathway; Pain system; Ascending pain pathways

Definition

Nociceptive neurons in the spinal cord and trigeminal nuclei send their axons to terminate within a large number of regions in the upper cervical spinal cord, brainstem and diencephalon. These neurons provide a link between peripheral nociceptors and pain perception in the brain. Precise roles for each ascending pathway in nociception have not yet been established with certainty and it is likely that their roles vary among species. This overview presents a summary of prominent findings on several of the most thoroughly examined ascending nociceptive projections.

Characteristics

Spinothalamic Tract (STT)

Several early clinical cases in which injury to the spinal cord blocked the sense of pain suggested that axons carrying nociceptive information crossed within the spinal cord and then ascended within the anterior white matter [1]. These observations led to the first surgical

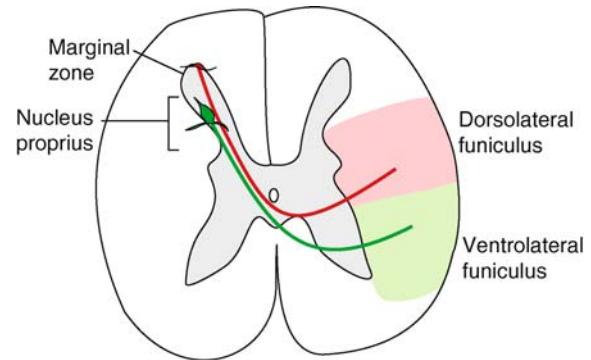
attempts to relieve chronic pain by ►cordotomy, i.e., cutting the anterolateral quadrant of the spinal cord, the area now known to carry an overwhelming majority of ►spinothalamic tract (STT) axons. Cordotomy can very effectively eliminate pain for patients, but the positive effects are short lived and pain frequently returns within several months. It is not known which tracts begin to carry the nociceptive information following a cordotomy.

Anatomical studies in a variety of species including primates demonstrated that lesions of the spinal cord caused degeneration of axons within the thalamus. Both ►anterograde and ►retrograde tracing studies have since determined the locations and numbers of the cells of origin of the STT, as well as the areas of termination of STT axons within the thalamus. ►Antidromic activation and extracellular recording techniques have been used to identify and functionally characterize the stimulus-response properties of STT neurons to mechanical, thermal, and chemical stimuli.

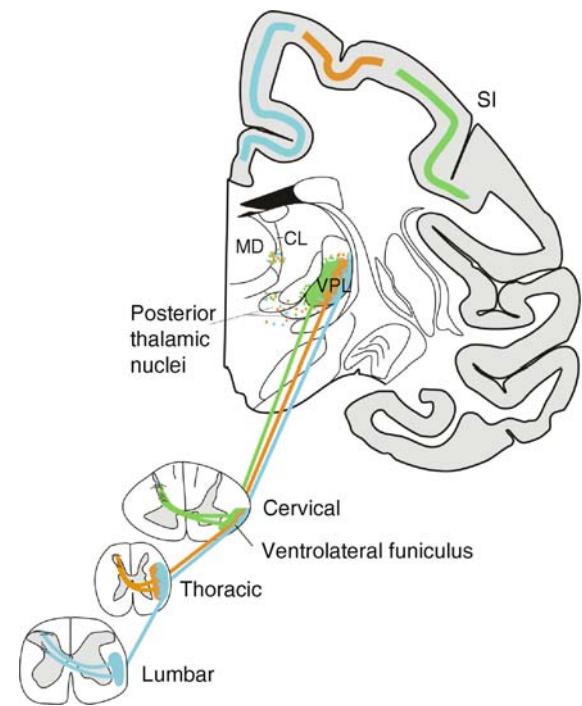
The cells of origin of the STT are found within the spinal gray matter at all levels of the cord. STT cell bodies and dendrites receive glutamatergic and several types of peptidergic inputs. It has been estimated that there are between 15 and 20 thousand STT neurons on one side of the spinal cord of primates [1,2]. The upper cervical segments have been shown to contain 1/3 of all cells of origin of the STT. Within the gray matter, STT neurons are concentrated in the marginal zone (lamina I) and within the deep dorsal horn (lamina V). STT neurons are also found within the intermediate gray zone and the ventral horn. Most axons of STT neurons decussate at a level near the cell body and then turn to ascend within the ►ventrolateral funiculus. STT axons originating from marginal zone neurons ascend in a position that is dorsal to STT axons originating from neurons within the deep dorsal horn. Within thoracic levels, STT axons of marginal zone neurons are generally located dorsal to the denticulate ligament in the dorsal lateral funiculus, whereas the axons of lamina V neurons are found within the ventral part of the lateral funiculus ([2], Fig. 1). There is a somatotopic organization of ascending STT axons such that axons from lumbosacral levels ascend on the periphery of the lateral funiculus, whereas STT axons from progressively rostral levels are located closer to the gray matter ([3], Fig. 2).

STT axons continue to ascend through the lateral and ventral brainstem. Collateral branches are frequently given off by these axons supplying nociceptive sensory information to a number of nuclei, particularly within the reticular formation.

STT axons terminate in three principle regions of the thalamus including the ventral posterior lateral (VPL), central lateral and adjacent parts of the medial dorsal nucleus, and posterior thalamic nuclei [1,4]. STT terminations within VPL are somatotopically organized.



Ascending Nociceptive Pathways. Figure 1 Axons of spinothalamic tract neuron cross to the contralateral side of the spinal cord and ascend the white matter within the antero-and dorsolateral funiculi.



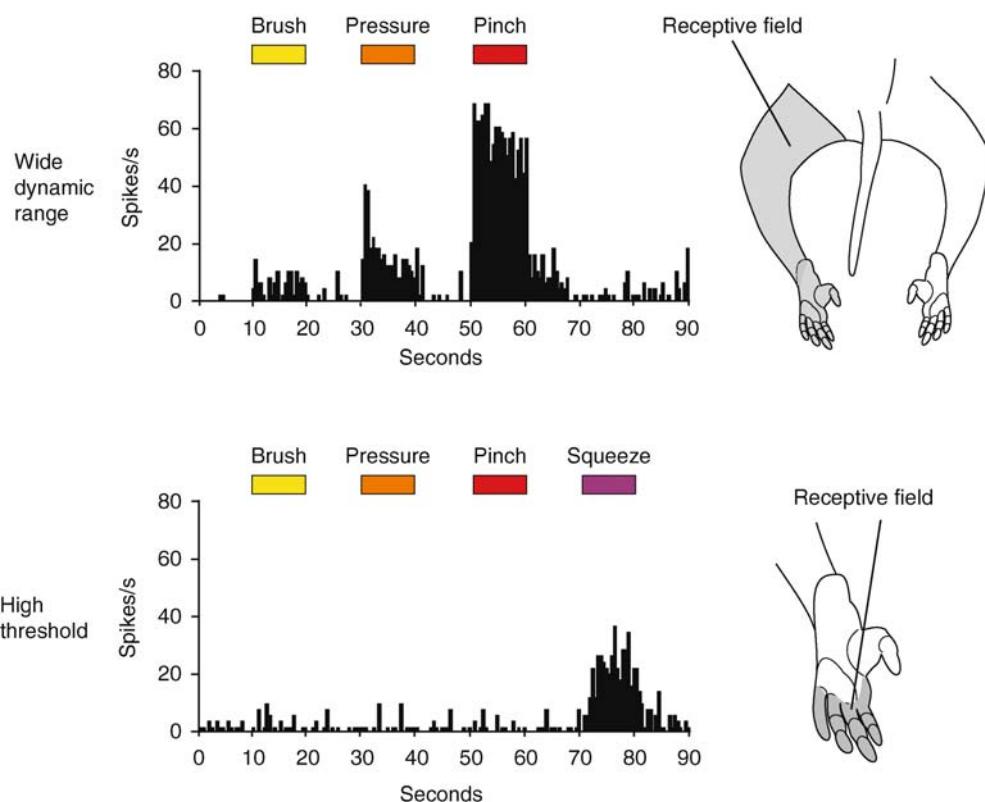
Ascending Nociceptive Pathways. Figure 2 The spinothalamic tract is somatotopically organized. Axons from neurons in rostral segments of the spinal cord ascend medially relative to axons originating from caudal segments. The somatotopy is maintained within the major target nucleus of the thalamus, the ventroposterior lateral nucleus. Primary sensory cortex is somatotopically organized with lumbar segments (e.g. leg) represented medially within the post-central gyrus and cervical segments (e.g. arm) represented laterally.

Axons ascending from lumbosacral levels terminate within the lateral part of VPL; those from cervical levels end within the medial part of the nucleus. Within VPL of primates, STT terminals are concentrated within small

areas that are surrounded by large regions that are dominated by the endings of medial lemniscal axons. A high percentage of nociceptive neurons within the primate VPL can be antidromically activated from primary somatosensory cortex, indicating that nociceptive input to VPL neurons via STT axons is transmitted to the cortex (Fig. 2). A second area of termination of the STT is the central lateral nucleus and the adjacent lateral region of the medial dorsal nucleus. STT neurons projecting to this region are often located within the intermediate zone and ventral horn of the spinal cord. Many of the nociceptive neurons within this area of the thalamus have large, bilateral, even whole-body receptive fields. Thus it is unlikely that this region is involved in localization of nociceptive stimuli, and instead may be involved in the production of affective/emotional responses to nociceptive stimulation. STT axons that terminate in the posterior thalamic nuclei appear to arise predominantly from neurons of the marginal zone. A recently described area of primate thalamus, the posterior part of the ventral medial nucleus, is suggested to receive a large proportion of STT inputs

[4]. Nociceptive information originating from receptors on the face in the oral and nasal cavities is carried to the ventral posterior medial nucleus of thalamus by trigemino-thalamic tract projections.

Responses of STT neurons to a variety of somatic and visceral stimuli have been examined [1]. In primates, the vast majority of STT neurons have been classified as nociceptive, responding either preferentially (wide dynamic range, WDR) or specifically (high threshold, HT) to mechanical noxious stimuli (Fig. 3). In most studies, higher percentages of HT-STT neurons have been found in the marginal zone and more WDR neurons within the deep dorsal horn. Cutaneous receptive fields of neurons in the marginal zone tend to be smaller, sometimes being restricted to a single toe. The receptive fields of deeper neurons often cover much of the ipsilateral leg. Many STT cells are activated by noxious thermal stimulation of their receptive fields. Response thresholds to noxious heat stimuli are often between 45 and 55°C. Repeated applications of noxious heat stimuli lead to sensitization, including reduced response thresholds, increased response magnitude



Ascending Nociceptive Pathways. Figure 3 Spinothalamic tract neurons are typically classified as one of two types: Wide Dynamic Range or High Threshold. Wide Dynamic Range neurons are responsive to innocuous stimuli applied to their receptive fields as well as noxious stimuli. High Threshold neurons do not respond to innocuous mechanically stimuli. Both types may respond to thermal and/or chemical stimuli.

to identical noxious heat stimuli, and the production of ongoing activity. STT neurons also receive nociceptive input from muscles and joints, and they can be activated by stimulation using noxious chemicals such as Capsaicin, mustard oil and histamine.

STT neurons also can be activated by noxious stimulation of visceral tissues. In almost all cases, STT neurons that respond to stimulation of a visceral organ have somatic receptive fields as well. Frequently, somatic receptive fields are located in areas to which noxious stimulation of an organ would produce ►referred pain in human. STT axons are therefore capable of carrying nociceptive visceral information, and the convergence of somatic and visceral nociceptive input probably contributes to the phenomenon of referred pain.

Spinohypothalamic Tract (SHT)

Burstein [5] noted that spinal cord neurons could be antidromically activated using small amplitude current pulses delivered through electrodes located within the hypothalamus of rats. In addition, injections of anterograde tracers into the spinal cord labeled axons within several areas of the hypothalamus, including the lateral, posterior, and ventromedial hypothalamus. Injections of retrograde tracers that were restricted to the hypothalamus labeled thousands of neurons within the spinal cords of rats. Spinohypothalamic tract (SHT) cell bodies were located in the marginal zone and the deep dorsal horn. SHT axons have been shown to ascend to the posterior thalamus, then turn ventrally to enter the supraoptic decussation. These axons continue to ascend in a position just dorsal to the optic tract and enter the hypothalamus (Fig. 4). Many SHT axons ascend to the level of the optic chiasm where they decussate a second time, turn posteriorly, and then descend within the supraoptic decussation on the side ipsilateral to the cell body from which they originated. SHT axons have been shown to terminate in the ipsilateral hypothalamus, posterior thalamus, and brainstem. Some have even been shown to descend as far as the level of the medulla. SHT neurons are frequently nociceptive. Some also receive an apparent input from innocuous thermoreceptors. It has been suggested that through their complex, bilateral projections and frequent branches, SHT axons could provide nociceptive input to a variety of areas of the brainstem and forebrain that are involved in nociceptive processing. SHT neurons have also been identified and characterized in monkeys. Large numbers of neurons within all divisions of the trigeminal complex and upper cervical segments similarly send axonal projections to the hypothalamus.

Spinoreticular Tract (SRT)

The spinoreticular tract (SRT) is a direct projection from spinal cord neurons to the reticular formation of medulla, pons and midbrain ([1,6], Fig. 4). Regions that receive

these direct spinal afferent fibers include the nucleus gigantocellularis and nucleus dorsalis, both within the medulla, and the cuneiform nucleus of the midbrain. Because several of these regions in the reticular formation in turn send ascending nociceptive projections to the forebrain, it is believed that the SRT is part of a multisynaptic projection system to the thalamus and probably is involved in providing nociceptive information that is used in producing cortical arousal.

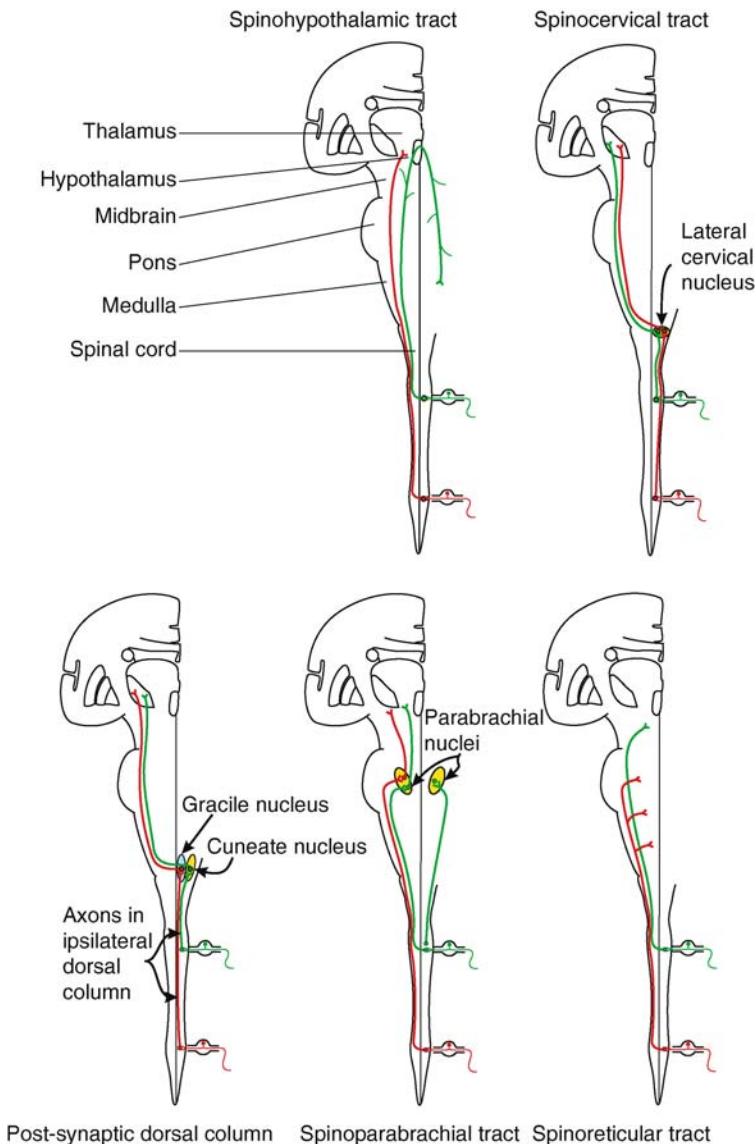
Studies in which antidromic methods have been used to demonstrate direct projection to the reticular formation have shown that many SRT neurons are nociceptive. These neurons have been frequently recorded deep within the spinal gray matter and have large complex receptive fields frequently including the face. Retrograde tracing studies indicate that SRT neurons are found within the marginal zone and deep dorsal horn, but a large percentage are located within the intermediate zone and ventral horn.

Spinoparabrachial Tract

Somatic sensory and nociceptive information ascends directly from the spinal cord to several sub-nuclei of the parabrachial nucleus, which is located lateral to the superior cerebellar peduncle within the rostral pons and caudal midbrain ([7], Fig. 4). The locations of the cells of origin of the spinoparabrachial tract have been established using electrophysiological and anatomical techniques. Injections of retrograde tracers that are restricted to the parabrachial nucleus label a large number of spinal neurons at all levels of the spinal cord of rats and cats. Although spinoparabrachial tract neurons are found throughout much of the gray matter, the fact that they are highly concentrated within the marginal zone has generated a great deal of interest in this projection. Anterograde tracing studies indicate that neurons in the marginal zone send a large projection via the dorsal part of the lateral funiculus to the parabrachial nuclei on both sides. Studies in which antidromic activation has been used to identify spinoparabrachial tract neurons in cats indicate that the overwhelming majority is activated by noxious stimuli. The parabrachial nuclei are known to have large projections to several areas of the forebrain that are involved in nociception, including the hypothalamus and the amygdala. Therefore, this projection appears well suited for providing nociceptive information that is used for producing cognitive, emotional or affective responses to pain.

Spinocervicothalamic Tract (SCT)

Spinocervical tract neurons are located throughout the length of the spinal cord. Many SCT neurons receive powerful afferent input from innocuous mechanoreceptors and as many as half of SCT neurons also receive nociceptive input [8]. These neurons send their ascending axons into the dorsal part of the ipsilateral lateral



Ascending Nociceptive Pathways. Figure 4 Illustrations of other ascending nociceptive pathways.

funiculus. SCT axons ascend to upper cervical segments where they terminate within the lateral cervical nucleus (LCN), an island of neurons extending from segment C3 through C1 that is located within the dorsal lateral funiculus (Fig. 4). The number of neurons that form the LCN varies greatly among species, but in carnivores may be as many as 10,000 neurons. The LCN is comparatively small in monkeys, although precise cell counts are not available. In humans the LCN has been reported to be highly variable. Some individuals appear to have a prominent LCN on one side and few if any LCN neurons on the other. Other individuals appear to have a clear LCN on both sides, and some have no LCN on either side. These findings suggest a lesser, variable role for the SCT in nociception in humans.

Roughly half of LCN neurons in carnivores are nociceptive and these have been shown to respond specifically or preferentially to noxious mechanical stimuli. Many of these neurons can also be activated by noxious heat stimuli. LCN neurons that receive mechano-receptive or nociceptive input are somatotopically organized; neurons in the lateral LCN receive input from lumbosacral segments, whereas neurons in the medial LCN receive input from cervical levels. A small number of neurons in the medial LCN have nociceptive whole-body receptive fields. Axons of LCN neurons decussate in upper cervical spinal cord and ascend to terminate in the contralateral VPL. As many as half of ascending axons of LCN neurons give off branches that terminate within the midbrain.

Postsynaptic Dorsal Column Projection (PSDC)

Injections of retrograde tracers into the dorsal column nuclei of cats, rats and monkeys label large numbers of neurons throughout the length of the spinal cord [9]. Many of these are located in nucleus proprius (laminae III and IV). A smaller number are found near the central canal. Anterograde tracing studies indicate that most axons of this type ascend within the ipsilateral dorsal columns, but some appear to ascend within the dorsal lateral funiculus (Fig. 4). In cats, PSDC axons frequently terminate in the periphery of the dorsal column nuclei while primary afferent fibers often terminate in the cores of the two nuclei. In rats, the terminations of these projections appear to overlap more substantially. In cats, roughly half of PSDC neurons can be driven exclusively by innocuous mechanical stimulation and the remainder can be classified as WDR neurons, indicating that this projection is capable of conveying nociceptive information. PSDC cells have been shown to be powerfully activated by noxious mechanical and heat stimuli. Several lines of evidence indicate that nociceptive visceral information is carried by this projection in rats, monkeys and possibly humans. An elegant series of studies show that PSDC neurons convey nociceptive visceral information that reaches the thalamus [10]. These authors have also pointed out that surgical section of the medial area of the dorsal columns relieves chronic visceral pain in patients.

References

- Willis WD Jr, Coggeshall RE (2004) Sensory mechanisms of the spinal cord, 3rd edn. Kluwer, New York
- Apkarian AV, Hodge CJ (1989) Primate spinothalamic pathways: I. a quantitative study of the cells of origin of the spinothalamic pathway. *J Comp Neurol* 288:447–473
- Applebaum AE, Beall JE, Foreman RD, Willis WD (1975) Organization and receptive fields of primate spinothalamic tract neurons. *J Neurophysiol* 38:572–586
- Craig AD (2004) Distribution of trigeminothalamic and spinothalamic lamina I terminations in the Macaque monkey. *J Comp Neurol* 477:119–148
- Burstein R, Cliffer KD, Giesler GJ Jr (1987) Direct somatosensory projections from the spinal cord to the hypothalamus and telecephalon. *J Neurosci* 7:4159–4161
- Yezierski RP, Schwartz RH (1986) Response and receptive-field properties of spinomesencephalic tract cells in the cat. *J Neurophys* 55:76–95
- Bernard JF, Dallel R, Raboisson P, Villanueva L, Le Bars D (1995) Organization of the efferent projections from the spinal cervical enlargement to the parabrachial area and periaqueductal gray: A PHA-L study in the rat. *J Comp Neurol* 353:480–505
- Brown AG (1981) Organization in the spinal cord: the anatomy and physiology of identified neurones. Springer, Berlin Heidelberg New York, pp 17–72
- Giesler GJ Jr, Nahin RL, Madsen AM (1984) Postsynaptic dorsal column pathway of the rat. I. Anatomical studies. *J Neurophysiol* 51:260–275
- Al-Chaer ED, Feng Y, Willis WD (1998) A role for the dorsal column in nociceptive visceral input into the thalamus of primates. *J Neurophysiol* 79:3143–3150

Ascending Pain Pathways

► Ascending Nociceptive Pathways

Aschoff's Rules

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Definition

Aschoff's Rules are a set of three statements used to describe, and predict, the circadian behavior of animals housed under ►constant lighting conditions. These rules were attributed to the circadian biologist Jürgen Aschoff (1913–98), based on his observations of the spontaneous frequencies (free-running periods) of several animal species.

Aschoff's First Rule

States that the endogenous free-running circadian period (τ_{au} , τ), observed in complete darkness (DD), will shorten for ►diurnal animals and lengthen for ►nocturnal animals when they are exposed to constant light (LL). The effects of LL are intensity dependent with brighter light enhancing these effects. Thus, Aschoff's First Rule predicts that $\tau_{LL} < \tau_{DD}$ for diurnal animals and $\tau_{LL} > \tau_{DD}$ for nocturnal animals.

Aschoff's Second Rule

States that under constant bright light, ►activity time (α , α) increases compared to ►rest time (ρ , ρ) for diurnal animals and decreases for nocturnal animals. As a result, the duration of daily activity in constant conditions increases with increasing light intensity for diurnal animals and decreases with increasing light intensity for nocturnal animals. Thus Aschoff's Second Rule predicts that $\alpha_{LL} > \rho_{LL}$ for diurnal animals and $\alpha_{LL} < \rho_{LL}$ for nocturnal animals.

Aschoff's Third Rule

States that the ►free-running period in DD is longer than 24 h for diurnal animals and shorter than 24 h for

nocturnal animals. Thus Aschoff's Third Rule predicts that: $\tau_{DD} > 24$ h for diurnal animals: $\tau_{DD} < 24$ h for nocturnal animals.

Characteristics

Historical Perspective

"Aschoff's Rule" is a term that was originally coined by Colin S. Pittendrigh (1918–96) in 1960 during the Cold Spring Harbor Symposia on Quantitative Biology (Vol XXV, Biological Clocks, 1960). During his symposium, Jürgen Aschoff presented a summary of the circadian behavior of diurnal and nocturnal animals housed under constant conditions (DD and various intensities of LL). Within the species reviewed, diurnal animals (finches, starlings, lizards) shortened their free-running period in LL and nocturnal animals (house mice and white-footed mice) lengthened their free-running period in LL compared to their period in DD. Pittendrigh, who was presenting after Aschoff, made several major empirical generalizations about circadian rhythms; one of these generalizations was "XII: τ_{FR} is light intensity dependent. There is evidence of a fairly strong further generalization which I propose to call *Aschoff's Rule*. This can be summarized by $\tau_{LL} > \tau_{DD}$ in nocturnal animals; $\tau_{LL} < \tau_{DD}$ in diurnal animals" (where $_{FR}$ means free-running) [1]. Because of this, the first rule is often referred simply as Aschoff's Rule. The other two of Aschoff's rules were not as explicitly stated by Pittendrigh in this article, but nonetheless became part of the circadian nomenclature.

The effects of constant light on the circadian behavior of animals have long been recognized, but Aschoff was among the first to systematically analyze and describe them [2]. At that time, the circadian research field was still in its infancy and the exact conditions that would affect the circadian **►oscillator**, or even the nature of such an oscillator, were unknown. A conceptual framework was needed in order to establish whether the circadian oscillator was endogenous or exogenous. For an endogenous oscillator to be revealed, one had to find conditions where extraneous entraining signals (see **►Zeitgebers**) were kept constant. Light is the most important Zeitgeber affecting circadian rhythms. In order to prevent its entraining role, light level was held constant, from complete darkness (DD) to LL of different intensities. The free-running circadian behavior could then be studied in an unperturbed system.

Behavioral Characteristics of Aschoff's Rules

In the absence of any light cues (DD), circadian rhythms persist with a spontaneous frequency of about one cycle per day, or a free-running period of approximately 24 h. This spontaneous frequency is species specific, with individuals within a given species showing some variability in their free-running periods. Free-running also occurs under constant illumination, suggesting that constant light does not provide any entraining cue

to the circadian clock. However, LL does affect the frequency of the circadian oscillation (period of circadian rhythms). Aschoff's observations showed that diurnal animals gradually increased the frequency of their circadian oscillation as the LL intensity increased (shortened free-running period), and that nocturnal animals decreased their spontaneous frequency (lengthened free-running period; Aschoff's First Rule). In addition to its effects on frequency, Aschoff observed that LL led to an increase in general locomotor activity for diurnal animals and to a suppression of locomotor behavior of nocturnal animals (Aschoff's Second Rule). Finally, based on a small initial sample of different animal species, Aschoff proposed that the free-running period in constant darkness is longer than 24 h for diurnal animals (finches, starlings, and lizards) and shorter than 24 h for nocturnal animals (house mice and white-footed mice (Aschoff's Third Rule).

Violation of Aschoff's Rules

Like every good rule, or set of rules, Aschoff's Rules have their exceptions. The initial summary and description of the behavior of animals in constant conditions made by Aschoff in 1960 surveyed a small number of animal species (finches, starlings, lizards, and mice). In a follow-up article, Aschoff reviewed practically all the available data on the behavior of a wider range of animal species under DD and LL of various intensities [3]. This review article covered the behavior of close to 80 species of diurnal and nocturnal birds, mammals, reptiles, fishes, and arthropods [3]. Although, in general, most species seemed to follow Aschoff's Rules, there were a few exceptions. Some arthropods (e.g. some species of ground beetles) and some diurnal mammals (e.g. some species of squirrels) violate Aschoff's First Rule. The effects of increasing intensities of LL do not produce the predicted changes in their free-running rhythms. Arthropods also seem to violate Aschoff's Third Rule: both diurnal and nocturnal species have free-running periods shorter than 24 h. However, these observations and the generalizations derived from them are complicated by the fact that prior lighting history will change **►pacemaker** properties of the circadian **►oscillator**, and cause **►after-effects** [4]. These history-dependent effects on the circadian period can last for a relatively long time and affect the observed compliance with Aschoff's Rules. It is unclear if all the species reviewed by Aschoff had the same lighting history.

Mechanisms Underlying Aschoff's Rules

There has been surprisingly little research aimed specifically at determining the physiological, anatomical, or molecular mechanism (s) underlying Aschoff's Rules. There is, fortunately, some evidence from attempts that were made (directly or not) at explaining the

mechanism through which constant light will accelerate (diurnal) or decelerate (nocturnal) the circadian oscillator (Aschoff's First Rule). However, the evidence comes mostly from nocturnal rodents, species that tend to follow Aschoff's Rules. These are discussed below.

Genetic Components of Aschoff's First Rule

When inbred strains of mice are compared for their expression of Aschoff's First Rule under ►dim red light versus LL, one can observe different magnitudes of the lengthening effect of LL on the spontaneous frequencies of the circadian oscillation. Because inbred mice are all species variants of the Genus *Mus*, this suggests that differences in genetic makeup, ability to perceive light, and/or circadian clock gene expression might account for these differences in the manifestation of Aschoff's First Rule in mice.

There is evidence that the ►clock gene *Period2* might be involved in the expression of Aschoff's First Rule. It has been shown that constant bright light, which increases the free-running period of mice, will also alter *Period2* protein levels. In rhythmic mice under LL, *Per2* mRNA is still rhythmic, but PER2 protein is elevated and non-rhythmic in the ►suprachiasmatic nucleus (SCN, the mammalian central circadian pacemaker) [5]. This is in contrast to mice kept in DD where both *Period2* mRNA and protein are rhythmic. In addition, mice bearing a mutation in the *Period2* gene violate Aschoff's First Rule. The free-running rhythm of *Period2* mutant mice is shorter in LL than it is in DD [6]. Thus, a differential regulation of putative clock genes (*Period2* or other) in mice appears to correlate with the differences in circadian behavior under LL.

Anatomical Components of Aschoff's Rule

The pathway through which light reaches the circadian clock in mammals, the ►retinohypothalamic tract (RHT), has been very well studied. This monosynaptic projection from the retina to the SCN conveys the photic information necessary for the effects predicted by Aschoff's Rules. The transduction of the light signal starts in the ►retina where specialized ►photoreceptor cells convert light into a neuronal signal that is then transmitted through the optic nerve towards the SCN and other brain centers. The classical ►photoreceptors (rods and cones) are not required for the transmission of light signals to the SCN. Mice lacking rods and cones entrain normally to ►light-dark cycles and show normal lengthening of their free-running period under LL [7]. This suggest that there are other means of ►phototransduction in rodless-coneless mice. Indeed, the novel ►photopigment melanopsin, exclusively expressed in ►retinal ganglion cells has been shown to be sufficient for the transmission of photic information to the circadian system. In melanopsin knockout

mice, the lengthening effect of LL on the free-running period is reduced [8]. This suggests that melanopsin-containing retinal ganglion cells that project to the circadian system participate in the expression of Aschoff's First Rule.

Besides the SCN, there is another structure that is part of the larger circadian system in mammals: the ►intergeniculate leaflet (IGL) of the thalamus. The IGL receives direct retinal inputs and sends information back to the SCN. Lesions of the IGL will reduce the lengthening effects of LL on the free-running period, but only in hamsters, not mice [9,10]. This suggests that, at least in hamsters, the IGL integrates part of the light information required for the increase in free-running period induced by LL.

Even after nearly 50 years, the observations made by Aschoff are still effective tools for the description of the effects of constant conditions on the spontaneous frequency of the circadian oscillator. Their real value for circadian biologists include: (i) they established that specific circadian behaviors are conserved across species and highly reproducible, (ii) that the circadian period is "plastic" and influenced by lighting history, and (iii) that, when combined with entrainment theory, they can be explained, at least in a qualitative way, to result from the effects of light on the ►phase-response curve of two coupled-circadian pacemakers (see ►morning/evening oscillators).

References

- Pittendrigh CS (1960) Circadian rhythms and the circadian organization of living systems. Cold Spring Harb Symp Quant Biol 25:159–184
- Aschoff J (1960) Exogenous and endogenous components in circadian rhythms. Cold Spring Harb Symp Quant Biol 25:11–28
- Aschoff J (1979) Circadian rhythms: influences of internal and external factors on the period measured in constant conditions. Z Tierpsychol 49:225–249
- Pittendrigh CS, Daan S (1976) A functional analysis of circadian pacemakers in nocturnal rodents: I. The stability and lability of spontaneous frequency. J Comp Physiol A 106:223–252
- Munoz M, Peirson SN, Hankins MW, Foster RG (2005) Long-term constant light induces constitutive elevated expression of mPER2 protein in the murine SCN: a molecular basis for Aschoff's rule? J Biol Rhythms 20:3–14
- Steinlechner S, Jacobmeier B, Scherbarth F, Dernbach H, Kruse F, Albrecht U (2002) Robust circadian rhythmicity of Per1 and Per2 mutant mice in constant light, and dynamics of Per1 and Per2 gene expression under long and short photoperiods. J Biol Rhythms 17:202–209
- Mrosovsky N (2003) Aschoff's rule in retinaally degenerate mice. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 189:75–78

8. Panda S, Sato TK, Castrucci AM, Rollag MD, DeGrip WJ, Hogenesch JB, Provencio I, Kay SA (2002) Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. *Science* 298:2213–2216
9. Morin LP, Pace L (2002) The intergeniculate leaflet, but not the visual midbrain, mediates hamster circadian rhythm response to constant light. *J Biol Rhythms* 17:217–226
10. Pickard GE (1994) Intergeniculate leaflet ablation alters circadian rhythms in the mouse. *Neuroreport* 5:2186–2188

more than one sensory modality. Speech areas in the inferior frontal and parietotemporal regions comprise high-order multimodal association areas. High-order association areas involved in behavioral synthesis and sequencing and the emotional, motivational and mnemonic content of behavior, sometimes referred to as “limbic association cortex,” occupy parts of all of the cortical lobes, but culminate in the prefrontal, insular and medial temporal lobes.

Aseptic Meningitis

Definition

Aseptic meningitis is an illness mainly characterized by inflammation of the linings of the brain (meninges) and is not caused by bacteria.

Aspinous Neuron/Cellular

Definition

Neurons that do not have spines on their dendrites are classified as aspinous neurons.

Association Cortex

Definition

Refers to cerebral cortex other than the primary sensory and motor areas and, thus, most of the cortical mantle. The hallmark of association cortex is dominant cortico-cortical input-output relationships, thus suggesting the function of combining and recombining cortically processed information in the service of increasingly elaborate cortical representations of the internal and external environments in relation to memory, mood and motivation. Unimodal association areas flanking the primary sensory areas are concerned with the elaboration of modality specific sensory processing. Multimodal association areas merge information arising from

Association Tracts

Definition

Commissures are fibers which exchange information between the hemispheres. Association pathways are fiber bundles within a hemisphere, while fibers between cerebral cortex and subcortical centers are called projection pathways.

► General CNS

Associative Learning

Definition

Associative learning is the learning of associations between events. In associative learning, a subject learns the relationship between two different stimuli or between the stimulus and the subject's behavior.

Classical conditioning and operant (or instrumental) conditioning are typical examples of the associative learning.

► Associative Memory
 ► Classical Conditioning (Pavlovian Conditioning)
 ► Operant Conditioning (Instrumental Learning)
 ► Learning

Associative Long-lasting Potentiation

► Associative Long-Term Potentiation

Associative Long-term Facilitation

► Associative Long-Term Potentiation

Associative Long-Term Potentiation

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Synonyms

Associative long-lasting potentiation; Associative long-term facilitation; LTP

Definition

Long-lasting increase in the efficacy of synaptic transmission, induced in an input that is active when LTP-inducing high-frequency stimulation is applied to another independent strong input.

In a weak input, high-frequency stimulation (e.g. 100 Hz for 1s) often fails to induce LTP; however, when the weak input is stimulated simultaneously with high-frequency stimulation of another independent strong input, the weak input can also exhibit Long-term potentiation (LTP) (►Long-term potentiation, ►Gene expression). This type of LTP is called “associative LTP.”

Characteristics

Quantitative Description

LTP is usually induced in a relatively strong input, and is not induced in a weak pathway. This characteristic of LTP is referred to as “cooperativity,” and LTP induction requires activation of the sufficient number of afferent fibers that enables the postsynaptic cell to depolarize beyond a certain threshold level. However, a weak pathway can be potentiated when it is activated simultaneously with a strong pathway, because the strong pathway can provide sufficient depolarization of the postsynaptic cell. This characteristic of LTP is referred to as “associativity,” and is regarded as the most fundamental property for associative learning.

Higher Level Structures

Associative LTP of excitatory synaptic transmission can be observed in the ►hippocampus and cerebral cortex.

Lower Level Components

Associative LTP is a form of synaptic plasticity (►Synaptic plasticity, ►selectivity) observed in certain kinds of excitatory central synapses.

Higher Level Processes

Associative LTP is regarded as a cellular model for associative learning, which is observed in brain regions such as the hippocampus and cerebral cortex.

Lower Level Processes

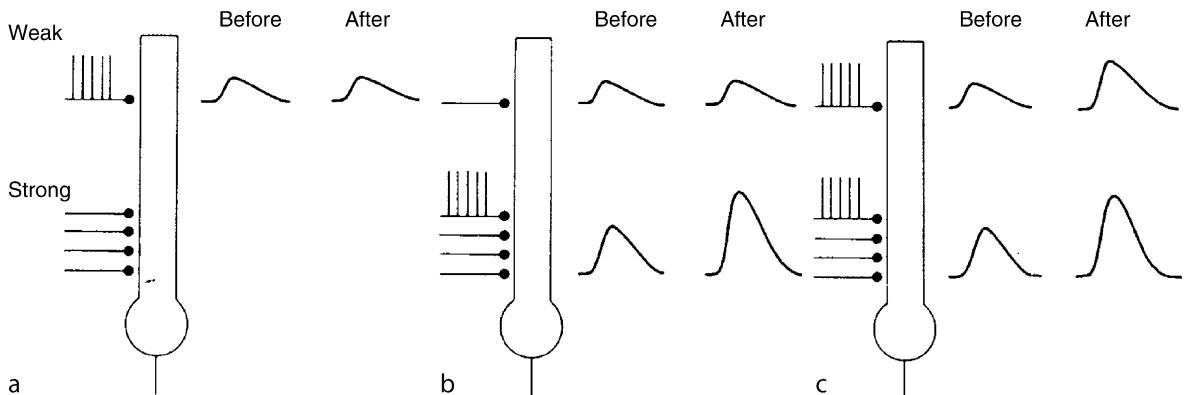
Associative LTP is usually observed at the synapse that exhibits NMDA receptor-dependent LTP (►NMDA-LTP). Standard tetanic stimulation at sufficiently strong stimulus strength causes depolarization in the postsynaptic cell, which is sufficient to relieve the Mg^{2+} block of NMDA receptor channels and to allow Ca^{2+} to flow into the postsynaptic cell. When one input is stimulated with a pattern that does not induce LTP by itself during the strong depolarization caused by tetanic stimulation of another independent input, the NMDA receptors of the former input become active and LTP is induced in both inputs. The LTP induced in this way in the former input is called “associative LTP” and the NMDA receptor plays an essential role in this process. In other words, the release of the neurotransmitter glutamate from the presynaptic terminal must occur simultaneously with the postsynaptic depolarization in order to induce LTP, and this is called a ►Hebbian rule.”

Process Regulation

The timing of synaptic activation and postsynaptic depolarization is extremely important for associative LTP. In order for associative LTP to occur, two independent pathways must be activated closely in time. A weak pathway must be active simultaneously with a strong pathway in order for the weak pathway to be potentiated. However, this process seems to be more complicated when we observe this phenomenon more carefully. As reviewed by Dan and Poo [1], associative LTP may be a type of spike-timing dependent plasticity: when the postsynaptic depolarization follows the synaptic activity, the synaptic response is potentiated. In contrast, when the synaptic activity follows the postsynaptic depolarization, the synaptic response is depressed. Thus, the sequence of the events, as well as the timing, may be a critical factor for associative LTP.

Function

Figure 1 demonstrates the three rules observed in synaptic plasticity in general [2]. In order to exhibit LTP, the strength of an input must be strong enough to depolarize the postsynaptic cell and activate NMDA receptors (Fig 1a). In other words, a relatively large



Associative Long-Term Potentiation. Figure 1 (a) Cooperativity. A weak input fails to exhibit LTP even if it receives tetanic stimulation. (b) Specificity (selectivity). LTP is restricted to the input that receives tetanic stimulation. (c). Associativity. A weak input can be potentiated if it is concurrently active when LTP is induced in another strong input. (cited from Nicoll et al. 2).

number of afferent fibers must be stimulated to include LTP, and this property is called “cooperativity” (Fig 1b). Figure 1b also indicates that the input that does not receive tetanic stimulation fails to show LTP, even if the other input in the same cell exhibits LTP. This property is called “selectivity” or “specificity.” This type of LTP is referred to as ►homosynaptic LTP because LTP is restricted to the tetanized pathway. Another important property is “associativity,” which is shown in Figure 1c. In some sense, these properties are common to those of learning and memory, and associativity especially may be a cellular process underlying the formation of associative memory.

However, there are some exceptions. Strictly speaking, in some condition, synapse specificity of LTP breaks down locally at short distances [3,4]. Thus, ►heterosynaptic facilitation and depression (►heterosynaptic depression) can occur, and in some case, ►heterosynaptic LTP can be observed in the hippocampus. Furthermore, LTP and ►Long-term depression (LTD) can interact heterosynaptically [5]. These phenomena are regarded as “non-Hebbian.”

References

1. Dan Y, Poo MM (2004) Spike timing-dependent plasticity of neural circuits. *Neuron* 44:23–30
2. Nicoll RA, Kauer JA, Malenka RC (1988) The current excitement in long-term potentiation. *Neuron* 1:97–103
3. Engert F, Bonhoeffer T (1997) Synapse specificity of long-term potentiation breaks down at short distances. *Nature* 388:279–284
4. Schuman EM, Madison DV (1994) Locally distributed synaptic potentiation in the hippocampus. *Science* 263:532–536
5. Muller D, Hefft S, Figurov A (1995) Heterosynaptic interactions between LTP and LTD in CA1 hippocampal slices. *Neuron* 14:599–605

Associative Memory

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Synonyms

Associatron; Content-addressable memory; Hopfield model

Definition

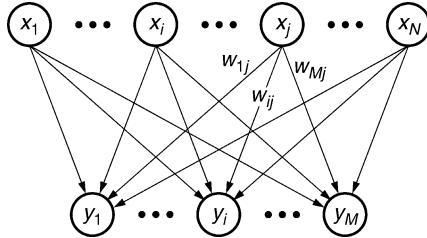
Associative memory is one type of neural network model for human memory. The network stores input–output pattern pairs to recall a stored output pattern when a noisy or incomplete version of a stored input pattern paired with it is presented.

Characteristics

Heteroassociative Memory

When looking at a banana, someone might recall a monkey. Human memory system probably represents the two different entities as two distinct firing patterns of neurons. So, it is possible that the associative recall is a transformation from the pattern “banana” to the different pattern “monkey.”

A neural network model that performs such a transformation from a pattern to a different pattern is referred to as ►heteroassociative memory (Cross-associative memory). The most simplified model is a two-layer feedforward network as shown in Fig. 1. Let $\{\xi_i^\mu\}$ ($i = 1, \dots, N$) and $\{\eta_i^\mu\}$ ($i = 1, \dots, M$) be the μ th ($\mu = 1, \dots, Q$) of a N -dimensional input and a M -dimensional output pattern, respectively. It is often assumed that each component of the patterns takes a value of either +1 (firing) or -1 (not firing) independently with



Associative Memory. Figure 1 Two-layer feedforward network for heteroassociative memory. Input–output pattern pairs are stored in the weights, w_{ij} , which connect the input units $\{x_j\}$ to the output units $\{y_i\}$ ($i = 1, \dots, M$; $j = 1, \dots, N$).

equal probability. Then, the network stores (learns) the Q pattern pairs (associations) as follows

$$w_{ij} = \frac{1}{N} \sum_{\mu} \eta_i^{\mu} \xi_j^{\mu},$$

where w_{ij} ($i = 1, \dots, M$; $j = 1, \dots, N$) is the weight from the j th unit (neuron) in the input layer to the i th unit in the output layer (Fig. 1).

When an input pattern is presented, the state of the input layer, $\{x_i\}$ ($i = 1, \dots, N$), is set to that pattern and is fed through the weights to the output units $\{y_i\}$ ($i = 1, \dots, M$)

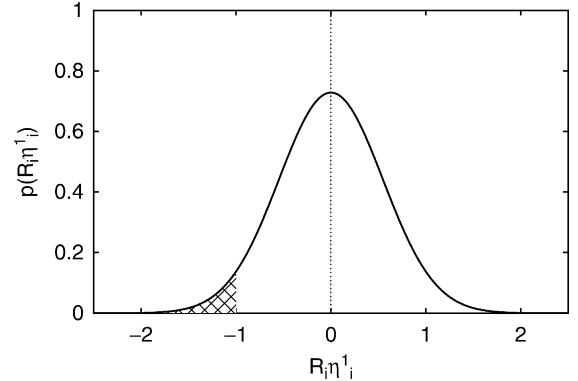
$$y_i = \text{sgn}(h_i), h_i = \sum_j w_{ij} x_j,$$

where $\text{sgn}(h)$ is $+1$ for $h > 0$ and -1 otherwise.

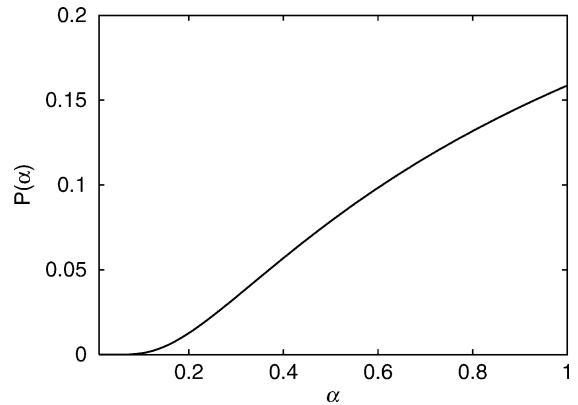
If an input is one of the stored patterns, say, $\{\xi_i^1\}$, we hope that $\{y_i\}$ would coincide with the target output pattern $\{\eta_i^1\}$. To see this possibility, we rewrite the activity h_i by putting $\{x_i\} = \{\xi_i^1\}$ and have

$$\begin{aligned} h_i &= \sum_j \frac{1}{N} \sum_{\mu} \eta_i^{\mu} \xi_j^{\mu} \xi_j^1 = S_i + R_i, \\ S_i &= \frac{1}{N} \eta_i^1 \sum_j \xi_j^1 \xi_j^1 = \eta_i^1, \\ R_i &= \frac{1}{N} \sum_{\mu \neq 1} \eta_i^{\mu} \sum_j \xi_j^{\mu} \xi_j^1, \end{aligned} \quad (1)$$

where S_i is the signal to stabilize the target η_i^1 , and R_i is known as cross-talk noise arising from the correlations of the stored patterns $\{\xi_i^{\mu}\}$ ($\mu \neq 1$) with the input $\{\xi_i^1\}$. The cross-talk noise often hinders the model from recalling the target, $\{\eta_i^1\}$: an error occurs at the i th output unit when R_i is of opposite sign to η_i^1 and has an absolute value larger than 1 (i.e., $R_i \eta_i^1 < -1$). Since the quantity $R_i \eta_i^1$ is the sum of many ($= N(Q-1) \approx NQ$) independent random variables, each of which takes a value of $+1/N$ or $-1/N$ with equal probability, the



Associative Memory. Figure 2 Distribution of cross-talk noise R_i times target η_i^1 , when an original input pattern $\{\xi_i^1\}$ paired with $\{\eta_i^1\}$ is presented. The hatched area gives the error probability $P(\alpha)$ for one output unit.



Associative Memory. Figure 3 Error probability for one output unit as a function of load level α . A higher α causes a wider distribution of cross-talk noise, resulting in a higher error probability (see Fig. 2).

central limit theorem guarantees that it has a Gaussian distribution with mean zero and variance Q/N . The fraction Q/N is often referred to as load level (hereafter denoted as α). Figure 2 shows a Gaussian ($\alpha = Q/N = 0.3$) where the hatched area (integral from $-\infty$ to -1 with respect to $R_i \eta_i^1$) gives the error probability $P(\alpha)$ for one output unit.

Rising load level α widens the Gaussian, resulting in a higher error probability $P(\alpha)$ as shown in Fig. 3.

Since the network has the N output units, the probability that the network recalls the target with no error is given by $(1 - P(\alpha))^N$. Perfect recalling is thus a severe condition, so we need to allow the network to make some errors. A different type of learning algorithm is needed to prevent the cross-talk noise [1,2], though we in this case have to present input–output pairs repeatedly during learning.

It is also important to see the ability to eliminate external noise. Let $\{\rho_i\}$ ($i = 1, \dots, N$) be a noise pattern, each component of which takes a value of either $+1$ with probability $(1+d)/2$ or -1 with probability $(1-d)/2$ ($0 \leq d \leq 1$). Then, a noisy version of a stored input pattern $\{\xi_i^1\}$ can be expressed as $\{\xi_i^1 \rho_i\}$. Since the sign of ξ_i^1 is reversed when $\rho_i = -1$, $\{\rho_i\}$ acts as external noise embedded in $\{\xi_i^1\}$. The similarity between the original pattern and the noisy version (overlap at the input layer or initial overlap) can be evaluated as

$$m = \frac{1}{N} \sum_i \xi_i^1 \xi_i^1 \rho_i = \frac{1}{N} \sum_i \rho_i \approx d.$$

Thus, m is approximately equal to the parameter value d for generating external noise.

When such a noisy input is given, the network should eliminate the noise so that the overlap of the target output pattern $\{\eta_i^1\}$ and the output state $\{y_i\}$ (overlap at the output layer), m' , is larger than the initial overlap m . To evaluate this possibility, we present a noisy input $\{\xi_i^1 \rho_i\}$ to the network and have

$$\begin{aligned} y_i &= \text{sgn}(S_i + R_i), \\ S_i &= \frac{1}{N} \eta_i^1 \sum_j \xi_j^1 \xi_j^1 \rho_j = m \eta_i^1, \\ R_i &= \frac{1}{N} \sum_{\mu \neq 1} \eta_i^\mu \sum_j \xi_j^\mu \xi_j^1 \rho_j. \end{aligned}$$

Then, the overlap at the output layer can be expressed as

$$\begin{aligned} m' &= \frac{1}{M} \sum_i \eta_i^1 y_i = \frac{1}{M} \sum_i \text{sgn}(S_i \eta_i^1 + R_i \eta_i^1) \\ &= \frac{1}{M} \sum_i \text{sgn}(U_i), \\ U_i &= m + R_i \eta_i^1. \end{aligned}$$

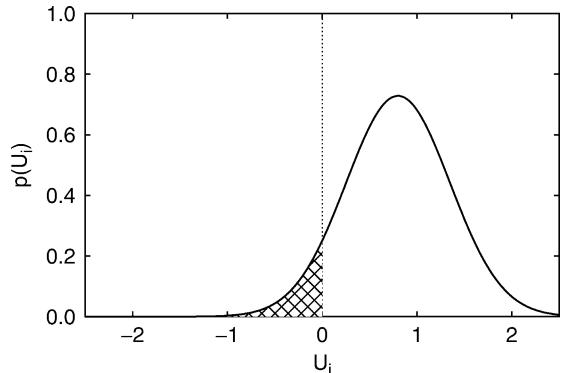
The quantity $R_i \eta_i^1$ has a Gaussian distribution with mean zero and variance α ($= Q/N$) for the same reason as above, and hence U_i is normally distributed with mean m and variance α as shown in Fig. 4.

Since $\text{sgn}(U_i)$ takes a value of either -1 with probability $P(\alpha, m)$ (indicated by the hatched area) or $+1$ with the remaining probability, the overlap m' , given as the sum of a large number ($= M$) of $\text{sgn}(U_i)$ divided by M , should converge to the average

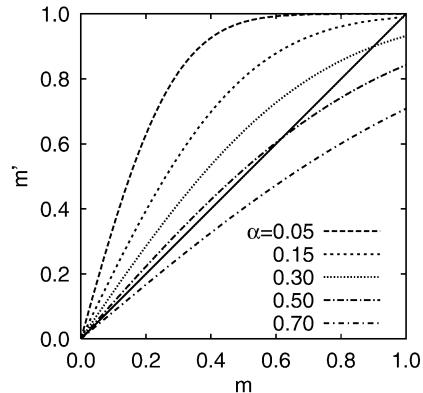
$$m' = (-1)P(\alpha, m) + (+1)(1 - P(\alpha, m)) = 1 - 2P(\alpha, m).$$

Figure 5 shows m' as a function of m for various values of load level α .

The network has a good performance to eliminate external noise ($m' > m$) if the initial overlap m does not



Associative Memory. Figure 4 Distribution of U_i (see text). The hatched area gives the probability of $\text{sgn}(U_i) = -1$.

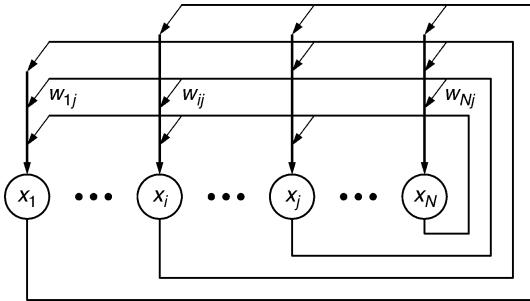


Associative Memory. Figure 5 Noise reduction ability of heteroassociative memory for various values of load level α . Overlap at the output layer, m , is plotted as a function of overlap at the input layer, m .

exceed a critical value $m_c(\alpha)$, which is the intersection of each curve with the solid line ($m' = m$). The critical value decreases with increasing α (e.g., $m_c(0.05) \approx 1.0$, $m_c(0.3) \approx 0.9$). Far more increase in α results in the disappearance of the intersection (e.g., $m_c(0.7) \approx 0.0$).

Autoassociative Memory

A neural network is referred to as ►autoassociative memory, when input and output patterns to be stored are the same. The network recalls the whole of a stored pattern when receiving a part (or a noisy version) of it as one might recall the whole concept of “apple” when smelling the scent of it. If we substitute $\{\xi_i^\mu\}$ for $\{\eta_i^\mu\}$ in the section of heteroassociative memory described earlier (and set $w_{ii} = 0$ and $M = N$), then we obtain a two-layer feedforward network for autoassociative memory storing $\{\xi_i^\mu\}$. This network has the same characteristics as the heteroassociative memory.



Associative Memory. Figure 6 One-layer recurrent network for autoassociative memory. The N units are mutually connected through the weights W_{ij} ($i \neq j$).

Here, we consider the case where the network has feedback connections to receive the current output as the next input (i.e., $\{x_i\} = \{y_i\}$). Then the network keeps updating its state (output), which may have more overlap with $\{\xi_i^1\}$ than a previous state does. Such a recurrent neural network for autoassociative memory can be constructed with only one layer of units as shown in Fig. 6.

Let $\{x_i(t)\}$ ($i = 1, \dots, N$) be the state of the network at time t . The initial state $\{x_i(0)\}$ is set to a given input pattern, after which $\{x_i(t)\}$ develops at every discrete time step according to the following dynamics

$$x_i(t+1) = \text{sgn}(h_i), h_i = \sum_{j \neq i} w_{ij} x_j(t), \quad (2)$$

where w_{ij} ($i, j = 1, \dots, N$) is the weight of the connection from the j th to the i th unit. If we again assume that each component of patterns to be stored, ξ_i^μ ($\mu = 1, \dots, Q; i = 1, \dots, N$), takes a value of either +1 or -1 independently with equal probability, the learning algorithm can be written in the form

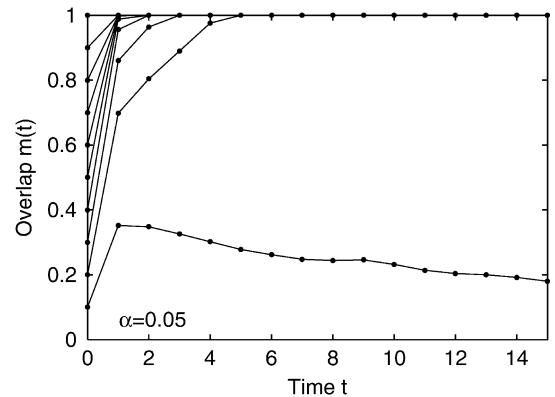
$$w_{ij} = \frac{1}{N} \sum_\mu \xi_i^\mu \xi_j^\mu. \quad (3)$$

Now, the network keeps changing its state $\{x_i(t)\}$. The time evolution of $\{x_i(t)\}$ could be captured in part by the overlap $m(t)$ with a stored pattern, say, $\{\xi_i^1\}$

$$m(t) = \frac{1}{N} \sum_i \xi_i^1 x_i(t).$$

Figure 7 shows simulation results for load level $\alpha = 0.05$, where the curves demonstrate the time courses of $m(t)$ for various values of initial overlap $m(0)$.

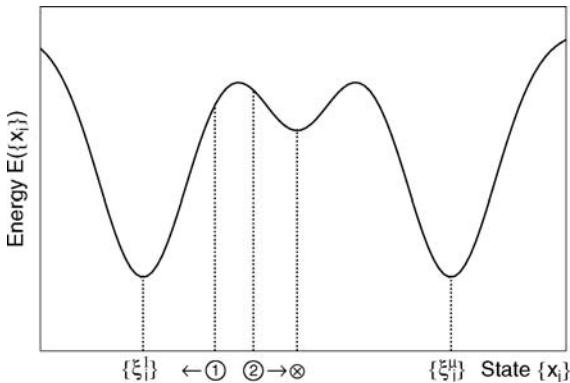
When starting from 0.2 or more, the overlap $m(t)$ converged to 1 after several steps. This means that the network was successfully attracted to a stable state (an attractor), which was just the target $\{\xi_i^1\}$. When $m(0) = 0.1$, $m(t)$ once went up, then went down, and finally converged to a small value (not shown). The increase in $m(t)$ at time $t = 1$ indicates that the network



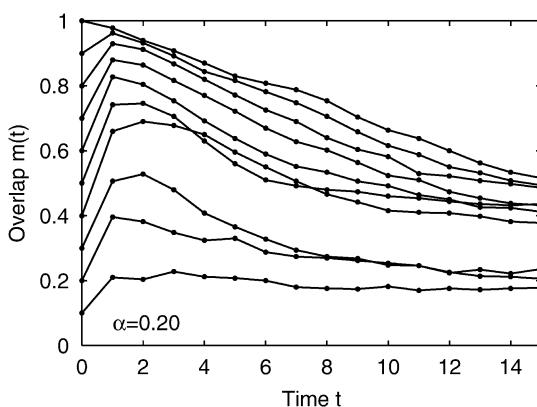
Associative Memory. Figure 7 Time courses of overlap $m(t)$ for various values of initial overlap $m(0)$, when $\alpha = 0.05$. If the network recalls a target pattern successfully, $m(t)$ takes a value of 1.

once approached to the target $\{\xi_i^1\}$. This initial phenomenon could be understood from the curve for $\alpha = 0.05$ shown in Fig. 5 where $m' = m(1) \approx 0.35$ when $m = m(0) = 0.1$. After the initial increase, the network state gradually moved away from $\{\xi_i^1\}$ and finally converged to an attractor that was different from $\{\xi_i^1\}$ (see [3] for estimation of $m(t)$ at time $t \geq 2$). One may think that another stored pattern was recalled, but this was not the case. This attractor, not intended to be stored in the network, is called a spurious state (a spurious memory or a spurious attractor).

Thus, the network seems to converge to an attractor, regardless of whether the attractor is $\{\xi_i^1\}$ or not. In fact, the convergence is guaranteed if the state of only one unit is updated at one time (although in the above simulation the states of all units were updated synchronously). This is because the network is governed by a lower bounded energy function, $E(\{x_i\})$, associated with its state $\{x_i\}$, and the dynamics given as Eq. 2 alters $\{x_i\}$ so as to reduce the value of $E(\{x_i\})$ [4]. The learning algorithm given as Eq. 3 is the process to make the intended patterns $\{\xi_i^\mu\}$ be local minimum points (states with local minima of the energy function). In addition to this, the algorithm implicitly forces states closer to $\{\xi_i^\mu\}$ to have lower energies and also creates additional local minima at unintended points (spurious states). The resulting landscape of the energy function is as shown in Figure 8. Since Eq. 2 always decreases the energy, the network state starting with the initial state starting with the initial state ① a noise version of $\{\xi_i^1\}$ moves toward and stops at the target $\{\xi_i^1\}$ (successful recall), whereas the state starting with ② a more noisy version of $\{\xi_i^1\}$ moves away from $\{\xi_i^1\}$ and reaches a spurious state ③. In the case of high load level α , however the possibility of stopping at $\{\xi_i^1\}$ becomes low: rising α increases the number of spurious states and reduces the size of the basins of attraction (the width



Associative Memory. **Figure 8** Landscape of energy function $E(\{x_i\})$. The network alters its state $\{x_i\}$ so as to reduce the value of $E(\{x_i\})$. The network state starting with the initial state ① (a noise version of $\{\xi_i^1\}$) moves toward and stops at the target $\{\xi_i^1\}$ (successful recall), whereas the state starting with ② (a more noisy version of $\{\xi_i^1\}$) reaches a spurious state \otimes .



Associative Memory. **Figure 9** Time courses of overlap $m(t)$, when $\alpha = 0.2$.

of valleys) around the intended patterns. It is known that the stored patterns are no longer stable states (local minimum points) if α is above about 0.15 [4,5]. The critical value of load level, α_c , is often called ►memory capacity (storage capacity). **Figure 9** shows the time courses of $m(t)$ for load level $\alpha = 0.2$. Even if just a target $\{\xi_i^1\}$ was presented ($m(0) = 1$), the network state moved away from the target.

Associative Memory for Storing Unbiased Patterns

Up to now, we assumed that each component of patterns to be stored took either +1 (firing) or -1 (not firing) independently with equal probability. Thus, the patterns are unbiased in the sense that the number of pattern components taking +1 is almost the same as that of components taking -1. This implies that single neurons respond to about one-half of stimuli.

However, this assumption would be physiologically implausible. Many physiologists have reported that neurons in the brain have selectivity for stimuli (e.g., face and object) or stimulus properties (e.g., orientation, shape, color, motion direction). It seems better to assume that, for a given stimulus, a small number of neurons are activated while the others are not.

The introduction of this alternative assumption allows an associative network to have a large memory capacity. Let $\{\xi_i^\mu\} (\mu = 1, \dots, Q; i = 1, \dots, N)$ be a biased pattern whose components take values of either +1 with probability $(1+b)/2$ or -1 with the remaining, where $-1 < b < 0$ (unbiased patterns if $b = 0$). Patterns with $b \approx -1$ are especially referred to as sparsely encoded patterns. The network stores the Q biased patterns according to the following covariance learning rule

$$w_{ij} = \frac{1}{N(1-b^2)} \sum_\mu (\xi_i^\mu - b)(\xi_j^\mu - b).$$

We also need to modify the dynamics as follows

$$x_i(t+1) = \text{sgn}(h_i), h_i = \sum_j w_{ij}(x_j(t) - b) + b.$$

Note that, if $b = 0$, this network is reduced to the associative memory for storing unbiased patterns (Eqs. 2 and 3).

If we input a stored pattern $\{\xi_i^1\}$ as did previously, we get

$$h_i = \sum_{j \neq i} \frac{1}{N(1-b^2)} \sum_\mu (\xi_i^\mu - b)(\xi_j^\mu - b)(\xi_j^1 - b) + b = S_i + R_i,$$

$$S_i = \frac{1}{N(1-b^2)} (\xi_i^1 - b) \sum_{j \neq i} (\xi_j^1 - b)(\xi_j^1 - b) + b \approx \xi_i^1,$$

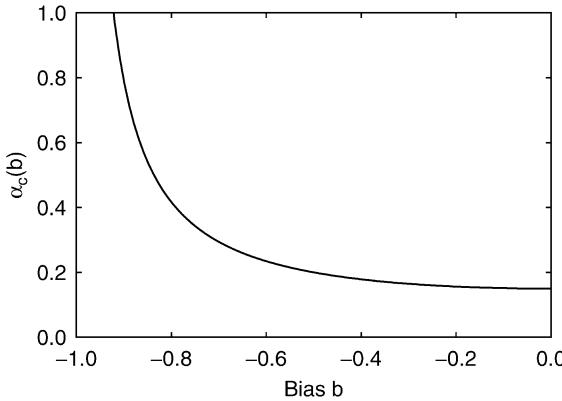
$$R_i = \frac{1}{N(1-b^2)} \sum_{\mu \neq 1} (\eta_i^\mu - b) \sum_{j \neq i} (\xi_j^\mu - b)(\xi_j^1 - b).$$

The cross-talk noise R_i follows a Gaussian with mean zero and variance $Q(1-b^2)/N$, which decreases with increasing b . The network storing biased patterns thus has smaller cross-talk noise than the network storing unbiased patterns (Q/N), while the two networks have almost the same signal S_i .

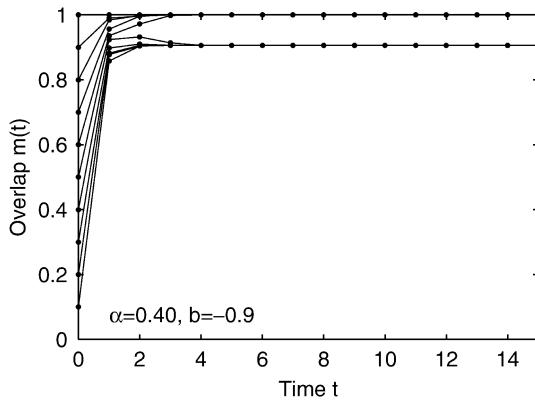
It is known that the memory capacity for biased patterns can be roughly estimated by

$$\alpha_c(b) = \frac{\alpha_c(0)}{1-b^2},$$

where ($\alpha_c(0) \approx 0.15$) is the memory capacity for unbiased patterns [6]. **Figure 10** shows $\alpha_c(b)$ as a function of $b (-1 < b < 0)$. The capacity $\alpha_c(b)$ increases with decreasing b . **Figure 11** demonstrates the time courses of overlap $m(t)$ when $b = -0.9$ and $\alpha = 0.4$. Even if the network is at double the load level



Associative Memory. Figure 10 Memory capacity of autoassociative memory, $\alpha_c(b)$, as a function of bias b of stored patterns.



Associative Memory. Figure 11 Time courses of overlap $m(t)$ for autoassociative memory storing biased patterns ($b = -0.9$, $\alpha = 0.4$).

as the network storing unbiased patterns (Fig. 9), the target $\{\xi_i^1\}$ was recalled after several steps ($m(t) = 1$) if the initial overlap $m(0)$ was 0.6 or above. When $m(0)$ was small, $m(t)$ converged to about 0.9. This means that all the units took $x_i(t) = -1$ ($m(t) = N^{-1} \sum \xi_i^1 x_i(t) \approx 0.9$).

Associative Memory for Storing Hierarchically Correlated Patterns

The patterns treated above are independent of one another, which is a prerequisite for many conventional networks such as the earlier network to work properly. The independent patterns are distributed over the pattern space such that each pattern is located at almost the same distance from all the others. In other words, similarities between any two patterns are the same (i.e., $N^{-1} \sum \xi_i^\mu \xi_j^\nu \approx b^2$ for $\mu \neq \nu$).

However, it seems better to suppose that similar things are encoded into similar patterns. Since a neuron,

in general, responds not only to an optimal stimulus but also to stimuli close to the optimal, presenting similar stimuli would yield similar firing patterns. Moreover, there are a plenty of (living and nonliving) things similar to one another, and we make use of their similarity in our daily life. For example, one would acquire a one's own concept "bird" (in part) by finding common (similar) properties among previously encountered instances (such as pigeons, sparrows, and crows), and the concept would, in turn, help us to recognize (categorize) a novel creature flying with wings as a member of that concept (the category represented by that concept). If the novel instance should be represented as an independent pattern, which is similar to neither patterns of the previous instances nor a pattern of the concept, we might be unable to identify it or may miscategorize it as a member of a different category such as "airplane," "ice cream," and "book." To begin with, we could not acquire concepts (similarities) from independent patterns of instances.

Hierarchically correlated patterns are often used to represent concepts and their instances (the second level concepts in a two-level hierarchy). Let $\{\xi_i^\mu\}$ ($\mu = 1, \dots, Q_1; i = 1, \dots, N$) be the μ th concept pattern (representative of the μ th category), which is not given to but acquired by the network (see later). For simplicity, each component of $\{\xi_i^\mu\}$ is assumed to take either +1 or -1 independently with equal probability. Each category $\{\xi_i^\mu\}$ has Q_2 instances $\{\xi_i^{\mu\nu}\}$ ($\nu = 1, \dots, Q_2; i = 1, \dots, N$). Each component $\xi_i^{\mu\nu}$ takes either the same value as ξ_i^μ with probability $(1 + c)/2$ or the different value from ξ_i^μ (i.e., $\xi_i^{\mu\nu} = -\xi_i^\mu$) with the remaining probability ($0 < c < 1$). In this case, the similarity between an instance and its concept is given by $N^{-1} \sum \xi_i^{\mu\nu} \xi_i^\mu = c$. So the instances are distributed around their concepts with equal distance $1 - c$. The similarity between any two instances of the same category is $N^{-1} \sum \xi_i^{\mu\nu} \xi_j^{\mu\nu} = c^2$ ($\nu \neq \nu'$), so that, in each category, each instance is located at the same distance $1 - c^2$ from all the others. The similarity between any two instances of different categories is of zero.

Here, we consider the case where only the instances are given in learning phase. If we use the network given as Eqs. 2 and 3, we get

$$w_{ij} = \frac{1}{N} \sum_{\mu, \nu} \xi_i^{\mu\nu} \xi_j^{\mu\nu}.$$

When one of the instances, say, $\{\xi_i^{11}\}$, is input to the network, the activity of the i th unit is given by

$$\begin{aligned} h_i &= \sum_{j \neq i} \frac{1}{N} \sum_{\mu, \nu} \xi_i^{\mu\nu} \xi_j^{\mu\nu} \xi_j^{11} = \xi_i^{11} + \frac{1}{N} \sum_{\nu \neq 1} \xi_i^{1\nu} \sum_{j \neq i} \xi_j^{1\nu} \xi_j^{11} \\ &\quad + \frac{1}{N} \sum_{\mu \neq 1, \nu} \xi_i^{\mu\nu} \sum_{j \neq i} \xi_j^{\mu\nu} \xi_j^{11}. \end{aligned}$$

The first term is the signal to stabilize the target ξ_i^{11} . The second and third terms are cross-talk noise arising from correlations of the input pattern $\{\xi_i^{11}\}$ with the other instances of the same category $\{\xi_i^1\}$ and of the different categories $\{\xi_i^\mu\} (\mu \neq 1)$, respectively. If we suppose that N and Q_2 are large enough, the mean values of the second and third terms are estimated as about $Q_2 c^3 \xi_i^1$ and zero, respectively. This suggests that when $Q_2 c^3 > 1$, the network comes to recall not the target instance $\{\xi_i^{11}\}$ but the concept $\{\xi_i^1\}$ to which the target belongs.

Thus, the network given as Eqs. 2 and 3 has the potential ability to acquire concepts by learning instances [2]. In return for this ability, however, the ability to recall instances is lost.

One way to overcome this problem is to introduce so-called nonmonotonic units to the network [7,8]. A usual monotonic unit emits an output value whose sign is always the same as that of an activity h_i (e.g., Eq. 2), whereas a nonmonotonic unit outputs a value opposite in sign to h_i if $|h_i|$ is above a threshold T and outputs a value with the same sign as h_i otherwise. Thus, units whose activities are large in absolute value are destabilized so that their contributions to state transition would be reduced. Since the activities are, on average, larger in absolute value when a concept $\{\xi_i^\mu\}$ is presented than when an instance $\{\xi_i^{\mu\nu}\}$ is presented, setting T at high and low level leads the network to recall a concept and an instance, respectively [8]. It is also known that a network with nonmonotonic units is effective for storing unbiased patterns [7]: it has a large memory capacity [9], large basins of attraction around stored patterns, and a small number of spurious states.

Another way to recall instances is to use a cascade of two associative networks [10]. The first network acquires concepts by learning instances, just described above. The second network stores difference patterns defined by $\{\eta_i^{\mu\nu}\} \equiv \{\xi_i^{\mu\nu} \xi_i^\mu\}$. Since $\eta_i^{\mu\nu} = 1$ for $\xi_i^{\mu\nu} = \xi_i^\mu$ and -1 otherwise, $\{\eta_i^{\mu\nu}\}$ contains information only on the difference of $\{\xi_i^{\mu\nu}\}$ from $\{\xi_i^\mu\}$, thus interpreted as distinctive features of the instance $\{\xi_i^{\mu\nu}\}$. Because they are biased patterns ($N^{-1} \sum \eta_i^{\mu\nu} = c$) independent of one another ($N^{-1} \sum \eta_i^{\mu\nu} \eta_i^{\mu'\nu'} = c^2$), we can use the above network for storing biased patterns as the second network. Therefore, the second network has a large memory capacity (Fig. 10). Combining a concept $\{\xi_i^\mu\}$ recalled by the first network and a difference pattern $\{\eta_i^{\mu\nu}\}$ recalled by the second, the cascade network outputs (recalls) a target instance $\{\xi_i^{\mu\nu}\}$ ($= \{\xi_i^\mu \eta_i^{\mu\nu}\}$). This cascade network is applicable, even if instances $\{\xi_i^{\mu\nu}\}$ each have their own similarity $c_{\mu\nu}$ ($= N^{-1} \sum \xi_i^{\mu\nu} \xi_i^\mu$) to their concepts $\{\xi_i^\mu\}$ (i.e., $c_{\mu\nu} \neq c_{\mu\nu'} \text{ for } \nu \neq \nu'$). In this case, a concept $\{\xi_i^\mu\}$ is more similar to an instance $\{\xi_i^{\mu\nu}\}$ than to another instance $\{\xi_i^{\mu'\nu}\}$ as a concept “bird” might be more similar to “pigeon” than to “owl.” In other words, instances of the

same category are ordered with respect to their similarity $c_{\mu\nu}$. It is known that, when being stored in the cascade network, the instance patterns are ordered with respect to stability: rising load level α destroys (destabilizes) memories of the instances in ascending order of their similarity. Moreover, when a concept pattern (instead of an instance pattern) is presented as an input, the network recalls an instance having a higher similarity to the concept with a higher probability and in a shorter period of recall time, which seems to be consistent with human behavior (known as the typicality effect). When we are asked to recall an instance of “bird,” “pigeon” would be more probable and faster to be recalled than “owl.”

References

1. Kohonen T (1974) An adaptive associative memory principle. *IEEE Trans Comput C-23:444–445*
2. Amari S (1977) Neural theory of association and concept-formation. *Biol Cybern* 26:175–185
3. Amari S, Maginu K (1988) Statistical neurodynamics of associative memory. *Neural Networks* 1:63–73
4. Hopfield JJ (1982) Neural networks and physical systems with emergent collective computational abilities. *Proc Natl Acad Sci USA* 79:2554–2558
5. Amit DJ, Gutfreund H, Sompolinsky H (1985) Storing infinite numbers of patterns in a spin-glass model of neural networks. *Phys Rev Lett* 55:1530–1533
6. Okada M (1996) Notions of associative memory and sparse coding. *Neural Networks* 9:1429–1458
7. Morita M (1993) Associative memory with nonmonotone dynamics. *Neural Networks* 6:115–126
8. Kakeya H, Kindo T (1996) Hierarchical concept formation in associative memory composed of neuro-window elements. *Neural Networks* 9:1095–1098
9. Yoshizawa S, Morita M, Amari S (1993) Capacity of associative memory using a nonmonotonic neuron model. *Neural Networks* 6:167–176
10. Hirahara M, Oka N, Kindo T (2000) Cascade associative memory storing hierarchically correlated patterns with various correlations. *Neural Networks* 13:51–61

Associative Priming

Definition

A form of priming in which the prime and test are associated due to the experience of repeated pairing between the two concepts or stimuli. Although many associatively related words are semantically related, association measured as free association norms can be distinguished from a more direct form of semantic relation such as object category.

► Latent Learning

Association

- Associative Memory

Astereognosia

Definition

Inability to recognize the form of an object by ► touch (► tactile sensation), resulting from lesions of the ► parietal cortex.

- Active Touch
- Haptics

Astrocyte

Definition

Also known as astroglia, astrocytes are characteristic star-shaped glial cells in the brain. Astrocytes are irregularly shaped with many long processes. They are the largest and most numerous neuroglial cells in the brain and spinal cord. They regulate the extracellular ionic and chemical environment. "Reactive astrocytes" along with microglia respond to injury and amyloid plaques.

- Central Nervous System Disease – Natural Neuro-protective Agents as Therapeutics

Astrocytoma

Definition

The most common primary glial brain tumor. It can be found throughout the central nervous system (CNS). It is characterized by diffuse (infiltrating) or circumscribed growth. Astrocytomas can be classified by their histologic appearance and by their malignant potential.

The most commonly used grading system was developed by World Health Organization (WHO). It recognizes four different grades of astrocytoma; grade I describes low grade slow growing tumors while grade IV the most aggressive and deadly form (glioblastoma).

Grades II and III correspond to intermediate levels of malignancy.

- Gliomas

Astrocytosis

- Glial Scar

Asymmetry in Neurons

- Neuronal Polarity

Asynergia

Definition

Lack of coordination and poor harmony among various components of a complex motor task.

Asynthesisia

Definition

Failure to bind visual features together into the perception of an object. For example, a patient suffering from a stroke had lost color vision as well as the ability to recognize faces. His main problem was that he could perceive the local features of an object, but could not bind them together into a coherent object that consequently could not be recognized, although drawing it went quite well. He could also fluently describe objects he had known before his stroke.

Ataractic Drug

- Antipsychotic Drugs

Atasia-Abasia

Definition

Inability to stand or walk.

Ataxia

Definition

Impaired motor coordination (= incoordination) usually related to disorders of the cerebellum or its connections with the brain and spinal cord. Ataxia [Greek, a (negative article) + taxi (order)] is characterized by slurred speech (ataxic dysarthria), nystagmus, dysmetria (undershooting or overshooting a target with trajectory limb movements), poor dexterity in performing rapid alternating movements (dysdiadochokinesis), and wide based gait (truncal ataxia). The term ataxia is also used to describe degenerative diseases of the cerebellum, most of them hereditary.

- ▶ Ischemic Stroke
- ▶ Posture Role of Cerebellum
- ▶ Proprioception: Effect of Neurological Disease
- ▶ Stroke

Ataxic Respiration

Definition

Uncoordinated respiratory movement characterized by complete irregularity of breathing, with irregular pauses and increasing periods of apnea.

- ▶ Development of the Respiratory Network

Atelectasis

Definition

The collapse of alveoli that are part of the lung.

Athetosis

Definition

Slow involuntary writhing movements, slower in character than chorea, but less sustained than dystonia.

Choreoathetosis is a mixture of fast and slow writhing movements.

- ▶ Chorea
- ▶ Dystonia

Atomic Hypothesis

Definition

A theory that postulates that all things are made of little particles, called atoms, which move around in perpetual motion.

- ▶ Brownian Motions

Atomoxetine

Definition

Atomoxetine is a selective noradrenaline transporter inhibitor drug that is used for the treatment of patients with attention deficit hyperactivity disorder (ADHD).

Unlike other ADHD medications (amphetamine, methylphenidate), atomoxetine appears to have little action on the brain dopamine neurotransmitter system in the dopamine-rich striatum. However, preliminary animal data suggest that the drug might increase extracellular levels of both dopamine and noradrenaline in the prefrontal cortex.

- ▶ Attentional Disorder
- ▶ Dopamine
- ▶ Noradrenaline
- ▶ Stimulants

Atonia

Definition

Absence of muscle tone (an extension of hypotonia, which is reduced muscle tone) seen in the acute phase of

spinal cord injury, or in disorders of the peripheral motor system, such as lower motor neuron disease, peripheral nerve disease, neuromuscular junction disorders, or myopathy. Atonia also occurs during ►rapid eye movement (REM) sleep.

(paroxysmal atrial fibrillation). Raises the risk of ischemic stroke five times over.

- Stroke
- Ischemic Stroke

Atonic Seizures

Definition

Brief losses of consciousness and postural muscle tone without muscular contractions, such that the patient (usually a child) drops to the floor ("drop attack"); the ►electroencephalogram (EEG) shows sequences of spikes and slow waves.

- Electroencephalography

ATP

Definition

Adenosine triphosphate: a high energy compound used by cells predominantly for metabolic purposes. ATP hydrolysis also provides the energy for muscular contraction.

- Sliding Filament Theory

ATP-sensitive K⁺ Channel(s)

Definition

- Neuronal Potassium Channels

Atrial Fibrillation

Definition

Abnormal heart beat caused by an irregular and fast activity in the atria that is irregularly conducted to the ventricles. This may be consistent or episodic

Attention

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Definition

Attention represents a set of cognitive abilities that allow living beings to cope with the enormous amount of information flooding the sensory system, and to use this information in goal directed and adaptive behavior. More than one hundred years of research distinguished several major aspects of attention. One refers to selective attention, which is the ability to filter relevant from irrelevant information. The second refers to divided attention, which is the ability to cope with more than one task at the same time. The third refers to the ability to move attention and therefore select stimuli. The fourth refers to the ability to sustain attention to a task. This essay describes these aspects of attention and discusses the neural systems that support these attentional mechanisms and pathologies that impair them.

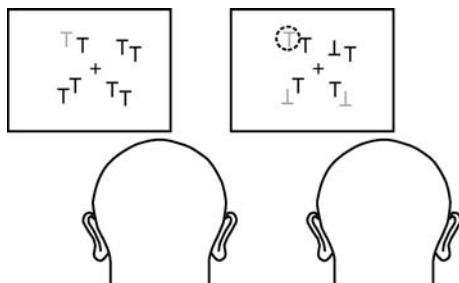
Characteristics

Selective Attention

Selective attention refers to the ability to preferentially process relevant above irrelevant information. This is a fundamental cognitive process and can occur for example at the perceptual level when attention is directed to locations in space, objects or object features such as color or shape, auditory pitch or any other sensory information. Selection can also occur at higher levels of processing, for example when semantic categories such as natural and man-made objects need to be distinguished. Two crucial issues in selective attention studies will be discussed here. The first concerns the question how information is selected. What determines the relevance of information? Is selection determined by perceptual features such as salient object features (bottom-up processes) or by top-down processes such as task instructions, memory, or cues that initiate a selection process? The second issue concerns the question where and when information is selected. Particularly at the perceptual level many studies investigated whether selection takes place in the

low level sensory system (early selection), or after the processing of sensory information (late selection). This is called the “early-late selection debate.” For both the “how” and “when” question of selective attention one has to distinguish between spatial and non-spatial attention. Spatial attention is assumed to affect the sensory system and is guided by top-down processes, whereas non-spatial attention may not. When stimuli are spatially segregated it is presumed that spatial attention works as a spotlight or zoom focusing on a location. When attention is directed to a particular location, objects within the focus of attention are preferentially processed as compared with conditions in which attention is divided between locations or when attention is directed to another location. Human brain imaging and animal neurophysiological studies suggested that spatial attention directly operates at the sensory system, and increases the sensitivity of perception by means of competition between stimuli in relevant and irrelevant locations (sensory gating). Spatial selection may also be biased by top-down processes, even before a stimulus is presented on the attended location [1].

Mechanisms of spatial selective attention are thought to be a prerequisite of object perception. It is thought that all object features within the focus of attention are selected in parallel. This may be intuitive, since an object requires space but can contain different features within this space, such as luminance, color, texture, orientation, or motion direction. In order for selection to occur all information coming from feature specific processing areas needs to be integrated within this space, and conjoined with other features at different locations that build an object. The visual search paradigm is often used to study the selection of objects within space (Fig. 1).



Attention. Figure 1 An example of a spatial attention task including a virtual spotlight of attention. On the left a pop-out condition is displayed, in which a target object can be detected on the basis of a salient feature without much attention. On the right side a serial search condition is displayed in which detecting a target object requires reorienting of attention over the display. Here, the target distinguishes from distractors on the basis of a specific conjunction of object features (upright grey “T”).

The paradigm uses displays with arrays of objects with multiple features such as colors or shapes. Many studies using this paradigm suggested that much less attention is required when an object can be recognized on the basis of a salient feature. The object then seems to pop-out of the display and attention is automatically directed to the target object. When, however, objects need to be detected on the basis of a conjunction of features, the search process is time consuming and depends on the number of irrelevant objects [2]. It is then assumed that the spatial focus attention searches through the display. Findings that “illusory conjunctions” between features are made due to a lack of spatial attention suggested that spatial attention is needed to detect an object with multiple features. Such and other evidence supported the idea that object features are bound together within the focus of attention. Taken together, ample evidence showed that selective attention within the visual domain differs between spatial and non-spatial attention. Whereas selection of locations is determined by top-down processes that accompany the competition between relevant and irrelevant locations and the increase of perceptual sensitivity, the selection of objects relies upon both bottom-up and top-down processes. Salient object features may capture attention by a bottom-up process, whereas top-down processes guide spatial attention, perceptually integrate object features and bias locations or object features by task instructions in favor of behaviorally relevant objects.

Characteristics: Divided Attention and Executive Control

The second aspect of attention deals with the cognitive resources that are available to allocate attention. The attentional resources are limited. For example, when two tasks are performed simultaneously performance may be impaired (driving a car in Cairo while using a mobile phone is virtually impossible). Subjects then have to deal with the coordination of goals. This is accompanied with a switch cost and can be attributed to limitations in ►attention control system. A large amount of research investigated how attentional resources are organized, which processes require attention and which do not, how much time it takes to switch between tasks, and whether there is one central limited attentional resource or several resources in different sensory systems. An influential model of the executive control system assumes that most behavior is controlled by a contention scheduling system that coordinates goals and actions and is determined by previous experience and memories of responses to stimuli [3]. Executive control only then interferes and inhibits concurrent goals when the situation requires an alternative response. Such an alternative response is

required during decision making, planning, correcting errors, during coping with novel situations or responses, when overcoming habitual responses or when a situation is considered difficult or dangerous. This executive control has a limited capacity. A typical task demanding executive control is the Wisconsin card sorting task. In this task, the examiner places four cards with symbols that differ in number, shape or color in front of the subject, who is given a set of response cards with similar symbols on them. The subject is then asked to place an appropriate response card in front of the stimulus card based on a sorting rule established, but not stated, by the examiner (i.e. sort by color, number or shape). The examiner then indicates whether the response is "right" or "wrong." After 10 consecutive correct responses, the examiner changes the sorting rule simply by saying "wrong." The subject must then ascertain the new sorting rule and perform 10 correct trials. The sorting rule is then changed again, until six cycles have been completed. In this task, the change of situation demands a new response to a similar stimulus. Hence, the response that was previously tagged to a stimulus must be inhibited and changed to a new response. The Stroop task is also often used to test executive processes [4]. Here, a simpler process is required when solving a response conflict. For example, if the word "red" is printed in blue and subjects are required to pronounce the color of the printed word, there is a strong tendency to pronounce red instead of blue. In other words, the irrelevant information competes with the relevant information for a response. Attention is then required to suppress the tendency to respond to the irrelevant information. The mechanisms underlying selection of the relevant verbal response above the conflicting irrelevant response is thought to be similar to the perceptual selection process. Many studies showed that neurons in the prefrontal cortex have the possibility to perform such a selection process. These neurons show selective responses to either response information if the stimuli are presented separately, but if they are presented together the neural response to the irrelevant stimulus decreases [5]. Brain lesion studies and neuroimaging studies have shown that the brain areas responsible for executive control are located in the frontal lobe, the cingulate cortex and prefrontal cortex. Prefrontal neurons have been related to this ability. These neurons are decision sensitive rather than stimulus sensitive and are capable to adapt to new situations.

Characteristics: Orienting Attention

Orienting of attention is particularly needed when searching in the environment for relevant information or during the tracing of stimuli through space. Searching in the environment is usually associated with the

foveation of a stimulus. This overt focusing with the eye can also be replaced by covert orienting of attention. As discussed under the term selective spatial attention that focusing attention improves detection of a stimulus. Moving a spotlight of attention from one stimulus location to another can also occur overtly and covertly by moving the eye or moving the "inner" eye. Several brain imaging and neurophysiological studies have shown that the neural mechanisms underlying overt and covert orienting of spatial attention has been associated with overlapping systems. Orienting attention has been associated with a network of at least three brain areas working strongly together, the posterior parietal lobe, the superior colliculus and the lateral pulvinar of the thalamus, representing the so called posterior attentional system [6]. These brain areas have been shown to contain representations of a spatial map that contain location sensitive neurons with relatively fixed relations among spatial locations and some more flexible spatial relationship to the body or the focus of attention. Neural activity in these neurons also suggests their capability to maintain and change the focus of attention. These three neural systems are thought to cope with subprocesses in orienting attention and in visual search. The movement of the attentional focus can be separated in at least three subprocesses; it requires the unlocking of attention to the old location (disengagement of attention), a shift of attention toward the new target location, and tagging to a new focus (engagement of attention). Lesions in the posterior parietal lobe have been associated with the disengagement of attention. Lesions in the superior colliculus have been associated with deficits in shifting the attention. These lesions not only result in slower shifts of attention and reduced capability to calculate the new target location, but patients with such lesions also return to a new location as easily as to a previously attended location. In healthy subjects, returning attention to a previously attended location is inhibited, in order to prevent searching at the same place again (inhibition of return). Finally, lesions in the lateral pulvinar of the thalamus have been associated with difficulties in engaging attention to a new location on the contralateral side of the lesion or to sustain attention to a location in particular when distracting stimuli are present in the ipsilateral visual hemifield. Indeed, this network of brain areas has been shown to be involved in visual search tasks. However, this network does not explain which stimulus locations are relevant and which stimuli draw and guide attention. Here, selective attention mechanisms are needed to distinguish relevant from irrelevant information. As discussed above, such selection mechanisms may be regulated in the occipital and temporal lobe. Thus, spatial orienting can be divided in several subprocesses and neural correlates, but this network does not operate without other

attentional processes and brain areas when coping with spatial attention demanding task.

Characteristics: Arousal and Vigilance

Arousal represents the state of cortical activity or wakefulness. Cortical activity is accompanied with a desynchronization of slow rhythmic activity in the encephalogram. Arousal is regulated by different neurotransmitters in the brain stem, particularly noradrenaline, which innervate different patterns of cortical structures via the thalamus along ascending pathways. Yet, the relation between arousal and attentional functions, such as vigilance, remain under investigation. Vigilance or sustained attention represents the ability to detect and respond to small changes occurring at infrequent random time intervals in the environment. A typical vigilance test is the Continuous Performance Task, which is a 15 minute letter discrimination task. Performing this task requires at least durable (tonic) and momentary (phasic) attention and possibly arousal, that is vigilance requires maintaining a durable state without overt behavior while initiating sudden behavior once a target occurs. Vigilance can be measured by increased error rates and longer reaction times as a function of time (usually at least 5 min). The decrease in performance over time can be due to both a reduced tendency to judge a stimulus as a target and to a reduced sensitivity to discriminate between targets and distractors. Vigilance is thought to be controlled by the cholinergic system and noradrenergic system in the

nucleus locus coeruleus of the brain stem, the intralaminar thalamic nuclei and the right prefrontal cortex [7].

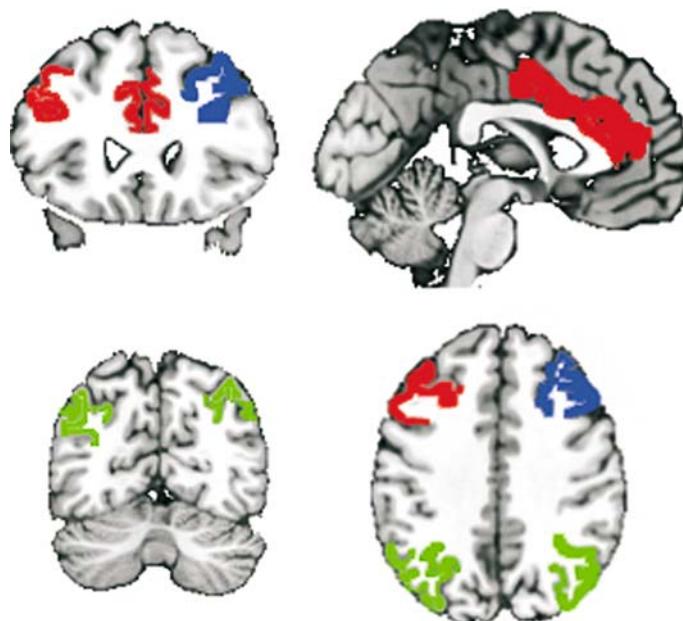
Neural Networks of Attention

The brain areas that are involved in the attentional functions described above form a neural network that strongly interact and are coactive in many task situations (Fig. 2).

One of the most influential neural models of attention [6] consists of three subsystems. The posterior attention system (parietal cortex, superior colliculus, pulvinar) is concerned with spatial attention, the anterior attention system (anterior cingulate, basal ganglia and dorsolateral prefrontal cortex) with target detection and executive control, and the vigilance system (right prefrontal cortex, intralaminar thalamic nuclei and brainstem nuclei) with sustained attention.

Pathology

Many patients with cognitive disorders also have attentional deficits. ►Attention deficit disorder is similar to the hyperactivity diagnosis in children and is referred to under the term ADHD (attention deficit/hyperactivity disorder). These diagnoses often have co-morbidity with disturbances in social behavior and the processing of emotions. Patients (children) are less persistent in performing a task, are overactive, impaired in short-term memory performance, and are often prone to make speeded errors and are less able to make decisions. These symptoms of ADHD can



Attention. Figure 2 A neural network of attention according to Posner & Petrides (1994). This model highlights brain regions that are involved in the attentional control system (red), orienting of attention (green) and vigilance (blue).

be summarized under sustained attention, selective attention and executive control. These deficits correlate with impairments in neural networks of the right frontal (vigilance), posterior parietal (orienting/selective attention), and respectively anterior cingulate cortex (executive control) [8]. Other pathologies with attention deficits have often been associated with damage to the prefrontal cortex or with an imbalance in the neurotransmitter system. Patients with lesions in the prefrontal cortex can be impaired in sensory gating operations, in discriminating between old and new items and a disability to sustain attention. Deficits to discriminate between old and new stimuli or a lack of inhibition to previous responses may also lead to dysfunctions in executive control. Patients with schizophrenia have also been associated with attention deficits. Schizophrenia is often associated with sensory gating dysfunctions and the disability to inhibit interference of irrelevant information, inhibiting previously relevant but currently irrelevant responses or stimuli. Though the neural underpinnings of schizophrenia are largely unknown, a frontal dysfunction and neurotransmitter imbalance of dopamine and noradrenalin may play a role [9]. Patients with hemispatial neglect suffer from lesions in the right parietal or right prefrontal lobe. Some of the heterogeneous dysfunctions of these patients may be related to attention. The disorder of orienting that impairs awareness of stimuli located on the side of space opposite to the lesion in one cerebral hemisphere may be related to a disinhibited orienting to the ipsilesional field or deficits in disengaging attention to the contralesional field [10]. Thus, a variety of attentional deficits have been related to different pathologies. We now begin to understand how specific attentional functions are impaired in different pathologies. However, knowledge about the relation between pathology and specific attention functions is far from complete.

References

- Mangun GR, Hillyard SA (1995) Mechanisms and models of selective attention. In: Rugg MD, Coles MGH (eds) *Electrophysiology of mind: event-related brain potentials and cognition*, Oxford University Press, New York, NY, pp 86–131
- Treisman AM, Gelade G (1980) A feature-integration theory of attention. *Cognit Psychol* 12:97–136
- Norman DA, Shallice T (1986) Attention to action: willed and automatic control of behavior. In: Davidson RJ, Schwartz GE, Shapiro D (eds) *Consciousness and self-regulation*, Plenum Press, New York, NY, pp 1–18
- Stroop JR (1935) Studies of interference in serial verbal reactions. *J Exp Psychol* 18:643–662
- Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. *Annu Rev Neurosci* 18:193–222
- Posner MI, Petersen SE (1990) The attention system of the human brain. *Annu Rev Neurosci* 13:25–42

- Parasuraman R, Warm JS, See JE (1998) Brain systems of vigilance. In: Parasuraman R (eds) *The attentive brain*, MIT Press, Cambridge, MA, pp 221–256
- Swanson J, Posner MI, Cantwell D, Wigal S, Crinella F, Filipek P, Emerson J, Tucker D, Nalcioglu O (1998) Attention-deficit/hyperactivity disorder: symptom domains, cognitive processes, and neural networks. In: Parasuraman R (eds) *The attentive brain*, MIT Press, Cambridge, MA, pp 445–460
- Nestor PG, O'Donnell BF (1998) The mind adrift: attentional dysregulation in schizophrenia. In: Parasuraman R (eds) *The attentive brain*, MIT Press, Cambridge, MA, pp 527–546
- Rafal RD (1998) Neglect. In: Parasuraman R (eds) *The attentive brain*, MIT Press, Cambridge, MA, pp 489–526

Attention Deficit

Definition

Many psychiatric and neurological diagnoses include deficits in attention. These diagnoses are, for example, neglect, attention deficit disorder, hyperactivity, schizophrenia, closed head injuries. Lesions in the prefrontal cortex, or deregulations of neurotransmitters may also accompany attention deficits. Patients with these diverse disorders suffer from a wide spectrum, yet specific patterns, of attention deficits. The spectrum may include impaired vigilance, concentration deficits, short-term memory, decision making, hyperactivity, perceptual, orienting deficits.

► Attention

Attention Deficit Hyperactivity Disorder (ADHD)

Definition

► Attentional Disorder

Attention Demanding Process

Definition

An attention demanding process is a process that involves cognitive resources, so another simultaneously performed task would suffer. For example, counting

backward is made increasingly demanding by counting backward in steps of two or three. Performing such a task impairs performance of the covert or overt rehearsal of numbers or words. Attention demanding tasks are suitable to demonstrate the limited capacity of attention.

► Attention

Attention Shifts

Definition

Attention can switch between tasks. If two tasks have to be performed simultaneously and processing resources are not able to perform the task in parallel, attention has to be divided and switched between the tasks. Task switches are accompanied with costs in processing in at least one of the tasks. It is assumed that the cost of processing is due to limitations in attentional resources.

Coping with task switches is thought to be part of the attentional control system.

► Attention

Attentional Control System

Definition

An influential model of the attentional control system consists of a set of brain regions that cope with the orienting of attention (posterior attentional control system, which includes the posterior parietal cortex, superior colliculus and lateral pulvinar of the thalamus), executive attention (anterior attentional control system, including the cingulate cortex and dorsolateral prefrontal cortex) and vigilance or alerting system (right prefrontal cortex). This model developed by Posner and Petersen (1990) covers about all attentional functions.

► Attention

Attentional Disorder

Definition

Many psychiatric disorders also include attentional deficits, while one percent of children suffer from

attention deficit disorder. Attention deficit disorder is not equivalent with hyperactivity, though attention deficit hyperactivity disorder (ADHD) is used as a common psychiatric diagnosis. The diagnosis includes impaired controlled processing of information, short-term memory, learning and decision making. The children are impaired in sustaining attention, are not able to focus long on a task, are disinhibited and overactive and reactions are less controlled. There is often a co-morbidity with social and emotional disorders.

► Attention

Attentional Filtering

Definition

Represents a particularly strong attentional effect, in which the context gates sensory input in an all-or-none fashion.

Attractive Stimulus

Definition

An attractive stimulus is a signal or a cue that is appealing and draws the receiver to the source of stimulation. The same stimulus can be attractive or aversive depending on physical features such as its intensity (for instance, concentration of an odor) or the behavioral context in which it is perceived.

► Aversive Stimulus

► Odor Coding

A-type K⁺ Current (IA)

Definition

Voltage-dependent K⁺ current, showing relatively rapid inactivation and contributing to action-potential repolarization in cortical neurons.

► Neuronal Potassium Channels

► Action Potential

Atypical Depression

Definition

This is a sub-type of dysthymia and major depression characterized by mood reactivity – being able to experience improved mood in response to positive events. It is also characterized by reversed vegetative symptoms, namely over-eating and over-sleeping. Leaden paralysis and sensitivity to personal rejection may also be observed.

- Major Depressive Disorder

Auditory Brainstem Response (ABR)

Definition

An early latency sound-evoked event-related potential.

Typically elicited by clicks or tone bursts, and more recently by complex stimuli such as speech, the ABR has a distinctive pattern of neural waves arising within the first 10 ms after stimulation. Uses of the ABR include hearing assessment, tumor detection, intraoperative monitoring. Also known as Brainstem Auditory Evoked Response (BAER).

- Auditory Evoked Potentials

Atypical Neuroleptic Drugs

Definition

Relatively newer neuroleptic drugs with less severe adverse effects on movements.

- Antipsychotic Drugs

Auditory Cortical Areas

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Definition

Auditory cortical (AC) areas are structurally and functionally distinct regions in the temporal lobe that process acoustic information. Parcellation of these regions and the identity of areas are based on joint considerations of structural and functional properties, including cytoarchitecture, myeloarchitecture, neuro- and histochemistry, connectivity, electrophysiology and functional imaging. The number of AC areas is a matter of debate and may be species specific.

Characteristics

Higher Level Structure

AC contains many areas as defined by tonotopic representations, i.e., an orderly progression of characteristic frequency (CF) or its absence; areas devoid of CF gradients are identified by their connectional affiliations or cytoarchitectonic attributes.

AC has a high degree of internal order, a stereotyped neuronal organization and intricate local microcircuitry. It is organized in all spatial axes. Thus, in cat AC, CF gradients are found in many (five of thirteen) areas, while other areas are polymodal (six) or limbic-related

Audiogenic Seizures

Definition

Seizures evoked by loud sound often beginning in the inferior colliculus.

- Inferior Colliculus

Audiogram

Definition

A chart showing the amount of hearing loss (in decibels) at each frequency.

- Hearing Aids

(two) [1,2]. The CF gradient differs among areas, with local expansions or reductions of particular frequencies that may serve specific behavioral or ecological roles.

A further axis is laminar organization, which segregates afferent input systems to specific layers (e.g., thalamic projections preferentially end in layers III and IV, while corticocortical input targets layers II and III) and output (corticofugal projections to the midbrain arise exclusively from layer V, while those to the thalamus concentrate in layer VI). Even in areas without a CF representation, there is connectional order on a laminar and topographic basis [1]. Thus, all areas have a topographic connectional order, even if the physiological expression is area specific.

Lower Level Components

Like all brain structures, AC has an intricate array of neuron types and connections that allow it to generate specific physiological responses by combining and recombining inputs in many ways. An elementary form of such order is in the membrane profile of cortical neurons, which is a consequence of genomic and ion channel-related features and endows cells with fundamental properties related to intrinsic excitability and filtering. A second basic level of this specialization is cell shape and chemical anatomy, which is diverse, ranging from glutamatergic pyramidal cells whose apical dendrites may be up to 2 mm long and which subserve vertical columnar organization within cortex, to tiny gamma-aminobutyric acid (GABA)-containing basket cells whose dendritic domain is confined completely to a cortical layer and whose range of synaptic action is a few hundred micrometers. Between these extremes a host of subtypes exist which endow AC with a multitude of processing regimes, including the ability to segregate and integrate streams of information entering it or exiting from it. Thus, even among pyramidal neurons there are subvarieties (giant versus small, classical versus inverted, single-spiking versus bursting, spinous versus smooth, corticothalamic versus corticotectal versus corticocortical) that confer diversity to intracortical intralaminar descending feedback and feedforward connections. Rather than serving as the final terminus for connections and processing, the cortex redistributes streams of information to the forebrain, thalamus, midbrain and medulla, enabling ongoing processing and filtering of ascending information and deconvolving an auditory stream into its constituent elements [1,2].

Higher Level Processes

Segregation and integration are two fundamental aspects of cortical organization that must interact to enable functional processes. Cortical processes can be characterized as a combination of highly localized

and specific processes within areal subregions and global computational procedures and algorithms that reflect operations common to all areas. A basic operational principle is the systematic representation of behaviorally relevant attributes of proximity, similarity or dissimilarity within an organized parameter space. This requires detecting relevant features of the acoustic biotope, performing computed correlations and organizing perceptual space to implement behavior. Cognitive processes that occur in AC entail the analysis and interpretation of the environmental scene based on higher order correlations and in comparison with previously stored information regarding the behavioral relevance of objects, backgrounds and events.

In a mixed set of hierarchical and parallel processes, global groupings of auditory cortical fields can be distinguished [3]. These areas may be broadly subdivided into families that subserve and elaborate specific functional relations (Fig. 1).

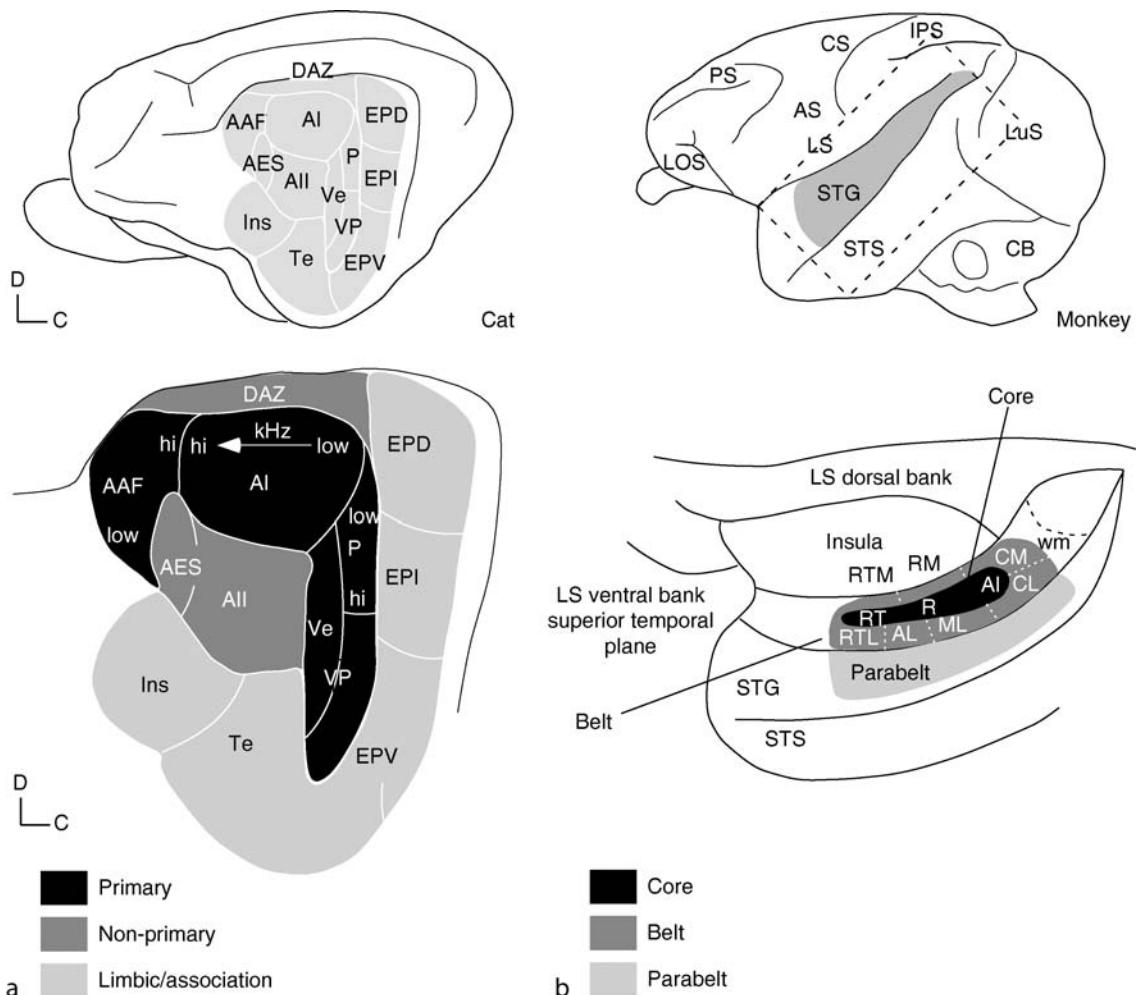
Primary (first order or core [5]) areas represent intermediate stages in the synthesis of percepts after brain stem analysis and precede higher cortical tasks. The primary cortical regions represent auditory information topographically and with receptive field parameters tightly coupled to stimulus aspects [2]. Neurons typically respond to pure tones with a relatively short latency, prefer a restricted range of frequencies and have a global tonotopic organization preserving CF [6]. Other functional properties, such as spectral integration bandwidth, preferred sound intensity or binaural interactions are multiplexed on the tonotopic map and have systematic local organizations [2,6,7].

Secondary (second order, non-primary or belt) areas probably participate in discrimination, categorization and integration of information. Neurons in these areas show high local variability in frequency organization, response latencies and spatial and spectral integrative properties. Responses to pure tones are often reduced and complex sounds elicit stronger responses. Extreme examples are echolocation-specific maps in the AC of some bats [7]. Systematic representations of highly specific parameter-combinations of biosonar sounds and their echoes reflect distance or velocity information.

Multimodal (association, parabelt) areas include the parabelt regions and may process complex multimodal percepts and contribute to the foundation of concepts (for perceptual unity and consistency in decision-making and behavior). Their receptive field properties are poorly understood. A role in the analysis of communication and non-communication sound categories and in speech perception is plausible.

Supramodal areas are involved in the executive control of cognitive networks including language.

Limbic areas receive extralemniscal auditory input, show little regional specificity for particular stimulus aspects and convey auditory information to subcortical



Auditory Cortical Areas. Figure 1 Subdivisions of cat (a) and macaque (b) auditory cortex in a lateral view of the hemisphere (*upper panels*) and with the principal subdivisions indicated (*lower panels*). The macaque subdivisions are redrawn from [4]. For cat primary and macaque core areas, the local tonotopic gradient from low to high frequencies is indicated (arrows). A potential correspondence between cat primary, non-primary and limbic/association areas and macaque core, belt and parabelt areas remains to be established. Abbreviations: AAF anterior auditory area, AES anterior ectosylvian area, AI primary auditory cortex, All second auditory cortical area, AL anterolateral belt area, AS arcuate sulcus, CB cerebellum, CL caudolateral belt area, CM caudomedial belt area, CS central sulcus, D dorsal, DAZ dorsal auditory zone, EPD dorsal area of the posterior ectosylvian gyrus, EPI intermediate area of the posterior ectosylvian gyrus, EPV ventral area of the posterior ectosylvian gyrus, Ins insular area, IPS intraparietal sulcus, L lateral, LOS lateral orbitofrontal sulcus, LS lateral sulcus, LuS lunate sulcus, ML mediolateral belt area, P posterior auditory area, PS principal sulcus, R rostral core area, RT rostrotemporal core area, RTL lateral rostrotemporal, RTM medial rostrotemporal, STG superior temporal gyrus, STS superior temporal sulcus, Te temporal area, Ve ventral auditory area, VP ventral posterior area, *wm* white matter.

structures (amygdala and central gray) implicated in the control of smooth muscle.

Lower Level Processes

A key feature of core areas is a gradual change in neurons' preferred frequency, creating a fundamental cochleotopic axis across AC. Within the continuous CF map are smaller pools of neurons with functional roles other than tonotopic organization, contributing

to specific representations of binaural differences, temporal patterns, stimulus intensity or sharpness of frequency tuning, which in turn are superimposed upon and integrated with CF maps [2]. Such representations could coordinate perceptual processes for binding and streaming, two prime functions for which AC is responsible, following processing in the brain stem. The functional organization of belt and parabelt regions is less well understood; however, they may have a local

order as demonstrated by the object-oriented maps in higher cortical areas of bats [2,7].

In the vertical axis, systematic functional distinctions between cortical laminae coexist with a columnar organization principle, i.e., with receptive field properties, such as CF, that are shared by neurons across the six layers. Lamina specific ensembles of cell types, modular microcircuits, thalamic and cortical inputs, as well as cortical and subcortical output targets, each suggest a fine-grained representation of functional properties within a column [1,6].

Neuromodulatory influences from many chemically specific subcortical sites, including cholinergic, serotonergic, noradrenergic and dopaminergic sources, converge onto AC areas and regulate cortical excitability, gate information processes, enhance signal-to-noise ratios and modulate receptive field synaptic plasticity [8]. These modulatory inputs can modify cortical function based on state, experience and behavioral context.

Function

Communicative, predatory and reproductive behaviors rely critically upon AC to combine, transform and distribute acoustic information. AC interfaces hearing and higher order communication and cognitive networks, including human language areas. Transformations of auditory information in the thalamus and cortex support representations of the auditory environment for essential perceptual tasks. The neural algorithms for such transformations are common to all sensory systems but can also involve unique, modality-specific processes. Different AC subregions contribute to task-related computations and probably serve object specific analyses, suggesting the cortical emergence of processes that are either object related or embody processing stages and streams dedicated to specific features of the auditory environment [9]. Functional differences underlying these processes are created by thalamic and cortical circuits and by local diversity and specialization in synaptic and cellular mechanisms.

AC areas create distinct streams for cortical sound representation [6,9]. They may be less concerned with the representation of specific auditory attributes (a task which we suggest is largely completed in the brain stem) and more with the conjunction and coordination of acoustic, multisensory and limbic frames of reference, each contributing globally to auditory behavior and communication. The computed entities probably serve several central processing tasks, construction of a global representation of the acoustic world, determining object features such as form, texture and position, generating a reliable and stable feature representation, allowing subsequent multisensory integration, permitting the assignment of significance to particular environmental constellations and ultimately,

the emergence of unique perceptual attributes and concepts that trigger behavior.

Functional properties of neurons and neural networks of auditory cortical areas can be dynamically modified through experience. Critical behavioral decisions can reflect the contextual influences within the acoustic scene and their modification by experience. Thus, limbic circuits influence auditory processing, auditory stimuli can modulate behavioral arousal level and sound content and meaning can be assessed based on context and memory.

Pathology

Dysfunction of AC results from many causes, including perinatal asphyxia, cerebrovascular disease (stroke), tumors, trauma, infection and developmental misadventures. In humans, consequences can range from minor auditory sensory disturbance, to auditory agnosia (impaired recognition of non-verbal sounds), to pure word deafness (impaired recognition of speech sounds), to cortical deafness (inability to recognize auditory stimuli). In human cases and infrahuman studies of AC lesions [10], perceptual deficits can involve discrimination of tone duration, auditory sequences and interaural order as well as impaired sound localization and reduced auditory speech perception. Often, tone detection and discrimination are unaffected. AC lesions also affect the construction of auditory objects, assessment of behavioral stimulus significance and decision-making in a learned stimulus/response contingency.

References

1. Winer JA (1992) The functional architecture of the medial geniculate body and the primary auditory cortex. In: Webster DB, Popper AN, Fay RR (eds) Springer handbook of auditory research, vol 1. The mammalian auditory pathways: neuroanatomy. Springer, Berlin Heidelberg New York, pp 222–409
2. Winer JA, Lee CC, Miller LM, Schreiner CE (2005) Auditory thalamocortical transformation: structure and function. *Trends Neurosci* 28:255–263
3. Jacob B, Scheibel AB (2002) Regional dendritic variations in primate cortical pyramidal cells. In: Schuez A, Miller R (eds) Cortical areas: Unity and diversity. Taylor & Francis London, pp 111–132
4. Ghazanfar AA, Hauser MD (2001) The auditory behaviour of primates: a neuroethological perspective. *Curr Opin Neurobiol* 11:712–720
5. Hackett TA, Preuss TM, Kaas JH (2001) Architectonic identification of the core region in auditory cortex of macaques, chimpanzees, and humans. *J Comp Neurol* 441:197–222
6. de Ribaupierre F (1997) Acoustical information processing in the auditory thalamus and cerebral cortex. In: Ehret G, Romand R (eds) The central auditory system. Oxford University Press, New York, pp 317–398

7. Suga N (1988) Auditory neuroethology and speech processing: Complex-sound processing by combination-sensitive neurons. In: Edelman GM, Gall WE, Cowan WM (eds) Auditory function. Neurobiological bases of hearing. Wiley, New York, pp 679–720
8. Gu Q (2002) Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience* 111:815–835
9. Rauschecker JP, Tian B, Pons T, Mishkin M (1997) Serial and parallel processing in rhesus monkey auditory cortex. *J Comp Neurol* 382:89–103
10. Heffner HE, Heffner RS (1990) Effect of bilateral auditory cortex lesions on sound localization in Japanese macaques. *J Neurophysiol* 64:915–931

fluctuations lasting about one half second, is an auditory evoked potential (AEP). With enough repetitions of an acoustic stimulus, signal averaging permits AEPs to emerge from the background spontaneous neural firing (and other non-neural interferences such as muscle activity and external electromagnetic generators), and they may be visualized in a time-voltage waveform. Depending upon the type and placement of the recording electrodes, the amount of amplification, the selected filters, and the post-stimulus timeframe, it is possible to detect neural activity arising from structures spanning the auditory nerve to the cortex.

Characteristics

In general, as the time after stimulation ([► latency](#)) of a response increases, the neural generator becomes more central. In far field recordings from humans, the three typically used response classifications, based on response latency, are: early (the first 10 ms), middle (10–80 ms) and late (80 ms to 500+ ms). In terms of generators, these classes correspond roughly to brainstem, thalamus/cortex and cortex, respectively [1].

Early Latency

Waves arising in the first ten ms after stimulation include both receptor potentials from the cochlea and neurogenic responses arising from the auditory nerve and low midbrain structures. With a near-field recording technique known as [► electrocochleography \(ECoG\)](#), two receptor potentials, originating in the cochlea's hair cells, can be recorded from the vicinity of the ear drum: the cochlear microphonic and the summing potential. They are AC and DC potentials, respectively, have an effective latency of zero, and last the duration of the stimulus. A millisecond and a half later, the dual-peaked neurogenic compound action potential of the distal auditory (eighth cranial) nerve can also be seen with ECoG. In contrast, using far-field electrodes, neurogenic responses known as the [► auditory brainstem response \(ABR\)](#), can be recorded from the scalp ([Fig. 1](#)) [2].

These waves depend upon synchronous firing in the first relays of the afferent auditory pathway. For a given stimulus type (often an abrupt broadband click) and intensity level, the expected latency of ABR peaks falls within a very tight range (less than half a millisecond). Deviations from this range are useful in clinical diagnoses.

In particular, the ABR is a valuable objective measure of hearing. With decreasing stimulus intensity, wave latencies increase systematically until the hearing threshold is reached, below which the response is absent. Thus, an accurate measure of hearing threshold is possible in individuals who are unable to be tested behaviorally. Although there is a developmental time course (adult-like responses are attained by age two),

Auditory Division of the Statoacoustic Nerve

►Auditory Nerve

Auditory Event-related Potentials

►Auditory Evoked Potentials

Auditory Evoked Potentials

NINA KRAUS¹, TRENT NICOL²

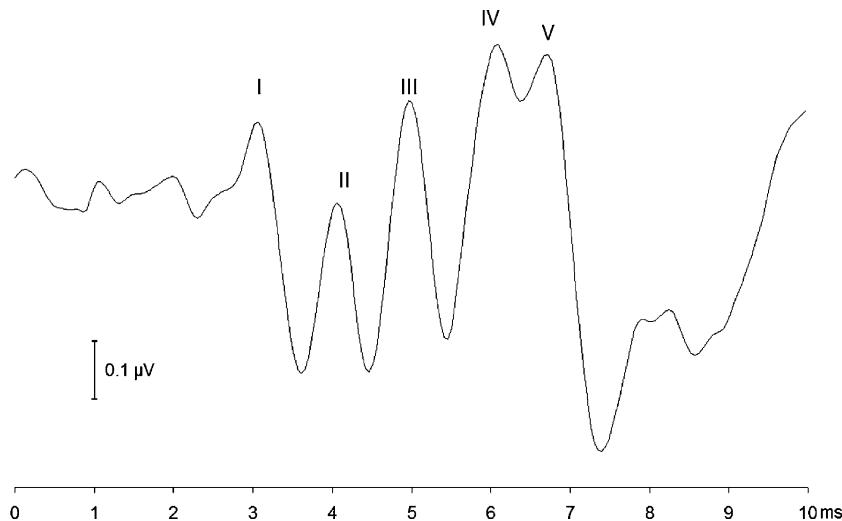
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Synonyms

Auditory event-related potentials; ERP

Definition

The firing of neurons results in small but measurable electrical potentials. The specific neural activity arising from acoustic stimulation, a pattern of voltage



Auditory Evoked Potentials. Figure 1 Early-latency auditory evoked potentials. The auditory brainstem response.

it is possible to test hearing in newborns with age-appropriate norms. Importantly, the ABR is unaffected by sleep or sedation, so obtaining hearing thresholds in babies or other uncooperative individuals is possible.

A second major clinical use of ABR is in the detection of lesions, tumors, demyelination, or conditions that cause increased intracerebral pressure (e.g., hydrocephalus, hematoma). ABR morphology, peak and interpeak latencies can have distinctive patterns that alert skilled clinicians to neural damage (e.g., eighth nerve tumors). Another major use of ABR is intraoperative monitoring. During neurosurgery, monitoring of ABR enables an immediate indication of whether any of the structures involved in the auditory pathway have been put at risk. Finally, the brainstem response provides a measure of neural synchrony necessary for normal perception of sound [3].

Brainstem Responses to Complex and/or Long Stimuli

Typical recordings employ short duration, relatively simple stimuli. However, complex sounds, some quite long in duration, are increasingly being used. Brainstem response to speech sounds can be used as a biological marker of deficient auditory processing associated with language and learning disorders [4]. A brainstem response whose nature depends on a long-duration stimulus is the ►frequency-following response (►FFR). The FFR, also known as auditory steady-state response, is an index of phase locking to a periodic stimulus. Examples of FFR-inducing stimuli are pure or modulated tones, tone complexes, modulated noise and speech [5]. Recorded from the scalp in humans, the FFR is a phase-locked response that, depending on electrode placement and stimulation and recording techniques, originates from as early in the auditory pathway as the auditory nerve or as late as the rostral brainstem. It is a measure of

both spectral and periodicity encoding, and because it is readily detectable in individuals, it has utility as a clinical measure of those processes as well as of hearing level. Brainstem responses are influenced by lifelong and short-term auditory experiences [6].

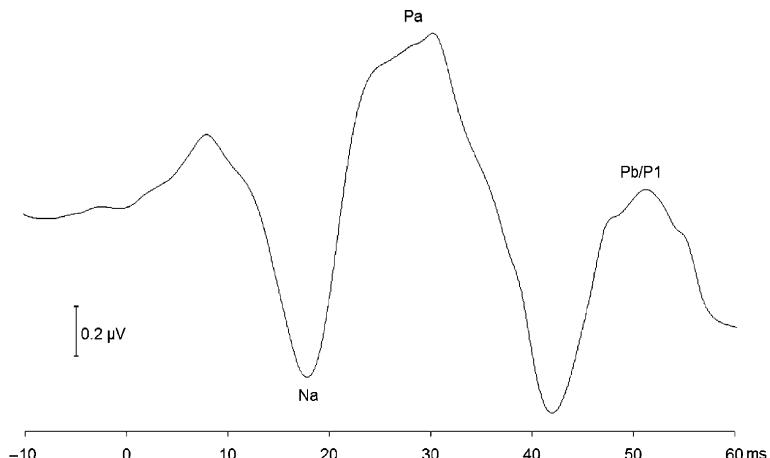
Middle Latency

The waves following the ABR, up to roughly 80 ms, are collectively known as the middle-latency response (MLR) (Fig. 2) [7].

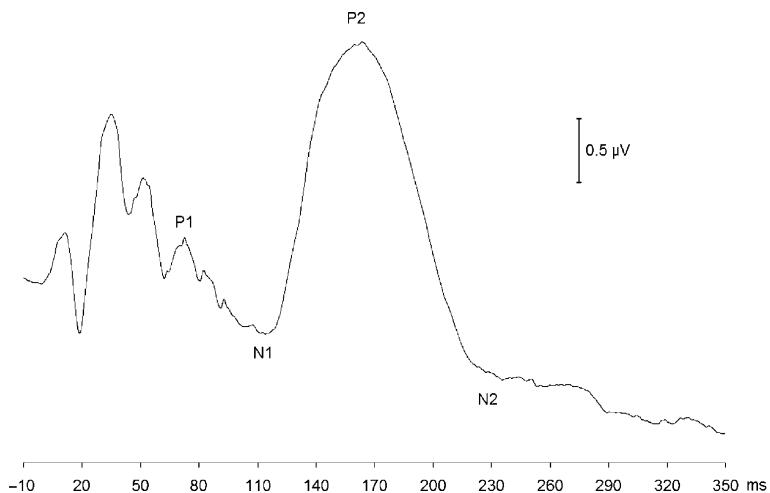
Although responses in this time frame are less mappable to specific neural generators than the earlier ABR waves, the thalamus (P0, Na) and cortex (Pa, Nb, P1) are involved. (Note: Unlike ABR waves, the names of middle- and late-latency responses typically begin with P or N indicating positive or negative polarity.) As ABR requires a high degree of neural synchrony, individuals with certain neurological disorders may exhibit absent ABRs despite normal hearing. Thus, MLR can be useful in assessing hearing sensitivity. For this same reason, a lack of sufficient synchrony in response to low frequency signals often makes MLR superior to ABR in assessing low-frequency hearing. Two major caveats in MLR as a hearing measure is that it does not reach its mature morphology until adolescence, and in children, there is a strong influence of sleep state.

Late Latency

Late-latency (>80 ms) AEPs, historically the first discovered, are cortical in origin and are much larger and lower in frequency than early and middle-latency potentials. Highly dependent upon stimulus type, recording location, recording technique, patient age and state, the late-latency responses may differ dramatically in morphology and timing and may overlap one another. Thus, categorization of responses



Auditory Evoked Potentials. Figure 2 Middle-latency auditory evoked potentials.



Auditory Evoked Potentials. Figure 3 Late-latency auditory evoked potentials. Exogenous responses.

into two broad types, exogenous and endogenous, is useful in describing these late potentials. Exogenous responses, which also describe early and middle-latency potentials, are more-or-less obligatory responses to a sound. Endogenous responses typically require a stimulus manipulation or the performance of a task by the patient.

Exogenous Responses

The archetypal late-latency exogenous responses are illustrated in Fig. 3.

Beginning with P1 (which is sometimes classified as middle-latency) at about 80 ms through to N2 at about 250 ms, all are cortical in origin and maximal in amplitude at the central top of the scalp. The maturational time course of the various components varies. Late cortical responses do not reach maturity until post-adolescence. They have value in assessing

cortical auditory processing. In addition to the classic pattern of responses to stimulus onset, changes within an ongoing stimulus also evoke a response called the acoustic change complex (ACC) [9]. Tones or tone complexes changing in frequency, complexity or intensity and speech syllables are typical stimuli. The response can be evoked by an acoustic change that is very near threshold.

Bridging the exogenous and endogenous categories is the ►mismatch negativity (►MMN). MMN is an acoustic change detector. It is evoked by a sequence of identical sounds that is interrupted occasionally by a different sound. This stimulus presentation technique is termed “oddball paradigm.” The response to that infrequent stimulus differs from that to the main stimulus, and appears as a slow negative deflection in the 150–300 ms time frame. The types of stimulus manipulations that evoke MMN include intensity,

frequency and complexity, and the contrasting stimuli can be at (or even below) perceptual threshold.

Endogenous Responses

Endogenous (literally “born within”) potentials are those that, while induced by external stimuli, originate not as an obligatory consequence of the inducing sound, but rather due to some level of cognitive processing. Examples of endogenous AEPs are the P300 and N400. Sequentially occurring later in time, the P300 and N400 represent successively higher levels of sound processing. Evoked using the oddball paradigm, the classic P300, unlike MMN, only occurs when the listener is consciously attending to the stimulus aberration. P300, which is also evoked by other sensory modalities, is considered an index of cognition because stimulus evaluation and classification must take place [10]. The response is further divided into P3a and P3b components. P3a either appears to a distracter stimulus which is presented along with the targets and non-targets within the oddball presentation, or, if stimulus differences are large enough, with no task at all. This component has more frontal lobe contribution than the classically elicited parietal-centered P3b. A higher level of cognition is required for the N400 response [11]. It requires a speech stimulus, and occurs in response to semantic incongruity and thus is an indication of language processing.

Considerations

A number of considerations and caveats are involved in the recording of reliable auditory evoked potentials. No response is monolithic, either in its etiology or in interpretation. A thorough description of stimulus factors alone could fill a volume: the length, intensity, complexity and repetition rate of the stimulus all affect the responses. Some responses differ dramatically depending upon whether the stimulus is delivered to one or both ears or whether there is accompanying visual stimulation; others are relatively unaltered by these factors. Characteristics of the recording device, particularly filters, also have an effect on response recording. Successively later responses have increasing low-frequency content and high-pass filters must correspondingly be opened. However, with increasingly more energy being passed on the low end, recordings are more prone to contamination by non-stimulus related activity: artifacts. Artifacts fall under two categories, those internal to and external to the testee. Internal artifacts include eye blinks, movements, muscle contractions including the involuntary sound-evoked postauricular muscle (PAM) reflex, and brain activity that is unrelated to the sound stimulus. External artifacts are those arising from electrical sources such as AC power line and the electrical signal traveling

through the earphone or loudspeaker cables (stimulus artifact). The degree to which artifacts adversely affect response recordings depends upon how alike in frequency the artifact and the response are. For example, eye blinks are very low in frequency, and thus are more damaging to low-frequency late-latency responses. Most artifacts are random in time of occurrence. Two exceptions are stimulus artifact and PAM. Stimulus artifact lasts as long as the stimulus. Therefore, it is not a concern if the stimulus is a 100 μ s click and the response of interest is the middle-latency Pa. However, the stimulus artifact from a 5 ms tone burst may obliterate an early-latency brainstem response. PAM reflex occurs in response to the stimulus in the 15 ms timeframe and thus most affects middle latency responses.

Much information can be gleaned from AEPs for both clinical and theoretical purposes. As the power and speed of computers increases, multiple-channel recordings and advanced signal processing techniques are better able to inform us about the underlying neural processes that are signified by these minute perturbations in the electroencephalographic activity resulting from auditory stimulation. Together with advances in neural imaging, the exquisite timing resolution of AEPs can help us approach a better understanding of the biological bases of auditory function responsible for human communication such as speech and music.

References

1. Kraus N, McGee T (1992) Electrophysiology of the human auditory system. In: Popper AN, Fay RR (eds) The mammalian auditory pathway: neurophysiology. Springer, New York, pp 335–403
2. Hood LJ (1998) Clinical applications of the auditory brainstem response. Singular, San Diego
3. Sininger Y, Starr A (eds) (2001) Auditory neuropathy: a new perspective on hearing disorders. Singular Thomson Learning, London
4. Banai K, Nicol T, Zecker S, Kraus N (2005) Brainstem timing: implications for cortical processing and literacy. *J Neurosci* 25:9850–9857
5. Galbraith GC, Threadgill MR, Hemsley J, Salour K, Songdej N, Ton J, Cheung L (2000) Putative measure of peripheral and brainstem frequency-following in humans. *Neurosci Lett* 292:123–127
6. Barai K, Kraus N (2008) The dynamic brainstem: implications for CAPD. In: McFarland D, Cacace A (eds) Current Controversies in Central Auditory Processing Disorder. Plural, San Diego
7. Kraus N, Kileny P, McGee T (1994) The MLR: clinical and theoretical principles. In: Katz J (ed) Handbook of clinical audiology. Williams and Wilkins, Baltimore, MD, pp 387–402
8. Burkard RF, Don M, Eggermont JJ (2007) Auditory Evoked Potentials: Basic Principles and Clinical Applications. Lippincott, Williams & Wilkins, Philadelphia

9. Martin BA, Boothroyd A (2000) Cortical, auditory, evoked potentials in response to changes of spectrum and amplitude. *J Acoust Soc Am* 107:2155–2161
10. Picton TW (ed) (1988) Human event-related potentials: EEG handbook. Elsevier, Amsterdam
11. Kutas M, Hillyard SA (1983) Event-related brain potentials to grammatical errors and semantic anomalies. *Mem Cognit* 11:539–550

Auditory Maps

- Tonotopic Organization (Maps)

Auditory-Motor Interactions

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Definition

Interactions between hearing and various motor functions, such as protective reflexes and vocal behavior.

Characteristics

Auditory signals guide a multitude of behavioral responses from simple reflex motor patterns for orientation to complex vocal communication behaviors in virtually all vertebrates and insects. Hence, auditory stimulation can elicit anything from simple motor patterns, such as head/neck turns or ear movements, to complicated, highly coordinated interactions of several motor patterns, such as calling, breathing, and postural changes that occur, for example, during birdsong. In turn, certain motor patterns, especially those associated with vocal behavior, can also affect how the brain processes auditory signals.

Auditory Orientation Reflexes

Orienting movements of the head, neck and/or eyes in response to auditory signals are generally thought to be controlled by auditory input to the superior colliculus in mammals, or its homologue structure in birds, the optic tectum. Most of our knowledge about what controls head movements in response to external signals is based upon studies of visually guided orienting responses, where the topographic representation of the stimulus that ultimately guides the motor response is naturally

determined by the retinotopic organization of the visual system. Auditory input to the superior colliculus/optic tectum is topographically organized only in barn owls. In mammals, the representation of auditory space appears to be less developed, and is often even more complicated by movements of the external ears, or pinnae. Very little is therefore known about the neuronal basis of acoustically elicited orienting responses. It appears that output from the superior colliculus/optic tectum to small areas in the midbrain tegmentum mediate the sensory-motor transformation of stimulus location into a direction-specific pre-motor command. This in turn gives rise to a directed behavioral response through activation of the various pools of motor neurons in the brainstem and spinal cord that control head/neck turns, turns of the body axis, and/or eye movements.

Pinna Movements in Mammals

The mammalian pinna plays an important role in sound localization, especially for sources in the midsagittal plane, which generate minimal interaural disparities. In species with mobile external ears, the pinnae can be oriented independently of the head's position, thus aiding in sound localization by allowing the animal to obtain multiple samples of an acoustic object. In such mammals, auditory targets elicit stereotyped pinna movements that typically consist of two parts: a short-latency component that is time-locked to the onset of the sound and a second long-latency component that is highly correlated with eye movements and is probably part of the animal's general orientation behavior. The second, slower response most likely involves the superior colliculus, and might be mediated by pathways linking the superior colliculus with the facial nucleus, either via the reticular formation (tectoreticular–facial pathway) or via the paralemniscal area (tectoparalemniscal–facial pathway). In particular, the paralemniscal area, situated in the lateral midbrain tegmentum, supplies an elaborate network of monosynaptic excitatory and inhibitory inputs to the medial portion of the facial nucleus, where the motoneurons that innervate the muscles of the pinna are located. It is not clear, however, if the superior colliculus is also involved in mediating the initial, faster response. This component of auditory-evoked pinna movements might be driven directly via the paralemniscal area, which receives multiple, binaural inputs from the ascending auditory pathway, notably from the dorsal nucleus of the lateral lemniscus.

Acoustic Startle Response

The startle response is a fast reflexive response to intense, unexpected acoustic, tactile or vestibular stimuli and protects the animal from injury by blows or predatory attacks. The acoustic startle response (ASR) of mammals, including humans, consists of a quick eyelid-closure and a contraction of facial, neck

and skeletal muscles, an arrest of ongoing behaviors, and an increased heart rate. This results in a brief stiffening of the limbs, dorsal neck, and body wall before the animal can perform directed evasive or defensive actions [1]. The ASR can be modulated by various experimental manipulations, expressing habituation, sensitization, and fear conditioning. ASR has thus been used as a behavioral assay to examine the neuronal basis of behavioral plasticity, and to model neuropathological dysfunctions of sensorimotor information transfer.

The ASR is phylogenetically widespread and can also be found in fish and aquatic amphibians where it is expressed as “►C-start escape” and is mediated by the ►Mauthner cell system [2]. An ASR is even present in some insects [3]. Its neuronal implementation is therefore rather diverse, although it has been suggested that the most fundamental mechanisms for rapid motor control by the Mauthner system may even be shared between fish and mammals.

The behavioral latency of the ASR in mammals is very short (5–10 ms in rats), indicating that a simple circuit with very few synapses underlies this reflex response. The neuronal elements linking the cochlear nucleus to motoneurons controlling neck and limb muscles are found within the reticular formation. All current models proposed for the neuronal implementation of the ASR include an initial central relay in the cochlear nuclear complex leading to a central, integrating brainstem element within the reticular formation, which relays its output to motor neurons in brainstem and spinal cord. A small cluster of giant neurons in the caudal pontine reticular nucleus (PnC) represents the key component of this sensory-motor circuit, and is involved in sensory-motor integration and its modulation by other central-nervous inputs. Auditory information reaches the PnC via different nuclei of the central auditory pathway, such as the dorsal and ventral cochlear nucleus, the lateral superior olive and neurons of the cochlear root nucleus, a ganglion located within the auditory nerve.

Middle Ear Muscle Reflex

The middle ear muscle reflex (MEMR) in mammals consists of contractions of two middle ear muscles, the ►stapedius and ►tensor tympani, respectively, in response to intense sound signals, thus protecting the inner ear from damage. Between the two muscles involved, the contraction of the stapedius contributes more to the overall MEMR. Measurements of the MEMR have become an important tool in audiologic examination and for detecting hearing loss in children and newborns [4].

In normal hearing humans, MEMR thresholds are approximately 95 dB SPL for tones and 75 dB SPL for wideband noise. As a result of the MEMR, hearing

thresholds increase between 15 and 20dB in all mammals tested, including humans. The short latencies for the MEMR of only 3–6 ms, with those for the tensor tympani reflex being slightly longer, suggest a simple underlying circuitry. However, the exact reflex pathways are still unknown. There is evidence for both, interneurons within or near the superior olfactory complex (most likely in the medial superior olive) and direct projections from cochlear nucleus neurons to facial and trigeminal motor neurons, which ultimately innervate stapedius and ►tensor tympani muscles, respectively.

A MEMR is also found in birds and involves a ►stapedius muscle (also called “musculus columellae”), which is, like its mammalian counterpart, innervated by facial motor neurons. Further details of the underlying circuitry are not known. Reptiles and ►anuran amphibians also possess a set of middle ear muscles that are attached to various structures in the middle ear, however, relatively little is known about their function(s) and the underlying neuronal control. It has recently been suggested that the middle ear muscle system in anuran amphibians (the so called “opercular system”), in addition to protecting the inner ear from sound shocks, might also play a protective role by reducing the large pressure changes that occur in the inner ear fluids during ambulatory or ventilatory movements.

Auditory Feedback Control of Vocalizations Mammals

While the importance of auditory feedback for vocal learning in birds and mammals is well documented, its role in adulthood is much less understood [5–7]. Whereas auditory experience affects the overall structure of a species' vocal repertoire on a large scale only in humans and songbirds, but not in non-human primates, more recent data indicate that subtle modifications of a fixed template indeed occur in a wide variety of call types in every major primate group. It appears, therefore, that vocal learning in non-human primates consists mostly of subtle spectro-temporal changes of an inherited basic call structure [8]. In certain songbirds, it has been demonstrated that auditory feedback also plays a major role in the maintenance of the bird's acquired song throughout its life (see below). Although the evidence is patchy, among adult mammals, only humans, bats, and possibly cetaceans appear to require auditory feedback for the maintenance of basic parameters of species-specific vocalizations.

In humans, the detrimental effects of deafness on human language are well known, even when deafness was acquired postlingually. In addition, language dysfluencies and stuttering in hearing human subjects appear to be caused by a malfunction of the auditory feedback circuit that controls the production of

vocalizations. Apart from these complex effects on human language, basic vocal parameters, such as the fundamental frequency are also affected. Speaking deaf humans tend to speak in a voice that contains higher fundamental frequencies than in hearing human speakers. When adequate auditory feedback is provided, as with a cochlear implant, however, the fundamental frequency is one of the earliest acoustic features to approach normal values again. Numerous psychoacoustic experiments in adult humans also demonstrate that the fundamental frequency of their voice changes when artificially modified auditory feedback is presented, such as frequency-shifted formants.

Auditory feedback is also essential in echolocating bats [9]: the dynamic, temporal, and spectral pattern of their echolocation cries crucially depends on the information contained in the returning echo signal.

Reports on neural interactions between auditory processing and vocalization control are scarce, and few studies have addressed this issue at the level of single neurons. Auditory stimulation can affect neural activity in certain motor structures in various mammals, such as the paralemniscal area in bats, the parabrachial nucleus in cats, bats, and monkeys, the nucleus ambiguus, which controls laryngeal activity, and the laryngeal nerve in bats and rats. Neurons with dual vocal premotor and auditory function occur in the bat and monkey midbrain. So far, however, no coherent concept of what mechanism might underlie auditory feedback control of call production has emerged.

Conversely, vocalization has been shown to affect processing of auditory information in the superior olfactory complex and adjacent areas (including the nucleus of the central acoustic tract), in the vicinity of the nuclei of the lateral lemniscus (within the paralemniscal area), adjacent to or within the inferior colliculus, in the medial geniculate body, and in the auditory cortex. This has been reported in several species of bats and in primates. In most cases, auditory responses were markedly suppressed during vocalization.

Songbirds

Songbirds are one of the best-studied examples for the role of auditory feedback in vocal learning: young male songbirds learn to produce their species-typical song patterns by first forming a song memory or “song template” (normally resembling the father’s song), and then shaping their vocal output by comparing auditory feedback from their own vocalizations with this template. In addition, more recent work has shown that auditory feedback is not only needed to acquire song, but that in adults of some species, hearing their own song is also required for maintaining proper song patterns during adulthood well beyond the age at which song is learned. As many components of the brain

circuitry that mediates song learning have been identified, birdsong provides a powerful model system for studying the neural mechanisms of auditory-guided vocal learning [6], including various aspects of human speech [7].

Birdsong research focuses mainly on the neuronal sites and mechanisms that underlie song memory and auditory feedback. So called “song-specific neurons”, which respond selectively to playbacks of the bird’s own song, or in some cases the tutor’s song, but not to song produced by other males of the same species, appear to play a key role. Such song-specific responses are created within a forebrain nucleus (the “High Vocal Center”, HVC) and are then relayed to other nuclei throughout the song system; they were even found in the hypoglossal nerve that innervates the bird vocal organ, the syrinx. One particular pathway, the “anterior forebrain pathway”, which is strikingly similar to the mammalian cortical-basal ganglia circuit, may be a key player in the auditory feedback control of song during vocal learning, as well as during adulthood [6]. Various lesion experiments indicate that this pathway is essential to the vocal plasticity necessary for song learning.

Many neurons in the song system show both premotor and auditory function. Currently, however, we still have little knowledge of what song feedback information reaches the sensory-motor structures of the song control system, or how sensory and motor activity interact at the cellular level. For instance, how can these neurons distinguish self-generated sounds from those emitted by external sources? A neural mechanism involving a ►corollary discharge (or “►efference copy”) might play a role in solving this problem. Such a mechanism entails subtracting a motor copy of the vocal command signal from the sensory input, thus canceling out anticipated sensory feedback from the bird’s own song. The plasticity in the processing of auditory feedback also appears to depend upon other behavioral states, such as wakefulness or sleep.

Fish

Sound communication is not unique to mammals or songbirds but rather is a trait shared with most vertebrates. ►Teleost fishes include many species that hear and also produce sounds for communication purposes, such as midshipman, toadfish, and weakly electric mormyrid fish [10]. Playback of sounds produced by these fish evokes calling behavior and ►phonotaxis. The vocal control system extends from forebrain to hindbrain levels and shares several organizational features with the vocal systems of birds and mammals. Various studies have also pinpointed sites where the auditory and vocal systems interface with

the ►neuroendocrine axis of the brain. Thus, the vocal and auditory feedback mechanisms identified in these simple systems are essential for producing vocal communication behaviors within the context of more complex social and reproductive behaviors.

Cerebellar Learning

Cerebellar computation has recently been portrayed as a straightforward example of feed-forward processing of inputs in order to improve movement accuracy. In the context of auditory stimulation, the cerebellum plays a major role in temporally specific learning that occurs in rhythmic motor entrainment, for example, movements observed in musicians in response to auditory feedback from the instrument they are playing.

Similar to the fact that vocal motor patterns can also affect the processing of auditory signals, cerebellar processing also appears to be able to affect sensory information processing. This has been demonstrated, for example, for the perception of pitch in humans. Neuroimaging studies have shown that fine auditory discrimination depends critically upon non-motor sensory support functions of the cerebellum.

References

1. Yeomans JS, Li L, Scott BW, Frankland PW (2002) Tactile, acoustic and vestibular systems sum to elicit the startle reflex. *Neurosci Biobehav Rev* 26:1–11
2. Eaton RC, Lee RK, Foreman MB (2001) The Mauthner cell and other identified neurons of the brainstem escape network of fish. *Prog Neurobiol* 63:467–485
3. Hoy RR (1989) Startle, categorical response, and attention in acoustic behavior of insects. *Annu Rev Neurosci* 12:355–375
4. Johnson KC (2002) Audiologic assessment of children with suspected hearing loss. *Otolaryngol Clin North Am* 35:711–732
5. Janik VM, Slater PJB (1997) Vocal learning in mammals. In: Slater PJB, Rosenblatt JS, Snowdon CT, Milinski M (eds) *Advances in the Study of Behavior*, vol. 26. Academic Press Inc., San Diego, California, USA; London, England, UK, 59–99
6. Zeigler HP, Marler P (eds) (2004) *Behavioral Neurobiology of Birdsong*. Annals of the New York Academy of Sciences, Vol. 1016. New York Academy of Sciences, New York, NY, 1–788
7. Doupe AJ, Kuhl PK (1999) Birdsong and human speech: Common themes and mechanisms. *Annu Rev Neurosci* 22:567–631
8. Egnor SE, Hauser MD (2004) A paradox in the evolution of primate vocal learning. *Trends Neurosci* 27:649–654
9. Moss CF, Sinha SR (2003) Neurobiology of echolocation in bats. *Curr Opin Neurobiol* 13:751–758
10. Bass AH, McKibben JR (2003) Neural mechanisms and behaviors for acoustic communication in teleost fish. *Prog Neurobiol* 69:1–26

Auditory Nerve

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Synonyms

Cochlear nerve; Auditory division of the statoacoustic nerve; Cochlear division of the vestibulocochlear nerve; Eighth cranial nerve

Definition

The auditory nerve is the peripheral pathway comprised of the central processes of the sensory ►spiral ganglion neurons of the cochlea that project to the ipsilateral cochlear nucleus, as well as the axons of the neurons of the ►olivocochlear efferent system that originates in the superior olive.

Characteristics

Quantitative Description

The number of spiral ganglion neurons in mammals ranges from about 10,000–50,000, 80–95% of which are classified as Type I, while the remainder are (Fig. 1) Type II. Type I neurons receive input from inner hair cells, while outer hair cells provide the input to Type II cells [1]. There are between about 475 and 2,500 olivocochlear efferent neurons in a range of mammals, approximately one-quarter to one-third of which belong to the medial olivocochlear system that contacts outer hair cells, while the remainder belong to the lateral olivocochlear system which projects primarily to the dendrites of the Type I spiral ganglion neurons within the organ of Corti [2].

Higher Level Structures

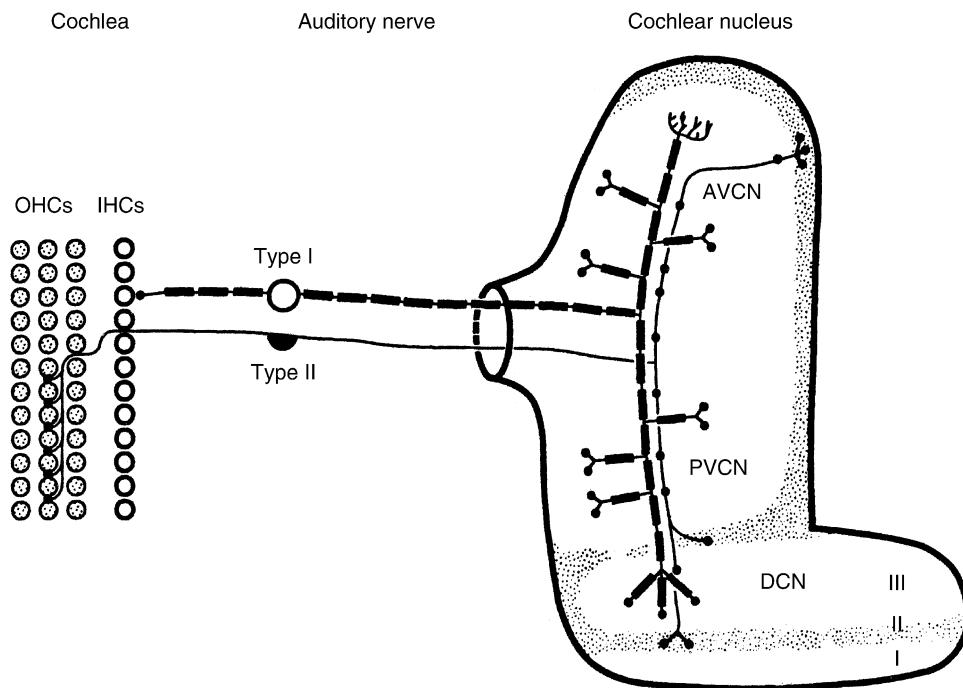
The auditory nerve is the beginning of the afferent auditory pathway that ascends through the brainstem and midbrain to reach the auditory cortex in the temporal lobe. The olivocochlear efferent system is the common final descending auditory pathway to the cochlea.

Lower Level Components

The auditory nerve is a subdivision of the ►statoacoustic nerve, the eighth cranial nerve, the other being the vestibular division. The nerve carries both afferent and efferent axons between the cochlea and the medulla.

Afferent

The spiral ganglion, located in Rosenthal's canal, coiled around the modiolus of the cochlea, gives rise to the



Auditory Nerve. **Figure 1** Diagram of the peripheral and central connection patterns of the spiral ganglion neurons. The type I neurons receive input exclusively from inner hair cells and bifurcate to terminate in ventral and dorsal regions of the cochlear nucleus that in turn project to other brainstem auditory nuclei. The type II neurons, which receive input exclusively from outer hair cells, follow the course of the type I neurons, but terminate in granule cell regions of the cochlear nucleus. (Reprinted from Fig. 2.19 of reference [1] with kind permission of Springer Science and Business Media).

afferent component of the auditory nerve. Two classes of bipolar ganglion cells provide separate sensory innervation for the inner and outer hair cells. The larger type I cells, which are 80–95% of the total, send mostly unbranched peripheral processes through the osseous spiral lamina to form small bouton endings on the inner hair cells. The remainder of spiral ganglion cells are generally smaller and their peripheral processes branch within the organ of Corti to form multiple small endings on outer hair cells.

Each inner hair cell typically contacts from about 10 (in the apical turn) to 25 (mid basal turn) different type I spiral ganglion cells. Each bouton ending is opposed by a specialized presynaptic complex in the hair cell typified by a presynaptic dense body that tethers synaptic vesicles via filamentous links. This synaptic organization, in which a single active zone provides the entire excitatory drive to a sensory neuron, is unique in the nervous system and undoubtedly exerts a strong influence on how auditory signals are encoded. On entering the cochlear nucleus the axons of the type I spiral ganglion cells bifurcate, with branches running rostral (ascending) and caudal (descending). The ascending type I axons terminate in the anteroventral cochlear nucleus (AVCN), forming large end-bulbs of Held on the somas and small bouton endings on

both the somas and dendrites of AVCN neurons. The descending branches form small to intermediate size endings on cells in both the posteroventral (PVCN) and dorsal (DCN) divisions of the cochlear nucleus.

The peripheral processes of the type II ganglion cells take a characteristic basal spiral course in the outer spiral bundles underneath the outer hair cells, before branching to form as many as 60 terminals on outer hair cells along their spiraling course. The type II cells and their processes are smaller than their type I counterparts and are far less heavily myelinated. While the central processes of type II ganglion cells follow the same course as the type I cells that originate in the same region of the cochlea, they terminate exclusively within the superficial granule cell regions of both the ventral and dorsal cochlear nucleus and thus do not appear to project to the same cochlear nucleus neurons that receive input from the type I spiral ganglion cells [1].

Efferent

The olivocochlear system provides the efferent component of the auditory nerve. Here too, there is specialization, with the medial division terminating on the basal somas of outer hair cells, while the lateral division terminating primarily on the peripheral processes of the type I spiral ganglion cells underneath the inner hair

cells. The cell bodies of the medial olivocochlear neurons are in the medial periolivary regions of the superior olfactory complex. The majority of their large, myelinated axons cross the midline to project to the contralateral cochlea, but some project ipsilaterally. The relatively small somas of the more numerous lateral olivocochlear neurons are located in and near the lateral superior olfactory nucleus and project primarily to the ipsilateral cochlea. Their axons are small in diameter and unmyelinated. Before leaving the brainstem, the axons of both medial and lateral olivocochlear neurons join to form the olivocochlear bundle, which leaves the brainstem in the vestibular division of the vestibulocochlear nerve, before crossing at the vestibulocochlear anastomosis into the cochlear division to enter the modiolus. Within the modiolus, the olivocochlear bundle forms the intraganglionic spiral bundle within Rosenthal's canal next to scala tympani of the cochlea. On entering the organ of Corti, the lateral olivocochlear neurons join the inner spiral bundle, running beneath the inner hair cells, where they terminate on the unmyelinated dendrites of the type I spiral ganglion cells. The medial olivocochlear neurons terminate in multiple large vesicular endings at the base of outer hair cells. The density of medial efferent terminations is greatest in the basal half of the cochlea, the region where the mechanical cochlear amplifier function of outer hair cells appears strongest [2].

Process Regulation

The process of afferent auditory nerve signaling can be considered to be under regulation by the olivocochlear efferent system, as well as the acoustic reflex activity of the middle ear muscles. The physiology of the lateral olivocochlear efferent subsystem is largely unknown. The small size of the unmyelinated lateral olivocochlear neurons and their axons has made recordings impractical. Because of its innervation pattern, this system undoubtedly must regulate the transmission of afferent information to the brain via the type I spiral ganglion cells. The medial efferent neurons are generally tuned to the same frequencies as their type I afferent neighbors, suggesting a highly tonotopic central reflex arc. Because this system terminates directly on outer hair cells, it is likely to regulate their role in amplifying vibrations of the basilar membrane, referred to as the cochlear amplifier. There is evidence that this action may optimize performance in detecting signals in background noise and in selective attention to auditory stimuli in the presence of competing visual stimuli [3].

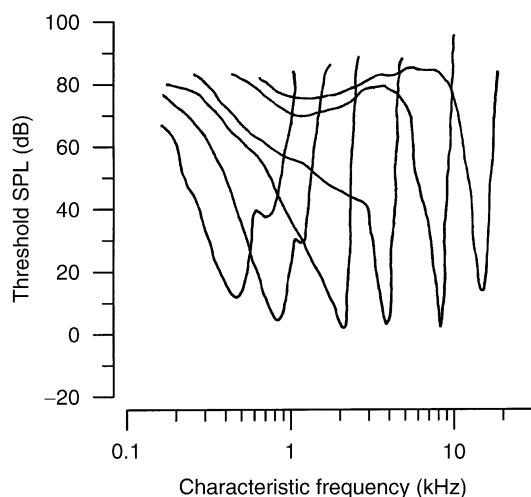
Function

All sharp electrode recordings of responses to sound from single units in the auditory nerve reported thus far have been from the type I spiral ganglion cells which receive input exclusively from inner hair cells.

No recordings have been reported from the type II spiral ganglion neurons, likely because of their small size. Auditory nerve fiber single units discharge action potentials in the absence of stimulation, quantified as an average spontaneous rate (SR). There are two distinct classes of auditory nerve fibers, one with relatively low SR (less than 15 spikes/s) and with relatively high SR with a broad distribution centered around 60 spikes/s. The majority (85% or so) are high SR. These two classes of neurons exhibit different relations between stimulus sound pressure level (SPL) and the average rate during a tone burst stimulus. The minimal SPL that produces a detectable rate increase above the SR is defined as the threshold level. Thresholds are somewhat higher for low SR than for high SR neurons. High SR neurons tend to reach a saturating discharge rate of ~300/sec with increasing stimulus level within 30 dB of threshold. Low-SR neurons can exhibit much more shallow rate-versus-level relations and may not saturate until much higher stimulus levels are reached [4].

The neural **tuning curve** is constructed by measuring the thresholds for the entire range of tone frequencies to which the neuron responds (Fig. 2).

The frequency at which the lowest threshold SPL is measured is called the characteristic frequency (CF). The characteristic frequency is determined by the location along the cochlear spiral where the type I neuron receives its input from an inner hair cell. The rapid rise of threshold above CF is due to the steep decline in vibration of the traveling wave apical to the peak. The region of the tuning curve that dips



Auditory Nerve. Figure 2 Schematic representation of **►auditory nerve tuning curves** measured from type I spiral ganglion neurons that receive input from hair cells in different regions of the cochlea, as indicated by the characteristic frequency, the frequency of minimum threshold.

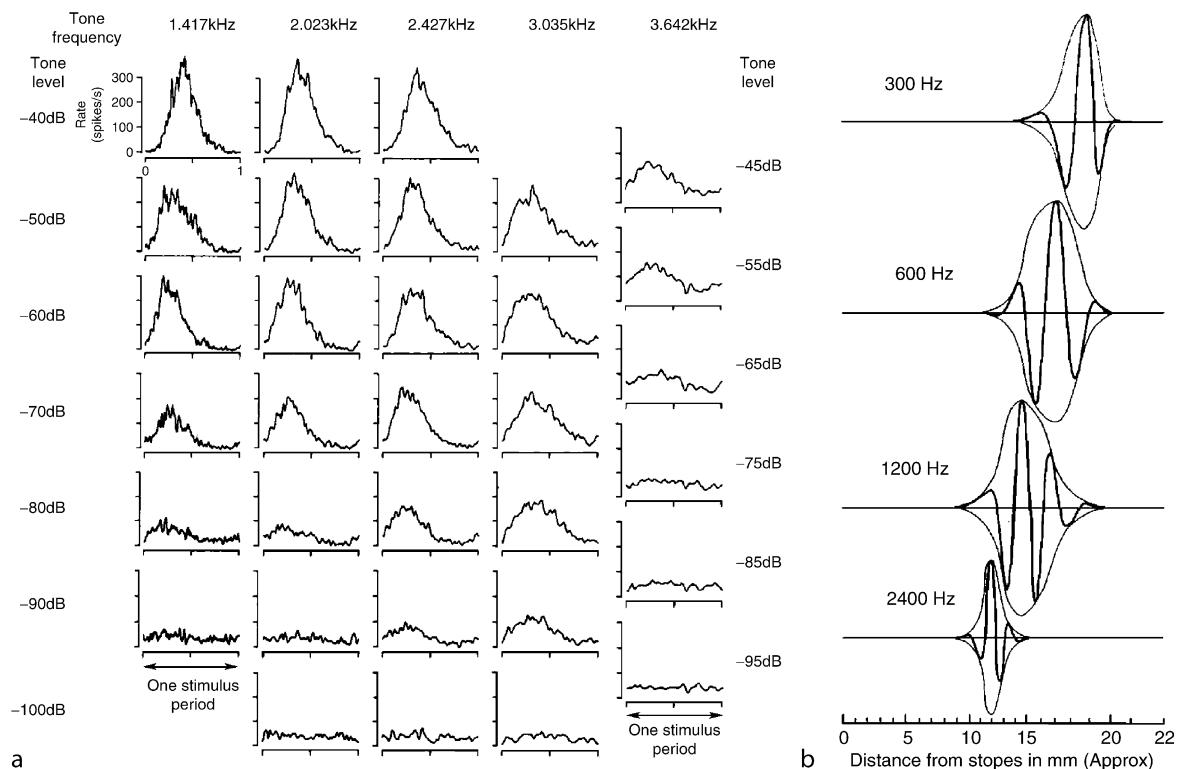
down to the CF is called the tip of the tuning curve, while the shallow low-frequency region is called the tail. The tuning curve resembles an inverted version of the low-level basilar membrane response because the amplitude of vibration of the hair bundle of the hair cells that contact the auditory neurons is determined fairly directly by the local vibration amplitude of the basilar membrane. In fact, the basilar membrane vibration threshold tuning curve closely resembles the tuning curves of both hair cells and the cochlear afferent neurons in the corresponding region of the cochlea. For stimulus level and frequency combinations above threshold the average rate of action potentials grows with increasing level and saturates as described above. So the neural threshold tuning curve allows us to know whether or not a particular neuron will respond to a stimulus with a given frequency and intensity, but nothing about how strongly it responds [4].

One of the most striking aspects of auditory nerve physiology is the ability of single neurons to encode the temporal waveform of acoustic stimuli, a phenomenon referred to as ►phase locking. This basic attribute is

illustrated in Fig. 3. Figure 3a, reproduced from a study by Don Johnson [5], shows histograms representing the relative probability that an action potential will be recorded at different phases of a single cycle of a sine wave stimulus tone.

The CF of the neuron was 2.5 kHz and the responses to tones ranging from 1.4 to 3.6 kHz all demonstrate a continuous modulation of discharge probability that corresponds to the temporal waveform of the stimulus. Note that the time axis (x-axis) for the 1.4 kHz tone represents 0.7 ms, while that of the 3.6 kHz tone is only 274 ms (the time of one period = 1/frequency), yet a modulation of probability within this short time is clearly seen. Phase-locked responses of auditory nerve units to tones have been used to demonstrate a neural version of the space-time pattern of basilar membrane vibration first described by von Békésy as a traveling wave (Fig. 3b) [6].

While fascination with temporal precision is understandable, Fig. 3a also demonstrates the equally significant feature that the encoded waveform remains remarkably undistorted, despite a change of stimulus



Auditory Nerve. Figure 3 Phase-locked responses of auditory nerve units. (a) Period histograms measured from a neuron with characteristic frequency of 2.5 kHz for tones of different frequencies and intensities. Each histogram represents one period of the stimulus, which decreases from left to right. The waveform is preserved from stimulus amplitudes near threshold to several orders of magnitude larger (bottom to top). (Reproduced with permission from [5] Copyright 1978, Acoustical Society of America) (b) Neural representations of the basilar membrane traveling wave demonstrated in recordings from a population of auditory nerve fibers in a single animal. (Reproduced with permission from [6], Copyright 1975, Acoustical Society of America).

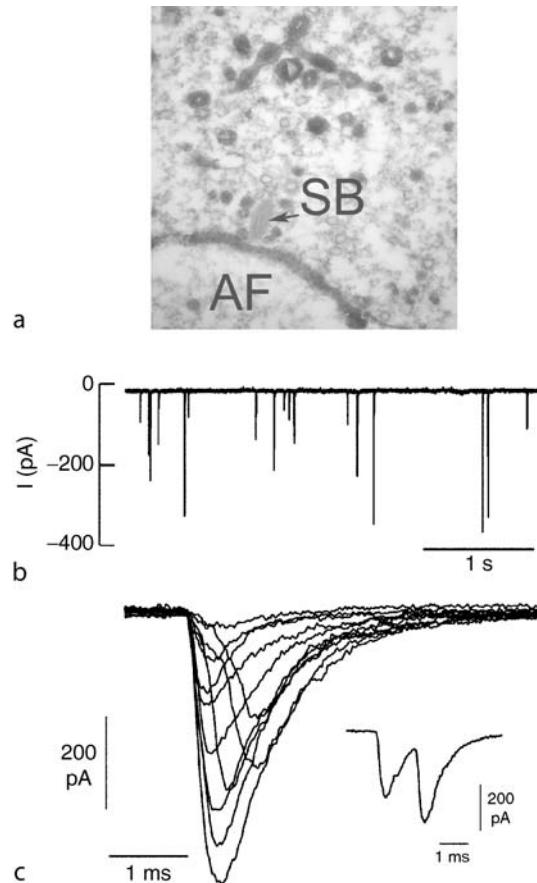
amplitude of three or more orders of magnitude. Much of this high-fidelity dynamic range is probably the result of the relatively mild compressive nonlinearity that originates in the cochlear amplifier. But it is still amazing that a signal passing through the essentially instantaneous and strongly saturating nonlinearity of the hair cell transducer, as well as what would be expected to be a highly nonlinear cascade of synaptic transmission and action potential generation, were this synapse typical of others in the nervous system. Such extreme timing precision and waveform preservation is undoubtedly essential to account for temporal auditory perceptual abilities including sound localization and the ability to extract speech from noisy backgrounds, or form mental images of auditory objects in three-dimensional acoustic space.

The cellular and molecular mechanisms that underlie this amazing performance of cochlear afferent neurons have been the focus of a spate of recent studies. Applying whole-cell patch-clamp recording techniques to hair cells has allowed presynaptic neurotransmitter release to be quantified as small cell capacitance changes caused by the fusion of synaptic vesicles with the hair cell membrane [7] at specialized active zones. The characteristic ►presynaptic dense body appears to be a temporary storage site to rapidly replenish a limited number of release sites with readily-releasable synaptic vesicles (Fig. 4a).

The dark reaction product filling the synaptic cleft and numerous vesicles and other membranous compartments within the hair cell in Fig. 4a indicates that the synaptic vesicles are derived from the cell surface. These synapses appear share basic mechanisms with other excitatory glutamatergic synapses with some important exceptions.

First, these synapses are each capable of unlimited sustained release of around 500 vesicles per second, a rate that would be expected to produce pronounced synaptic depression in conventional chemical synapses. This means that one inner hair cell can release around 10,000 vesicles per second at its ~20 afferent synapses for an indefinite period of time. This profound specialization of the inner hair cell for synaptic transmission compliments the outer hair cell's specialization for its participation in the process of amplifying sound-induced vibrations of the basilar membrane.

Second, this synaptic organization appears essential for the temporal precision and waveform preservation discussed above. Elisabeth Glowatzki has recorded spontaneous and stimulated synaptic currents from mammalian type I nerve terminals on inner hair cells using patch-clamp [8]. Even though most of her recordings represented activity of a single hair cell active zone, individual synaptic events appeared to have far too much amplitude variation to be explained by a single population of unitary quanta with a normally



Auditory Nerve. Figure 4 Ultrastructural and functional basis for auditory nerve stimulus encoding. (a) electron micrograph of an active zone at the synapse between an inner hair cell and a type I spiral ganglion neuron (AF). A characteristic presynaptic dense body (SB), with attached synaptic vesicles, is seen in the hair cell. (b) Excitatory postsynaptic currents recorded from an afferent terminal on an inner hair cell using patch-clamp show large amplitude variation. (c) Higher time resolution of postsynaptic currents reveals evidence for synchronized multiquantal release. (b and c Reprinted by permission from [5], Copyright 2002).

distributed amplitude distribution (Fig. 4b, c). Instead, synaptic events appeared to represent highly synchronized subunits that could sometimes be resolved when synchrony was not perfect (Fig. 4c). This finding confirmed preliminary measurements made by this author using sharp electrodes, but has provided the ability to address synaptic mechanisms with much greater power. This group has subsequently verified that the pronounced rate adaptation seen in the auditory nerve following the onset of a tone burst is due to synaptic depression caused by depletion of transmitter. Depolarizing voltage steps within the normal

physiological range for hair cell receptor potentials yielded a fairly linear relation between presynaptic calcium currents and the rate of synaptic transmission [9]. This near-linearity appears to arise from an interaction between the voltage-dependence of calcium channel activation, reduced driving force for calcium with depolarization and cooperativity of 3–4 calcium ions to activate exocytosis. Since the synchronized multiquantal postsynaptic potentials usually exceed the threshold for action potential initiation in the sensory neuron, there is a nearly 1:1 relation between the rate of postsynaptic action potentials and presynaptic release events. So the strong saturation of average rate observed in most auditory nerve units in the intact system is very likely due to saturation of the dc component of the hair cell receptor potential. The dc receptor potential saturates due to a combination of the compressive growth of the basilar membrane response for stimuli near CF, along with the saturating nature of the hair cell transducer function. By extension, the waveform preservation in phase-locked auditory nerve responses described above would be expected, as long as the probability of transmitter release is modulated by cycle-by-cycle variations in presynaptic calcium currents that are controlled by calcium channels with gating rate constants modulated extremely rapidly by changes in membrane voltage. Molecular mechanisms of hearing loss specifically related to synaptic transmission by the inner hair cells are beginning to be identified [10].

The implications are clear: extreme temporal precision is achieved in this system by generating excitatory postsynaptic potentials with extremely short rise-times which may reach action potential threshold in less than 50 µs. At least for most synaptic events, this means that the statistics of action potential discharge of the postsynaptic neurons is determined by the statistics of presynaptic neurotransmitter release, which is largely determined by the statistics of presynaptic voltage-gated calcium channels at the active zones. Thus, the hair cell receptor potential temporal waveform appears to be encoded in individual type I spiral ganglion action potentials in a way very similar to that of an analog-to-digital converter with a pulse code modulation scheme. The presence of as many as 20–30 statistically independent synapses per hair cell assures a sufficient bit rate to encode the hair cell receptor potential waveform with reasonably good fidelity.

References

- Ryugo DK (1992) The auditory nerve: peripheral innervation, cell body morphology, and central projections. In: Webster DB, Popper AN, Fay RR (eds) The mammalian auditory pathway: neuroanatomy. New York, Berlin, Hiedelberg, Springer-Verlag, pp 23–65
- Guinan JJ (2006) Olivocochlear efferents: anatomy, physiology, function, and the measurement of efferent effects in humans. *Ear Hear* 27:589–607
- Delano PH, Elgueda D, Hamame CM, Robles L (2007) Selective attention to visual stimuli reduces cochlear sensitivity in chinchillas. *J Neurosci* 27:4146–4153
- Ruggero MA (1992) Physiology and coding of sound in the auditory nerve. In: Popper AN, Fay RR (eds) The mammalian auditory pathway: neuroanatomy. New York, Berlin, Hiedelberg, Springer-Verlag, pp 34–93
- Johnson DH (1980) The relationship between spike rate and synchrony in responses of auditory-nerve fibers to single tones. *J Acoust Soc Am* 68:1115–1122
- Pfeiffer RR, Kim DO (1975) Cochlear nerve fiber responses: distribution along the cochlear partition. *J Acoust Soc Am* 58:867–869
- Nouvian R, Beutner D, Parsons TD, Moser T (2006) Structure and function of the hair cell ribbon synapse. *J Membr Biol* 209:153–165
- Glowatzki E, Fuchs PA (2002) Transmitter release at the hair cell ribbon synapse. *Nat Neurosci* 5:147–154
- Goutman JD, Glowatzki E (2007) Time course and calcium dependence of transmitter release at a single ribbon synapse. *Proc Natl Acad Sci USA* 104:16341–16346
- Roux I, Safieddine S, Nouvian R, Grati M, Simmler MC, Bahloul A, Perfettini I, Le Gall M, Rostaing P, Hamard G, Triller A, Avan P, Moser T, Petit C (2006) Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. *Cell* 127:277–289

Auditory Neuroscience – Introduction

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Definition

All animals, including man, must interact with their environment to survive. Such interaction is dependent on sensory information obtained from the environment, which is then processed by the brain and elicits specific motor and mental reactions. Amongst all types of sensory information, the perception of sound is one of the most important tasks the human brain has to accomplish. Sound allows us to communicate through speech (see essay on ►Speech perception), to detect prey or localize a predator. In higher and more complex life forms, sound can also be perceived as music. Sound enables us to process information about our environment in total darkness and over long distances, where visual and olfactory information might not be available.

Sound consists of pressure waves in the air or in any substrate that can transmit such waves (e.g. water). The

exact nature of sound is described by a branch of physics called acoustics (see essay on ► [Acoustics](#)).

The Auditory Neuroscience section consists of a series of essays describing how acoustic information reaches the brain, where it is processed in the brain and some fundamental properties on how we believe the information is coded. While the main focus of this section lies on the mammalian brain, it also makes references to hearing in birds as well as several invertebrates. Two chapters also touch on clinical applications, where scientifically acquired knowledge can be used to treat certain hearing-related disabilities (Fig. 1).

Ears and Auditory Brain Areas

The external ear, called the auricle, directs sound waves towards the tympanic membrane and middle ear. Within the middle ear, a set of mechanical structures functions as a transformer to increase the force of the pressure waves such that more of their energy can be transmitted into an aqueous medium. This aqueous substrate is contained in a structure called the inner ear. The inner ear contains the organs of balance, the vestibular epithelia, and the organ of hearing, called the cochlea (see essay on ► [Cochlea](#)). Within the cochlea, a sensory epithelium translates pressure waves into electrical activity that is then passed on to higher auditory centers in the brain. The cochlea

is also the first place in the auditory system where incoming sound information is sorted according to spectral components or frequency bands (see essay on ► [Tonotopic organization](#)), a characteristic of the auditory system that is preserved throughout all levels in the brain as acoustic information is passed on to higher areas. From the cochlea, acoustic information is transferred to the brain via the auditory nerve (see essay on ► [Auditory nerve](#)). The auditory nerve also carries efferent information from the brain to the cochlea, presumably to fine-tune the cochlea for specific signals.

As in other parts of the brain, neurotransmitters are responsible in the auditory system for transmitting information from one neuron to another, or from sensory cells to neurons (e.g., hair cells to cells in the cochlear nucleus) (see essay on ► [Neurotransmitters in the auditory system](#)).

The first area within the brain to receive sound information from the auditory nerve is the cochlear nucleus, which serves as a relay station for ascending auditory information, but also executes a fair amount of information processing. The cochlear nucleus itself is divided into three subnuclei (see essay on ► [Cochlear nucleus](#)). These subnuclei have remarkably different characteristics in terms of the synaptology of auditory nerve afferents, cellular phenotypes, afferents from other locations and efferent projections.



Auditory Neuroscience – Introduction. Figure 1 Afferent auditory pathways in the cat brain. AN auditory nerve, CN cochlear nucleus (D dorsal, AV and PV anterior and posterior ventral), LSO lateral superior olive, MSO medial superior olive, MNTB medial nucleus of the trapezoid body, VNLL and DNLL ventral and dorsal nucleus of the lateral lemniscus, CNIC central nucleus of the inferior colliculus, MGB and LGB medial and lateral geniculate body, SC superior colliculus, A1 primary auditory cortex, AAF anterior auditory field (drawing by David M. Harris).

Coming from the cochlear nucleus, the information is distributed to nuclei located in the auditory brainstem (see essay on ►Superior olivary complex, ►Nuclei of the Lateral lemniscus). The auditory brainstem is the first area within the brain where sound information from the two ears is compared, a phenomenon of critical importance for sound localization and hearing in noisy environments (see essay on ►Binaural pathways and processing). Neurons in both the cochlear nucleus and the auditory brainstem have specialized functional properties for the initial processing of sound signals (see essay on ►Intrinsic properties of auditory neurons).

From the brainstem, afferent information is conducted to the auditory midbrain (see essay on ►Inferior colliculus) and to the superior colliculus (see essay on ►Superior colliculus and hearing). The inferior colliculus, which comprises the auditory midbrain, acts as an integrative station as it receives input from virtually every auditory area in the brain. The superior colliculus is where acoustic information is integrated with other sensory information, such as visual and somesthetic cues.

The medial geniculate body, the principle thalamic target of neurons in the inferior colliculus is the source of auditory information to the neocortex, specifically the regions of the auditory cortex (see essay on ►Medial geniculate body, ►Auditory-motor interactions).

Eventually sound information arrives in the auditory cortex, where the conscious perception of sound is thought to be created (see essay on ►Auditory cortical areas). The perception of sound can be described with psychoacoustical experiments (see essay on ►Psychoacoustics).

As a whole, neuronal activity in the brain caused by an auditory stimulus can be detected by auditory evoked potentials. This method records patterns of voltage changes due to acoustic stimulation that can be detected with electrodes placed on the head (see essay on ►Auditory evoked potentials).

The brain areas described here are by no means static: Auditory brain centers can change their structural and functional properties in response to changing stimuli. These changes are an active process and are described as plasticity (see essay on ►Plasticity in the central auditory system).

Hearing in Birds and Invertebrates

While structurally very similar, the auditory system of birds possesses several specializations in order to process the very complex bird songs (see essay on ►Avian Auditory System). Two properties are particularly interesting. First, in contrast to the mammalian auditory system, the sensory epithelium of the hearing system in birds can regenerate sensory cells after damage, leading to functional recovery. Second, the

forebrain areas related to the production of acoustic information are hypertrophied and show remarkable seasonal plasticity in some species of songbirds.

Insects are, apart from a few species of crustacea, the only invertebrates that have been shown to exhibit a sense of hearing. The hearing mechanism in insects can be very different from the mammalian hearing system, although the basic feature of pressure wave detection is preserved (see essay on ►Invertebrate ears and hearing). Characteristic for the hearing of insects is the widespread use of substrate sound.

Clinical Applications

Two essays on clinical applications related to hearing loss are also included in this volume: Hearing Aids and Cochlear Implants. Hearing Aids amplify sound to make it more accessible, e.g. in the case of presbycusis. Cochlear Implants on the other hand stimulate a functional auditory nerve directly. This can restore hearing when the sensory epithelium is not functional or irreparably damaged (see essays on ►Hearing aids, ►Cochlear implant).

Epilogue

To conclude, it is worthy of note that the hearing system, in contrast to the visual or the sensory system, cannot rely on a spatial representation of stimuli on its receptor surface. Frequency is extracted by the sensory epithelium via a matching of the physical properties of the sound waves to unique structural and functional properties of the sensory epithelium. It is solely because of an elaborate computational mechanism that a sound source can be understood and localized.

While often in the shadow of the literally more colorful visual system, the field of auditory neuroscience is a fascinating subject to study and unique in terms of its complexity.

Acknowledgments

We thank David M. Harris for the sketch of the cat auditory system; Nicole C. Schmitt, Vincent Lin and Henry Ou for comments on the manuscript.

Auditory Pathways

Definition

Auditory pathways are neural connections between auditory centers of the brain along which mainly information originating from the ears is passed on.

Auditory Processing

- Binaural Pathways and Processing

Auditory Psychophysics

- Psychoacoustics

Auditory Sensillum

- Invertebrate Ears and Hearing

Auditory Space Map

- Superior Colliculus and Hearing

Auditory System

Definition

The network of auditory centers and auditory pathways of the brain involved in processing mainly information from the ears. The auditory system divides into two parts, the ascending part and the descending part. The ascending system starts in both ears and ends in the highest auditory representations, which are the auditory cortex where mammals including humans are concerned. The descending system starts with projections from the auditory cortex to lower centers and ends with nerve fiber terminals in the inner ear.

Auditory System of Birds

- Avian Auditory System

Auditory Thalamus

- Medial Geniculate Body

Auditory Tuning

Definition

Ability of the auditory system to discriminate between sounds of different frequencies.

- Hearing Aids

Aura

Definition

Focal, reversible neurologic dysfunction that precedes, accompanies or rarely follows a migraine headache. Most aura is visual, developing over several minutes and usually lasting less than 60 min. An aura may also precede some epilepsies, e.g., complex partial seizures (temporal-lobe or psychomotor seizures).

- Complex Partial Seizures (Temporal-lobe or Psychomotor Seizures)
- Headache

Autapse

KAZUHIKO YAMAGUCHI

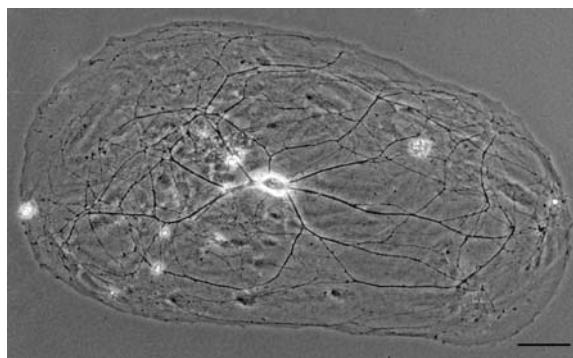
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Synonyms

Self-synapse, recurrent synapse

Definition

► **Autapse:** ► **Synapse** formed by the axon of a neuron on its own dendrites *in vivo* or *in vitro*. Autapses of solitary neuron grown on a micro-island of collagen or non-neuronal cells utilized widely as a simple, useful



Autapse. Figure 1 Solitary hippocampal neuron cultured on a glial micro-island that has many autapses, synapses formed by the axon of a neuron on its own dendrites. Bar, 50 μ m.

model of synaptic transmission (Fig. 1). Originally, autapse was defined in rabbit cortical neuron impregnated with Golgi methods [1].

Characteristics

Functional autapse was found in solitary neuron cultured on a micro-island (diameter, 300–500 μ m) of cardiac myocytes [2]. Acetylcholine (ACh) released from synaptic terminal onto itself, at autapses, evoked fast nicotinic excitatory postsynaptic potentials (►EPSPs). Autapse provides an advantageous model to investigate factors affecting differentiation and development of a single neuron. In addition, autapse is adequate for image-analysis of single neurons using fluorescent dyes. Especially, autapse has a unique value to investigate the heterogeneity of presynaptic terminals belonging to one neuron.

Purpose

Autapse provides the simplest model of epilepsy [3]. If a solitary hippocampal neuron grown in the micro-island culture has excitatory autaptic connections, it generates paroxysmal depolarizing shifts (PDSs) and sustained depolarizations, characteristic epileptiform activities. Thus, kynureneate, a non-specific blocker of glutamate receptors, is required to be added in culture medium. Washout of kynureneate elicits large depolarizing events or sustained depolarization with repetitive firings. Both NMDA- and AMPA-receptors are involved in the generation of these epileptiform activities. The generation mechanism for such epileptiform activities is attributable to self-regenerative excitatory pathway through autaptic connection. The autapse of excitatory neurons provides the opportunity to study in a very simple context the pharmacology of the initiation, continuation and termination of epileptiform activities [3]. A computational approach to examine conditions for long-lasting firing of autapse is also performed.

To widely utilize autapse as one of the standard models of the central synapse, basic characteristics of autaptic transmission should be proved normal. Electrophysiological characteristics of autaptic transmission of hippocampal neurons are analyzed by using the patch-clamp method [4]. Using this voltage-clamp method, epileptiform discharge is suppressed by controlling the membrane potential. For excitatory autapse, excitatory post-synaptic current (►EPSC) amplitude is changed depending on the holding voltage of the cell body, and the estimated reversal potential is -4 mV, which is almost the same as that for glutamate receptor channels in a usual synapse. This indicates that both autaptic and synaptic glutamate receptor channels have common ion-selectivity. Some excitatory autaptic transmission, like some excitatory synaptic transmission, is dual function: an early, rapid non-NMDA component and a prolonged NMDA-component, the latter is blocked by Mg^{2+} in a voltage-dependent manner. Some neurons make inhibitory autapse, which shows similar physiological and pharmacological properties to those of usual inhibitory synapse. Under a condition of low ►release probability, amplitude of autaptic EPSC shows probabilistic fluctuation. In the tail of stimulus-evoked large EPSC, spontaneous mini-EPSCs (►asynchronous EPSCs) appear, which are attributable to the ►quantal release of glutamate. The probability of recording an autaptic current of a particular size is well described by the quantal theory of transmitter release, like physiological synapse. In general, autaptic transmission is considered the same as the normal synaptic transmission. Therefore, autapse provides a simple and reliable model for the synaptic transmission in mammalian CNS. Especially, autapse contributes to the analysis of synaptic properties of CNS neurons cultured from gene knocked-out animals.

Functional analysis of proteins relating to ►presynaptic exocytosis are difficult in the mammalian central synapse, because the size of the pre-synaptic terminal of the mammalian central synapse is very small (usually, less than 1 μ m), and synaptic exocytosis is composed of several sub-steps and each step involves various types of proteins. A reconstruction system such as *Xenopus* oocyte for ion channel is not available for presynaptic exocytosis. Furthermore, presynaptic exocytosis is a very fast process. Time between spike arrival at the presynaptic terminal and transmitter release is less than half of a millisecond. Therefore, biochemical analysis of protein-protein interaction *in vitro* alone is not sufficient for the understanding of the molecular mechanism of the presynaptic exocytosis. To investigate the molecular mechanism in the presynaptic exocytosis, autapse of central neurons cultured from a gene knocked-out animal is widely utilized as one of the standard tools [5,6]. Presynaptic exocytosis consists

of several sub-steps such as docking, priming, membrane-fusion and endocytosis. Autapse has the advantage of estimating the total size of the ►readily releasable pool, a physiological counterpart of the docked vesicle pool, of each neuron. The total RRP size of autapses of one neuron is around several thousand quanta, estimated by hypertonic sucrose methods. Each action potential elicits release of a few hundred quanta from one neuron. Release probability, estimated from the released vesicle number divided by the readily releasable pool size, is several percent of the readily releasable pool [6]. Applying such a quantitative analysis to the autaptic transmission of a gene knocked-out animal, physiological function of a particular protein is assigned to some particular sub-steps of presynaptic exocytosis. For example, neurons lacking complexins, presynaptic proteins, show a remarkable reduction in release probability, while the readily releasable pool size is normal. Reduction in transmitter-release is attributable to decreased Ca^{2+} sensitivity of the membrane fusion process. Complexins are demonstrated to be acting at or following the Ca^{2+} triggering step of fast synchronous transmitter release by regulating the exocytosis Ca^{2+} sensor, its interaction with the core complex fusion machinery, or the efficiency of the fusion apparatus itself [5].

Autapse provides a model system for investigating the presynaptic type of synaptic plasticity. In the micro-island culture, one neuron has a few hundred presynaptic sites where synaptic vesicles are accumulated. These presynaptic sites, identified as synaptophysin- or synapsin I-immunoreactive sites, are not homogeneous in functional features. In autapses of cultured dentate gyrus neurons, about one third of the synaptophysin-positive sites are functional release sites that are visualized with styryl fluorescent FM dyes. FM dyes are up-taken by synaptic vesicle membranes through endocytosis following membrane-fusion at the functional autaptic terminals, but not at silent presynaptic sites. The presence of silent presynaptic sites is also demonstrated electrophysiologically. Some cortical neurons in the micro-island culture show spontaneous autaptic mini-EPSCs, but no evoked EPSC, which indicate silent presynaptic site [7]. In autapses of cultured dentate gyrus neurons, silent presynaptic sites are converted into functional ones by activation of the PKA cascade, which would be the underlying mechanism for the synaptic plasticity at the mossy fiber terminal in the hippocampus [8].

Autapse of central neuron cultured on a glial micro-island is utilized to address glial cell – neuron interaction in synaptic transmission. Evoked synchronous release of glutamate from an autaptic terminal activates rapid electrogenic glial glutamate-transporter currents, while clearance of released glutamate by glial cells may affect the decay time-course of autaptic EPSC [9].

Neuronal synaptogenesis is enhanced by the glial cell in the co-culture system; however, it is unclear whether diffusible or membrane-bound astrocyte-derived factors are responsible for the increase in synaptogenetic efficiency. To address this question, autapse provides an advantageous experimental system [10]. Under the condition of continual supplementation of astrocyte-diffusible factors from the rims of culture dishes, solely grown hippocampal neurons on a micro-island of collagen also forms autapses. After 8–9 days in culture, neurons may or may not be overlaid with astrocytes. Local contact with astrocytes enhances autaptic synaptogenesis robustly via integrin receptor elicited PKC activation [10]. Autapse is a useful model system for exploring both soluble and cellular factors affecting synaptogenesis.

Principles

Though autaptic connection exists in normal cortical neurons *in vivo* [1], autapse in cultured neurons is formed under rather artificial conditions, the micro-island culture. A solitary neuron is grown on the micro-island and forms an autapse. However, neurons in the multi-cellular culture of the micro-island rarely form autapses.

To make the micro-island culture [3], the cover glass is coated with agarose and then attached to the bottom of a holed-plastic culture dish by Sylgard. Collagen solution is then sprayed from a glass micro-atomizer onto a dried film of agarose. The collagen is cross-linked by ammonium gas. The diameter of the micro-island distributes 50–500 μm . The exposed agarose surface is resistant to cell attachment. Glial cells, plated 1–2 days before neural cell plating, grow to cover the micro-island. Hippocampal neurons of newborn rat, isolated by papain-treatment, are plated at a low density (2,000 cells per cm^2). Soluble glial factors are supplied from glial cells grown on the outer rims of the plastic bottom. After 7–9 days in culture, neurons solely grown on the micro-island form an autaptic connection. A blocker for glutamate receptors (kynurename) or NMDA receptor (APV) is required to obtain healthy autaptic responses.

Advantage and Disadvantage

Advantage

As a simple model of synaptic connection, autapse provides the following advantage; first, all autaptic terminals belonging to one cell share common basic properties, such as excitatory or inhibitory, though there are heterogeneity in detail. Cell types are selected by means of electrophysiology, pharmacology, immunocytochemistry and GFP-tag methods. Selective culture of the neurons from a specific brain region, such as “hippocampus CA3” or “dentate gyrus” is also available. Second, quantification of synaptic terminals per one neuron is possible in the autaptic system. Thus, autapse

provides a reliable assay system to examine synaptogenesis-ability of various chemicals or cells [10]. Third, unlike conventional approaches, in which pairs of neurons and electrodes are required (one presynaptic, the other postsynaptic), physiological experiments using autapse require only one electrode. Furthermore, we can inject chemicals into the cell through a whole-cell recording electrode. Fourth, since all presynaptic terminals contact on one neuron, it is possible to estimate the size of the total releasable pool belonging to one neuron [5,6]. Fifth, autapse provides a unique system to address heterogeneity among synaptic terminals from one neuron.

Disadvantage

Though autaptic connection in cultured neurons provides a useful assay system to elucidate the roles of proteins and other chemicals in synaptic transmission, synaptogenesis and so on, it has a limitation. The age of the animal is restricted to be very young, since neurons should be cultured. Basic physiological properties of autapse and physiological synapse are proved the same [4], but this does not mean that all properties of autapse are necessarily the same as those in normal synapse. Even though autaptic connection exists in mammalian cortical circuits *in vivo*, most axon collaterals terminate to other neurons. In autapse, all axon terminals contact on one cell. Therefore, possible effects of a retrograde signal on a synaptic terminal could be different between autapse and normal synapse. In excitatory autapse, synaptic activities are restricted to some extent during culture. This restriction may affect autaptic synaptogenesis. Nevertheless disadvantage, autapse provides very useful and the simplest model of the neuronal circuit for investigation of synaptogenesis, synaptic transmission, plasticity and modulation.

References

1. Van der Loos H, Glaser EM (1972) Autapse in neocortex cerebri: synapses between a pyramidal cell's axon and its own dendrites. *Brain Res* 48:355–360
2. Furshpan EJ, MacLeish PR, O'Lague PH, Potter DD (1976) Chemical transmission between rat sympathetic neuron and cardiac myocytes developing in microculture: Evidence for cholinergic, adrenergic and dual-function neurons. *Proc Natl Acad USA* 73:4225–4229
3. Segal MM (1991) Epileptiform activity in microcultures containing one excitatory hippocampal neuron. *J Neurosci* 65:761–770
4. Bekkers JM, Stevens CF (1991) Excitatory and inhibitory autaptic currents in isolated hippocampal neurons maintained in cell culture. *Proc Natl Acad Sci USA* 88:7834–7838
5. Reim K, Mansour M, Varoqueaux F, McMahon HT, Südhof TC, Brose N, Rosenmund C (2001) Complexins regulate a late step in Ca^{2+} -dependent neurotransmitter release. *Cell* 104:71–81
6. Yamaguchi K, Tanaka M, Mizoguchi A, Hirata Y, Ishizaki H, Kaneko K, Miyoshi J, Takai Y (2002) A GDP/GTP exchange protein for the Rab3 small G protein family up-regulates a postdocking step of synaptic exocytosis in central synapses. *Proc Natl Acad Sci USA* 99:14536–14541
7. Kimura F, Otsu Y, Tsumoto T (1997) Presynaptic silent synapses: Spontaneously active terminals without stimulus-evoked release demonstrated in cortical autapses. *J Neurophysiol* 77:2805–2815
8. Tong G, Malenka RC, Nicoll RA (1996) Long-term potentiation in cultures of single hippocampal granule cells: A presynaptic form of plasticity. *Neuron* 16:1147–1157
9. Mennerick S, Zorumski CF (1994) Glial contributions to excitatory neurotransmission in cultured hippocampal cells. *Nature* 368:59–62
10. Hama H, Hara C, Yamaguchi K, Miyawaki A (2004) PKC signaling mediates global enhancement of excitatory synaptogenesis in neurons triggered by local contact with astrocytes. *Neuron* 41:405–415

Autism (Autistic Disorder, Childhood Autism)

Definition

Autism is classified as a pervasive neurodevelopmental disorder including key characteristics such as abnormal communication skills and social interactions as well as repetitive and stereotyped patterns of behavior. Autism is thought to result from defective neuronal circuitry.

Autoantibodies

Definition

Serum immunoglobulins that react to self-antigens (own body).

Auto-associative Memory

Definition

A neural network that associates patterns with themselves to recall a stored pattern by receiving a noisy or incomplete version of that pattern.

► **Associative Memory**

Auto-associative Network

Definition

A neural circuit in which the outputs of a region feedback as input onto elements within that same region.

Autobiographical Memory

Definition

Remote memory is classified into autobiographical memory and public memory. Autobiographical memory is a recollection of the earlier events of one's own life.

It includes factual knowledge about oneself (e.g., addresses where lived, names of teachers/friends/colleagues) so-called personal semantics, and one's personal memory of events or episodes specifiable time and place so-called autobiographical incidents.

► Long-Term Memory

Autocellular Septate Junctions

Definition

Septate junctions are formed between the plasma membrane of the same glia cells.

► Alternative Splicing and Glial Maturation

Auto-Covariance Function

Definition

The cross-covariance is a linear measure of the relationship between two functions of time (variables), one taken at time t and the other at time t_i . The cross-covariance is computed as the average of the products of the deviations of each variable from their respective mean. The auto-covariance is the cross-covariance of a function at time t and itself at time t_i .

► Signals and Systems

Autocrine Feedback Control

Definition

A series of molecular events that originate on the same cell secreting neurotransmitters or hormones and possessing membrane receptors selective for these molecules (autoreceptors). The activated autoreceptors mediate a sequence of reactions, which usually compensate the original triggering event.

Autogenetic Excitation and Inhibition of Motoneurons

Definition

Excitation and inhibition of the motoneurones innervating the muscle from which the afferents eliciting the excitation and inhibition originate. Autogenetic inhibition was originally described as a disynaptic inhibition of motoneurones evoked by activation of Ib afferents from muscle tendons belonging to the muscle innervated by the motoneurones. The interneurones in the pathway (Ib inhibitory interneurones) receive input from a number of sensory modalities (including gr. Ia afferents and cutaneous afferents) in addition to descending motor tracts and the transmission in the pathway may therefore be greatly modulated in relation to movement. Subsequent experiments have demonstrated that the inhibition is depressed during functional tasks such as walking, whereas transmission in excitatory Ib pathways is facilitated. These excitatory pathways include at least a disynaptic autogenetic excitatory pathway in addition to a longer (polysynaptic) pathway.

► Integration of Spinal Reflexes

Autografting

Synonym: autotransplantation

Transplantation of tissues or organ pieces between the different parts of the same individual or animal.

Autoimmune Demyelinating Disorder (ADD)

Autoimmune Demyelinating Disorder (ADD) is an autoimmune disorder affecting nervous system, leading to neurodegeneration.

►Autoimmune Demyelinating Disorders: Stem Cell Therapy

vitro and in vivo – into a wide range of specialized (post-mitotic) daughter cells (►cellular potency). Two major categories of stem cells exist in mammals: ►embryonic stem (ES) cells, derived from blastocyst, and adult (somatic) stem cells, which are found in adult tissues.

Neuroprotection

Cellular and molecular mechanisms spontaneously taking place – or being fostered by a given therapy – within the central as well as peripheral nervous system by which neural cells are protected from apoptosis and/or degeneration (for example following a brain injury or as a result of chronic neurodegenerative diseases) (►neuroprotection).

Multiple Sclerosis

Chronic disease of the central nervous system (CNS) occurring as a consequence of an autoimmune attack against certain (*self*) myelin antigens. ►Multiple sclerosis (MS) primarily affects young adults, with an age of onset typically between 20 and 40 years, and is more common (2:1 ratio) in women than in men. Distinctive characteristics of MS is the presence of multifocal perivascular infiltrates in the CNS white matter, mainly composed of cells of the immune system (e.g., macrophages and lymphocytes), that cause demyelination and secondary axonal degeneration. Symptoms of MS include changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, and pain. More severe MS cases can also be associated with impaired mobility and disability.

Autoimmune Demyelinating Disorders: Stem Cell Therapy

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Synonyms

Autoimmune demyelinating disorder ADD; Multiple sclerosis; Experimental autoimmune encephalomyelitis; Neuroprotection; Remyelination; Neural stem cells; Cell transplantation

Definitions

Stem Cell Transplantation

Medical procedure in the field of hematatology, oncology or regenerative medicine that involves transplantation of ►stem cells (►stem cell transplantation) of different origin (e.g., ►neural stem cells, hematopoietic stem cells, mesenchymal stem cells, cord blood stem cells, etc.). It is most often performed on people with diseases of the blood or bone marrow, certain types of cancer or diseases of the central nervous system [e.g., ►multiple sclerosis (MS), Parkinson's disease (PD), Huntington's disease (HD), etc.]. Transplanted stem cells are usually administered either locally (e.g., intraparenchymally), intravenously or intrathecally (e.g., through the cerebrospinal fluid circulation). The main aims of the procedure are either: the repopulation of the host bone marrow and the production of new blood cells, the replacement of lost and/or injured neural cells or the induction of peripheral immune tolerance.

Stem Cells

Stem cells are primary cells common to all multi-cellular organisms that retain the ability to ►self-renew through asymmetric cell division and can differentiate – both in

Experimental Autoimmune Encephalomyelitis (EAE)

Widely used animal model of the human demyelinating disease MS. ►Experimental autoimmune encephalomyelitis (EAE) is generally induced in rodents or primates by either immunization with myelin antigens [e.g., myelin oligodendrocyte glycoprotein (MOG), proteolipidic protein (PLP), myelin basic protein (MBP), etc.] in adjuvant (►active induction) or adoptive transfer of myelin-specific T cells (►passive induction). Induction of EAE typically results in ascending flaccid paralysis of limbs with inflammation and tissue damage primarily targeting the spinal cord.

Neural Stem Cells

Heterogeneous population of mitotically-active, self-renewing, multipotent cells of both the developing and the adult central nervous system (CNS). Neural stem cells (NSCs) have been successfully isolated from the entire embryonic as well as adult CNS. The ganglionic eminence(s), in the embryo, and both the subventricular zone (SVZ) of the lateral ventricles and the sub-granular zone (SGZ) of the hippocampus dentate gyrus (DG), in the adult, have been shown to consistently contain

stem-like cells capable of driving neuro- and gliogenesis. These regions are then defined as highly specialized ►CNS germinal niches. Protocols to obtain in vitro large-scale numbers of NSCs are available, thus supporting the concept that these cells might represent a renewable source of uncommitted ready-to-use cells for transplantation purposes.

Characteristics

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) (►Autoimmune Demyelinating Disorder (ADD)), whose aetiology is still unknown. MS pathology is characterized by the presence within the CNS of perivascular lympho/mononuclear inflammatory infiltrates inducing patchy demyelination, axonal loss and reactive astrogliosis/scarring.

Substantial proportion of demyelinated lesions within the CNS from MS patients are fully or partially remyelinated. Furthermore, in some MS cases the clinical course appears to be benign with no long-term accumulation of disability. Characteristic sclerotic plaques are identified in individuals without neurological disability, suggesting the existence of “►clinically silent” MS.

In this context, spontaneous remyelination may spontaneously occur and some axons may recover their capacity to conduct action potentials [1]. However, spontaneous repair is inefficient over time and, in the vast majority of MS cases, neurological disability progresses as irreversible axonal loss and neuronal damage accumulates [1].

Remyelination Failure in MS

The most likely causes of remyelination failure in MS may be summarized as follows: (i) selective depletion of oligodendrocyte progenitor cells (OPCs) around demyelinating areas; (ii) failure of the recruitment of OPCs to the demyelinated areas; (iii) failure of recruited OPCs to differentiate into remyelinating oligodendrocytes; (iv) inhibition of remyelination as a net result of protective vs. detrimental effects of cytokines; (v) anatomical and molecular inhibition of remyelination associated with astrogliosis/scarring; and (vi) acute and/or chronic axonal loss and/or dysfunction [1,2].

Cell-Based Therapies for Myelin Repair in Autoimmune CNS Demyelination

The intrinsically complex nature of MS poses great challenges for cell-based remyelinating therapies. Two major requirements have to be satisfied: (i) an unlimited source of cells; and, (ii) the possibility of accessing several CNS damaged areas at the same time. Current studies are mostly aimed at addressing some preliminary issues that need to be solved before prospecting

any potential human application of cell-based therapies such as (i) the ideal stem cell source for transplantation; (ii) the route of cell administration; (iii) and, the differentiation and persistence of cells transplanted into the targeted tissue.

Several experimental transplantation procedures aimed at restoring the myelin architecture within CNS demyelinated areas have been developed so far. Different types of myelin-forming cells have been transplanted into rodent models of either genetic, chemical or autoimmune CNS demyelination. These approaches show serious limitations. In particular, lineage-restricted myelin-forming cells – either OPCs, Schwann cells or olfactory ensheathing cells – possess in vitro limited growth and expansion characteristics and, once transplanted, may drive remyelination only within restricted CNS areas close to the transplantation site [3].

The functional and morphological properties of stem cells might therefore represent a promising alternative for transplantation approaches in MS [4].

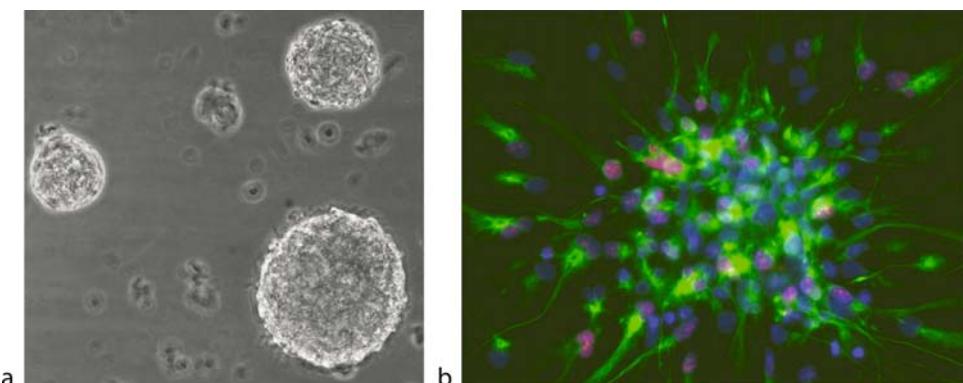
The therapeutic use of embryonic stem (ES) cells is still constrained by some key issues – such as feeder-independent growth (expansion) and in vivo teratocarcinoma formation – which need to be solved before proposing any ES cell-based therapy for human applications.

Adult stem cells represent a ready-to-use cell source for cell-based therapies, since they can be obtained by different tissues (e.g., bone marrow, brain, etc.) and have been widely used in experimental and clinical settings in vivo without causing tumor formation and overt toxic/side effects.

Neural Stem Cells

Mammalian neural stem cells (NSCs) support neurogenesis and gliogenesis within restricted areas (germinal niches) of the CNS throughout adulthood, can undergo extensive in vitro expansion and possess the capacity to generate a progeny of daughter cells which can integrate into and repair the tissue of origin. These cells show: (i) growth factor (GF)-dependent proliferation and stable growth rate; (ii) capacity for ►self-renewal; (iii) multipotentiality; and, (iv) functional plasticity either over serial in vitro passaging or after several freezing-thawing cycles [4] (Fig. 1).

The route of cell administration represents a major constraint for NSC transplantation and appears to be dependent on the CNS lesion site(s). The anatomopathological features of certain focal CNS disorders, such as Parkinson’s disease (PD) or acute spinal cord injury (SCI), might suggest that direct local (*intraleisional*) cell transplantation might facilitate tissue regeneration, while the multifocality of other CNS disorders – such as MS and epilepsy – would represent a major limitation for *intraleisional* cell-transplantation approaches. In multifocal CNS disorders,



Autoimmune Demyelinating Disorders: Stem Cell Therapy. **Figure 1** In vitro characteristics of NSCs used for transplantation in CNS autoimmune demyelinating disorders. Upon continuous mitogen stimulation in serum-free growth media, NSCs appear in vitro as free-floating neurospheres (A, phase contrast). After plating on proteic substrates (e.g., poly-L-lysine, matrigel, etc.), display chain-like radial migration, still undergo cell cycle and express Ki67 (B, red) while maintaining immunoreactivity for nestin (green). Nuclei in B have been counterstained with dapi (blue). Magnification in A and B 40 X.

systemic (e.g., intravenous, intrathecal) transplantation of NSCs can be therapeutically efficacious owing to the ability of transplanted cells to follow, via the blood stream or cerebrospinal fluid circulation, a gradient of chemoattractants (e.g., pro-inflammatory cytokines and chemokines) occurring at the site of inflammatory lesions [4,5]. Specific homing of transplanted NSCs has been shown in SCI, epilepsy, and stroke. However, the exact molecular mechanism sustaining this phenomenon has been detailed, so far, only in experimental autoimmune encephalomyelitis (EAE). Tethering, rolling, and firm adhesion to inflamed endothelial cells and extravasation into inflamed CNS areas are sequentially mediated by the constitutive expression of functional cell adhesion molecules (CAM) (e.g., CD44), integrins (e.g., $\alpha 4, \beta 1$), and chemokine receptors (e.g., CCR1, CCR2, CCR5, CXCR3, CXCR4) on NSC surface [4,5].

Therapeutic Functions of Transplanted NSCs

Irrespective of the characteristics of the experimental disease and type of inflammation, functional recovery obtained by NSC transplantation barely correlates with absolute numbers of transplant-derived newly generated terminally differentiated neuronal cells. Transplantation of NSCs into rodents with experimental PD or Huntington's disease (HD), very scarcely differentiate into tyrosine hydroxylase (TH)-immunoreactive neurons despite significant behavioral improvement. Mice with SCI, acute stroke and intracerebral hemorrhage do improve despite pathological evidence of preferential astroglial fate of transplanted NSCs. The large majority of NSCs injected into mice with experimental cerebral hemorrhage or with acute ischemic stroke, express markers of undifferentiation (e.g.,

nestin) when surrounding damaged CNS areas. In EAE, very low differentiation of transplanted NSCs into myelin forming oligodendrocytes is accompanied by striking neurophysiological evidence of axonal protection and remyelination. In the very same context, more than 20% of transplanted cells reaching inflammatory demyelinated areas do not express differentiation markers. This limited terminal differentiation and propensity for maintaining an undifferentiated phenotype within the host tissue, suggests that transplanted NSCs might also be therapeutic efficacious via a bystander mechanism(s) alternative to cell replacement. Indeed, transplanted NSCs reduce the scar formation and/or increase survival and function(s) of endogenous glial and neuronal progenitors surviving to the pathological insult. This neuroprotective effect is accompanied by increased in vivo bioavailability of major neurotrophins [e.g., nerve growth factor (NGF), brain-derived growth factor (BDNF), etc.]. Also, transplanted NSCs promote bystander immunomodulation as they release soluble molecules (e.g., cytokines and chemokines), express immune-relevant receptors (e.g., chemokine receptors, CAMs), capable of profoundly altering the inflammatory environment and up-regulate membrane expression of certain functional death receptor ligands (e.g., FasL, TRAIL, Apo3L) by which they induce programmed cell death (apoptosis) of inflammatory T lymphocytes [5]. Transplanted NSCs also significantly and specifically contribute to the down-regulation of effector functions of inflammatory T cells and macrophages within both the target tissue as well as within draining lymph nodes [6]. Major NSC transplantation studies in animal models of CNS disorders are summarized in Table 1 (reproduced from [4]).

Autoimmune Demyelinating Disorders: Stem Cell Therapy. Table 1 Neural stem cell (NSC) transplantation studies in animal models of CNS disorders

Neural stem cell source	Route of cell administration	Disease model	Mechanism(s) of therapeutic efficacy		Outcome
			Cell replacement	Bystander effect	
<i>Demyelinating disorders</i>					
Adult brain SVZ NSCs (mouse)	Icv and iv single cell injection	Chronic EAE in mice	Oligodendroglial and neuronal differentiation	Rescue of endogenous OPCs and modulation of NGFs in vivo	Attenuation of clinical, neurophysiological and pathological parameters of EAE
Adult brain SVZ NSCs (mouse)	Iv single cell injection	Relapsing EAE in mice	Not tested	Induction of apoptosis of CNS-infiltrating T lymphocytes	Attenuation of clinical, and pathological parameters of EAE
Adult [19–64 years] brain NSCs (human)	Intralesional (<i>epicentre</i>) cell transplantation	EB-X focal demyelination of the thoracic (T10) spinal cord dorsal column in rats	Schwann cell-like driven remyelination (P0 immunoreactive cells)	Not tested	Functional restoration of peripheral nerve conduction
Adult brain striatal NSCs (rat)	Icv neurosphere injection	Acute EAE in rats	Not tested	Inhibition of MOG-specific lymphocyte proliferation	Attenuation of clinical and pathological parameters of EAE
<i>Traumatic brain injury</i>					
Neonatal cerebellum C17.2-CD NSCs (mouse)	Stx intraparenchymal (<i>ipsi or contralateral</i>) cell transplantation	Parieto-temporal CCI brain injury in mice	60% neuronal and 40% astroglial differentiation	Not tested	Improved coordination and vestibulomotor functions
Embryonic [E14.5] brain NSCs (mouse)	Stx ipsilateral intrastratial neurosphere transplantation	Fronto-parietal CCI brain injury in mice	No neuronal or astroglial differentiation, 85% of NG2 immunoreactivity	Not tested	Improvement of motor and learning performances No effects on necrotic cavity size or hippocampal degeneration
<i>Stroke</i>					
Neonatal cerebellar C17.2-CD NSCs (mouse)	Intralesional (<i>infarction cavity</i>) transplantation of PGA-NPC complex	Transient (3 hours) unilateral CCAO in mice	Neuronal, astro- and oligodendro-glia differentiation	Decrease mononuclear cell infiltration and astrogliosis	Not tested
Embryonic [E14] hippocampal MHP36 NSCs (mouse)	Stx unilateral striatal cell graft	Transient (17 min.) bilateral CCAO in mice	50% neuronal differentiation	Rescue of endogenous neurons	Not tested
Foetal [15 weeks] brain immortalized [clone HB1. F3]NSCs (human)	Iv single cell injection	Stx intrastratial administration of bacterial collagenase in mice	10% neuronal and 75% astroglial differentiation	Increase of viable NGFs	Improvement of motor performances

Autoimmune Demyelinating Disorders: Stem Cell Therapy. Table 1 Neural stem cell (NSC) transplantation studies in animal models of CNS disorders (Continued)

Neural stem cell source	Route of cell administration	Disease model	Mechanism(s) of therapeutic efficacy		Outcome
			Cell replacement	Bystander effect	
Foetal [15 weeks] brain immortalized [clone HB1. F3] NSCs (human)	Iv single cell injection	Transient (90 min,) MCAO in mice	20% neuronal and 60% astroglial differentiation 20% undifferentiation	Decreased atrophy Increase of viable NGFs	Lower sensory motor deficits
Fetal [16–20 weeks] brain NSCs (human)	Stx multiple cortical cell deposits	Transient (1 hour) distal MCAO in rats	50% neuronal and 15% astroglial differentiation	Less macrophage/microglial cell infiltration at lesion borders	Not tested
Parkinson's disease					
Neonatal cerebellar C17.2-CD NSCs (mouse)	Stx unilateral cell graft in the SN-VTA	MPTP-induced nigrostriatal degeneration in mice	10% neuronal differentiation	Rescue of endogenous TH ⁺ neurons Increase of viable GDNF	Decrease of amphetamine-induced turns
Foetal [10–12 weeks] brain NSCs (human)	Stx bilateral (CN) and unilateral (SN) cell graft	MPTP-induced nigrostriatal degeneration in monkeys	Low neuronal differentiation	Rescue of endogenous TH ⁺ neurons	Not tested
Foetal [12–20 weeks] brain NSCs (human)	Stx unilateral intrastriatal neurosphere graft	MPTP-induced nigrostriatal degeneration in mice	Infrequent TH ⁺ immunoreactivity	Not tested	Not tested
Foetal [P3] brain SVZ NSCs (mouse)	Stx unilateral intrastriatal graft of VM neurons/ NPCs (1:1 and 1:8 ratios)	6-OHDA-induced nigrostriatal degeneration in rats	No evidence of neuronal differentiation. 12.5–31% increased neuronal survival, decrease of caspase-3 ⁺ /TH ⁺ neurons, less cell debris,	Increase of viable Shh	Decrease of amphetamine-induced turns
Foetal [22 weeks] brain NSCs (human)	Stx unilateral intrastriatal neurosphere graft	6-OHDA-induced nigrostriatal degeneration in rats	Low neuronal differentiation, predominant astroglial differentiation	Not tested	Weak behavioral improvement
Embryonic [E14.5] brain NSCs (rat)	Stx unilateral cell graft into the MBF	6-OHDA-induced nigrostriatal degeneration in rats	13–16% doublecortin immunoreactivity, 20–25% GFAP immunoreactivity, infrequent TH ⁺ immunoreactivity	Not tested	Not tested
Embryonic [E12] brain NSCs (rat)	Stx unilateral cell graft into the SN	6-OHDA-induced nigrostriatal degeneration in rats	Poor integration, infrequent TH ⁺ immunoreactivity	Not tested	No behavioral differences

Autoimmune Demyelinating Disorders: Stem Cell Therapy. Table 1 Neural stem cell (NSC) transplantation studies in animal models of CNS disorders (Continued)

Neural stem cell source	Route of cell administration	Disease model	Mechanism(s) of therapeutic efficacy		Outcome
			Cell replacement	Bystander effect	
Adult brain SVZ NSCs (rat)	Stx unilateral intrastratal cell graft	6-OHDA-induced nigrostriatal degeneration in rats	No evidence of NeuN and Tuj1 immunoreactivity, nestin immunoreactivity, DAT immunoreactivity	Increase of viable neuroprotective and neuroregenerative factors	Decrease of amphetamine-induced turns
<i>Huntington's disease</i>					
Foetal [12 weeks] brain NSCs (human)	Stx unilateral intrastratal cell graft	QA-induced striatal degeneration in rats	1% NeuN, 3.5% GFAP immunoreactivity, ki67 immunoreactivity (<i>in vivo proliferation</i>)	26% greater striatal volume Increase of viable CNTF, BDNF, GDNF	Improvement of motor function
Foetal [15 weeks] brain NSCs (human)	Stx unilateral intrastratal cell graft	3-NP-induced striatal degeneration in rats	Predominant nestin immunoreactivity, low NeuN and GFAP immunoreactivity, certain calbindin and GAD immunoreactivity	Extensive survival of striatal neurons, increase of viable BDNF	Improvement of motor function
<i>Acute spinal cord injury</i>					
Neonatal cerebellar C17.2-CD NSCs (mouse)	Intralesional transplantation of PGA-NPC complex	Lateral thoracic (T9-T10) spinal cord hemisection in rats	Majority of cells immunoreactive for nestin	Major contribution of NPCs as trophic support	Improvement of motor function
Neonatal cerebellar C17.2-CD NSCs (mouse)	Intralesional (<i>epicentre</i>) cell transplantation	Dorsal cervical (C3) Kopf microwire knife-mediated spinal cord lesion in rats	No evidence of differentiation	In vivo secretion of NGF, BDNF, GDNF	Not tested
Foetal [15 weeks] brain NSCs (human)	Multiple (n = 4) intraspinal cell deposits	Dorsal thoracic (T9) spinal cord weight drop injury in NOD-scid mice	2.9% astroglial, 26.3% neuronal, 64.1% oligodendroglial differentiation	Not tested	Improvement of coordinated forelimb-hind limb motor function
Embryonic [E15] hippocampal NSCs (rat)	Iv single cell injection	Dorsal thoracic (T7) spinal cord weight drop injury in rats	4.7% neuronal, 47% astroglial, 48% oligodendroglial differentiation	Cell accumulation within the injured spinal cord lesion,	Not tested
Adult spinal cord NSCs (rat)	Multiple (n = 4) intraspinal cell deposits	Dorsal thoracic (T8-T9) spinal cord weight drop injury in rats	74% astroglial, 17% oligodendroglial and 3% neuronal differentiation	Not tested	Improvement of motor function

Autoimmune Demyelinating Disorders: Stem Cell Therapy. Table 1 Neural stem cell (NSC) transplantation studies in animal models of CNS disorders (Continued)

Neural stem cell source	Route of cell administration	Disease model	Mechanism(s) of therapeutic efficacy		Outcome
			Cell replacement	Bystander effect	
Epilepsy					
Foetal [15 weeks] brain NPCs (human)	iv single cell injection	Lithium chloride/pilocarpine seizures model in rats	Hippocampal distribution of transplanted cells, ~60% neuronal (26% GABA ⁺ , 31% PV ⁺ , 3% GluR ⁺ immunoreactivity), 21% astrogial differentiation, ~25% undifferentiation	Not tested	~85% decrease of generalized convulsive seizure frequency and severity, increase of GABAergic synaptic inhibition

*Neural stem cells includes cells derived from embryonic, foetal, neonatal, and adult tissues. Abbreviations used: 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; BDNF, brain-derived neurotrophic factor; CCAO, common carotid artery occlusion; CCI, controlled cortical impact; CN, caudate nucleus; CNS, central nervous system; CNTF, ciliary neurotrophic factor; DAT, dopamine transporter; EAE, experimental autoimmune encephalomyelitis; EB-X, -X irradiation and ethidium bromide-induced focal demyelination; GAD, glutamic acid decarboxylase; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; icv, intracerebroventricular; iv, intravenous; MBF, medial basal forebrain; MCAO, middle cerebral artery occlusion; MOG, myelin-oligodendrocyte glycoprotein; MMP-2, matrix metalloprotease-2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NeuN, neuronal nuclear antigen; NGF, nerve growth factor; NGFs, neurotrophic growth factors; Ngn-2, neurogenin-2; NOD-scid, non-obese diabetic-severe combined immunodeficient mice; NPCs, neural stem/progenitor cells; OPCs, oligodendrocyte-progenitor cells; P0, peripheral nerve myelin protein P0; PGA, poly-glycolic acid; QA, quinolinic acid; SN, subtalamic nucleus; Shh, sonic hedgehog; Stx, stereotaxic; SVZ, subventricular zone; TH, tyrosine hydroxylase; VM, ventral midbrain; VTA, ventral tegmental area.

Hematopoietic Stem Cells

The transplantation of hematopoietic stem cells (HSCs) from autologous or allogeneic bone marrow, umbilical chord or peripheral blood is a widely utilized form of therapy for patients with hematopoietic malignancies and solid tumors. Evidence suggests that HSCs may contribute to the generation of new neurons in the adult brain by means of (i) trans-differentiation; and/or (ii) cell fusion, thus suggesting that HSC transplantation might in principle be useful as a therapeutic tool for brain repair [7]. Other results indicate that in rats with a demyelinated lesion of the spinal cord, HSC transplantation – upon either intravenous or intraparenchymal cell injection – results in varying degrees of remyelination which appears proportional to the number of injected cells [7].

In addition to mechanism aiming at replacement of damaged CNS cells, HSC transplantation is successfully utilized to target the autoimmune response at the peripheral level in several autoimmune diseases including MS [8]. The efficacy of HSC transplantation (following intense chemotherapy) is likely to be based on the intense immune suppression, which ends up in the eradication of most autoimmune cells, followed by the successful engraftment of the transplanted stem cells leading to the reconstitution of the immune system representing a recapitulation of ontogenesis and thus

accompanied by the acquisition of self-tolerance [9]. Moreover, HSC transplantation induces immune tolerance in rodents with EAE, as sustained by increased numbers of circulating regulatory T cells, a shift in T cell epitope recognition and a strong reduction of autoantibodies [9].

Mesenchymal Stem Cells

The adult bone marrow contains a non-haematopoietic cell lineage which is capable of differentiating into osteoblasts, adipocytes, and chondrocytes. Due to their preferential capacity of differentiating into cells of the mesodermal lineage, these cells are currently defined as “mesenchymal” stem cells (MSCs). MSCs constitute the stromal scaffold providing the appropriate microenvironment for maturation and differentiation of blood-derived progenitor cells possibly by means of the release of survival factors [10].

MSCs can also be induced to differentiate in vitro into cells with biochemical, anatomical, and electrophysiological characteristics of neuronal cells [10]. Upon intravenous injection, MSCs engraft into different tissues – including the brain – where they escape immune surveillance and differentiate expressing some microglial and astroglial markers [9]. Migration of intravenously-injected MSCs to the brain may well depend upon tissue injury, as demonstrated by their

minimal engraftment when transplanted into healthy non-human primates [9]. In contrast, in rodents with cerebral ischemia and traumatic brain injury, systemically-injected MSCs migrate to the injured CNS. These migratory properties are regulated by cell adhesion molecules and receptors for inflammatory chemokines, such as CXCL12, which plays a key role in the migration of CXCR4-positive mesenchymal stem cells to peripheral tissues [9].

MSCs can also significantly modulate many immune functions. MSCs inhibit T cell proliferation and induce T cell energy [9]. MSCs also affect dendritic cell maturation both *in vitro* and *in vivo*, thus resulting in the generation of tolerogenic antigen presenting cells (APCs) [9]. Interestingly, proof of MSC-dependent induction of CD4⁺ T cell subsets with a regulatory phenotype has recently been provided *in vitro*. Human MSCs also affect B lymphocyte proliferation and maturation to antibody secreting cells [9].

In vivo, transplantation of syngenic MSCs ameliorates chronic EAE in mice. Moreover, systemically-injected MSCs also improve relapsing-remitting EAE and migrate to the CNS where they promote BDNF production and induce proliferation of endogenous oligodendrocyte progenitor cells [9].

All together these results consistently challenge the view that stem cells therapeutically work exclusively throughout cell replacement. Indeed, NSC transplantation may also promote CNS repair via intrinsic *neuroprotective* bystander capacities, mainly exerted by undifferentiated stem cells releasing, at the site of tissue damage, a milieu of *neuroprotective* molecules once temporally and spatially orchestrated by environmental needs. The intrinsic nature (*pleiotropism and redundancy*) of these molecules as well as their “►constitutive” characteristics, might represent a *stem cell signature* that also reconciles data showing that other sources of somatic stem cells (e.g., HSCs, MSCs), may efficiently promote CNS repair despite very low capabilities of neural (trans) differentiation.

The exact knowledge and the potential impact of *non-conventional* stem cell-mediated therapeutic mechanisms might result, in certain circumstances, in more efficacious curative alternatives.

References

- Franklin RJ (2002) Why does remyelination fail in multiple sclerosis? *Nat Rev Neurosci* 3:705–714
- Waxman SG (2006) Axonal conduction and injury in multiple sclerosis: the role of sodium channels. *Nat Rev Neurosci* 7:932–941
- Franklin RJ, Blakemore WF (1997) To what extent is oligodendrocyte progenitor migration a limiting factor in the remyelination of multiple sclerosis lesions? *Mult Scler* 3:84–87

- Martino G, Pluchino S (2006) The therapeutic potential of neural stem cells. *Nat Rev Neurosci* 7:395–406
- Pluchino S, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, Martinello M, Cattalini A, Bergami A, Furlan R, Comi G, Constantin G, Martino G (2005) Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* 436:266–271
- Einstein O, Fainstein N, Vaknin I, Mizrahi-Kol R, Reihartz E, Grigoriadis N, Lavon I, Baniyah M, Lassmann H, Ben-Hur T (2006) Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression. *Ann Neurol* 2006 [Epub ahead of print]
- Pluchino S, Furlan R, Martino G (2004) Cell-based remyelinating therapies in multiple sclerosis: evidence from experimental studies. *Curr Opin Neurol* 17:247–255
- Gratwohl A, Passweg J, Bocelli-Tyndall C, Fassas A, van Laar JM, Farge D, Andolina M, Arnold R, Carreras E, Finke J, Kotter I, Kozak T, Lisukov I, Lowenberg B, Marmont A, Moore J, Saccardi R, Snowden JA, van den Hoogen F, Wulffraat NM, Zhao XW, Tyndall A (2005) Autologous hematopoietic stem cell transplantation for autoimmune diseases. *Bone Marrow Transplant* 35:869–879
- Uccelli A, Zappia E, Benvenuto F, Frassoni F, Mancardi G (2006) Stem cells in inflammatory demyelinating disorders: a dual role for immunosuppression and neuroprotection. *Expert Opin Biol Ther* 6:17–22
- Gregory CA, Prockop DJ, Spees JL (2005) Non-hematopoietic bone marrow stem cells: molecular control of expansion and differentiation. *Exp Cell Res* 306:330–335

Autoimmune Disease

Definition

Diseases caused by immune responses targeting a self component that leads to subsequent tissue/organ damage and dysfunction. Autoimmune diseases can be organ/tissue specific or systemic depending on the distribution of the self components attacked by the immune system. Both cell-mediated and humoral (antibody mediated) immune responses are involved in tissue damage. Susceptibility of autoimmune disease is controlled by both environmental and genetic factors.

►Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens

Autoimmune Neuroinflammation

Definition

Inflammation caused by immune reactivity towards self antigens within the nervous system. Multiple sclerosis

and its animal model experimental autoimmune encephalomyelitis are prototype diseases for autoimmune neuroinflammation.

- ▶ Multiple Sclerosis
- ▶ Experimental Autoimmune Encephalomyelitis

Autoimmune Response

Definition

Humoral (antibody) or cellular (T cell) immune responses against self antigens (autoantigen). Autoimmune diseases are caused by autoimmune responses, and can be divided into organ specific and systemic autoimmune diseases. For example, among neurological diseases, myasthenia gravis is mediated by autoantibody against the acetylcholine receptor. Although multiple sclerosis has been suggested to be mediated by autoimmune responses against myelin and/or oligodendrocytes, no single myelin antigen has been identified as the autoantigen.

- ▶ Multiple Sclerosis
- ▶ Myasthenia Gravis

Autoimmune T Cells

Definition

T cells that recognize specific self-antigens. These T cell subpopulations mediate an autoimmune response (i.e. a response to self-antigens), which can be either protective (e.g. fighting off cancer cells or neurodegenerative conditions) or – if not properly regulated – destructive (causing an autoimmune disease).

- ▶ Autoimmune Response

Autoimmunity

Definition

A condition in which the body produces an immune response recognizing its own proteins. Autoimmune responses can be mediated by either T or B lymphocytes.

- ▶ Autoimmune Response

Autologous Macrophage Therapy for Spinal Cord Injury

Definition

A treatment for acute spinal cord injury, in which systemic monocytes withdrawn from the patient's own blood are activated ex-vivo and reintroduced into patient for the purpose of carrying out their innate therapeutic functions.

- ▶ Autologous Macrophages for Central Nervous System Repair

Autologous Macrophages for Central Nervous System Repair

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Synonyms

Blood-borne monocytes for CNS repair

Definition

Restoration of damaged neural (brain and spinal cord) tissues by the peripheral immune system; specifically, by blood derived monocytes injected following activation, into the margins of the lesion site, or by boosting of adaptive immunity as away of enhancing recruitment of blood-borne monocytes injected autologous activated macrophages or by endogenous innate immune cells recruited via T cell-based vaccination.

Characteristics

Recovery from acute central nervous system (CNS) injuries requires recruitment of blood-borne monocytes whose numbers, activity, and localization are rigorously controlled. CNS-resident microglia also participate in the recovery process, but their ability to acquire the needed activity is limited. Spontaneous recruitment of blood-borne monocytes is also limited, but can be boosted either by vaccination (with T cell-specific antigens or dendritic cells loaded with such antigens) or by exogenous application of specifically activated autologous macrophages. The cells are harnessed for restoration of homeostasis by removing cell debris, balancing exogenous ionic and neurotransmitter concentrations, providing growth factors, attracting reparative cells, and supporting tissue recovery and renewal.

Based on the realization that peripheral monocytes are needed for CNS repair, a number of ►immune-based approaches have been developed. One such therapy for spinal cord injury makes use of specifically activated autologous macrophages [1–3]. Macrophages are prepared from the patient's blood, activated on the patient's skin to adopt a phenotype that promotes repair, and then reintroduced into the patient. The activated macrophages, unlike "classically" activated macrophages programmed to dispose of hostile invading organisms, express the cell-surface markers CD80, CD86, and CD54, as well as class II major histocompatibility complex molecules (MHC-II). All of these features are characteristic of antigen-presenting cells (APCs) reminiscent of 'alternatively activated macrophages' rather than classical pro-inflammatory macrophages [1]. In addition, they secrete the growth-promoting brain-derived neurotrophic factor but not the cytokine tumor necrosis factor- α . The abundant presence of the former coupled with the absence of the latter is suggestive of beneficial neuroprotection. The cellular features of these activated macrophages are reminiscent of those of microglia/macrophages recruited or activated by the adaptive immune system [4].

Background

Up until about 10 years ago, activated macrophages were viewed simply as cells that secrete the inflammatory mediators needed to kill intracellular pathogens. Data accumulated over the last decade suggested, however, that monocytes are multi-talented cells that are capable of expressing different functional programs in response to distinct micro-environmental signals. The differentiation of monocytic phenotypes is profoundly affected by microbial products and cytokines. Microbial products are associated with the "classical" activation that turns monocytes into potent effector cells that kill microorganisms and tumor cells. At the other extreme are the "alternatively" activated macrophages, conditioned by APC-secreted cytokines to control local inflammation (shechter, London, unpublished observations), [5] promote angiogenesis, tissue remodeling, and repair [1].

Over the last decade, the activities of blood-borne macrophages and resident microglia in the CNS, which formerly were considered to be wholly detrimental, began to be viewed in a different light. It is now widely accepted that immune cells are essential players in CNS repair (See review). Experiments in rats with completely transected optic nerves or spinal cords demonstrated that local application of macrophages preincubated with fragments of sciatic nerve (a peripheral nerve, and thus capable of regeneration) promotes motor recovery [3]. Similar results were reported by Benowitz and his colleagues, who showed that macrophage-derived factors stimulate growth [6].

The early experiments in which autologous activated macrophages were locally injected into the injured optic nerve were repeated in a paradigm of rat spinal cord contusion in which blood-borne monocytes were activated by preincubation with autologous skin [1]. In these and subsequent experiments the macrophage phenotypes were characterized, and parameters such as the site of injection, dosage, regimen, and therapeutic window were established. Specifically, macrophages are needed at the margin of the lesion site, not at the hyperacute phase, and express factors needed for scar resolution and for controlling inflammation.

These and related studies made it clear that the reparative role of activated macrophages which exert beneficial effects on the injured spinal cord differs from that of the resident microglia. This raised an important question: are such macrophages spontaneously recruited after a CNS insult? Addressing this question became feasible with the introduction of chimeric mice in which a visible marker, green fluorescent protein, is expressed by bone marrow-derived monocytes [5,7] shechter et al., Rolls et al. unpublished observations. Studies showed that the majority of innate cells accumulating at the site of injury were the resident microglia, while hardly any blood-borne monocytes were seen to infiltrate the damaged CNS. Recruitment of blood-borne monocytes turned out to be a key factor in recovery from any CNS injury [8].

Quantitative regulation

When Are Macrophages Needed?

In studies aimed at establishing the optimal time for macrophage intervention after spinal cord injury it became clear that in the CNS, as in any other tissue, repair and restoration are dependent not only on context, but also on timing. The following time windows were examined in a rat model of spinal cord injury, each representing a different post-injury physiological stage: (i) 3–4 days after spinal cord injury, a period characterized by decline in primary infiltration of neutrophils participating in inflammation and a high incidence of apoptotic cells (ii) 7–10 days after injury, a period of maximal proliferation and/or accumulation of ED1-positive cells (activated microglia/macrophages), T cells, and progenitor glial cells (iii) 14 days after injury, when the numbers of ED1-positive cells and T cells are still very high, while cytokines and chemokines in the injured tissue are decreasing or disappearing; and (iv) 21 days after injury, by which time many of the injury-induced biochemical and cellular activities in the spinal cord have peaked and begun to return to normal. The best effect was observed when cells were implanted 7–9 days after the injury.

The outcome, assessed in terms of recovery of motor function, is also critically affected by the choice of injection site. Injection close to the caudal margin of a

contusive spinal injury was found to be beneficial. Injections one or three segments below that level yielded no significant improvement in recovery [9].

Other immune-based therapies

Macrophages that beneficially affect recovery resemble APCs [1]. Studies of immune system participation in recovery from CNS insults disclosed that the peripheral immune system, traditionally viewed as being affected only in a passive way by CNS injury, in fact, plays an active role in CNS repair and is an integral part of it. That discovery led to a series of studies that culminated in formulation of the seminal concept of “►protective autoimmunity” [10,11]. According to this concept, T cells that react with specific CNS autoantigens (“autoimmune” T cells), by locally controlling the activity of resident microglia, play a central role in the physiological processes of CNS protection and repair. Active vaccination (using specific T cells) and passive vaccination (using myelin-derived peptides or dendritic cells loaded with those peptides) yielded similar results, manifested by better locomotion and reduced scar tissue. Recovery was accompanied by changes in the behavior of microglia/macrophages at the margins of the lesion, such that they were found to express the phenotype reminiscent of that of the activated macrophages.

It was further discovered that a principal role of the T cells has to do with shaping microglial behavior and recruiting blood-borne monocytes [5,12]. The activated microglia can act as APCs, produce growth factors, and scavenge neurotoxins such as excessive quantities of glutamate. Thus, not only do they support neuronal survival but they also promote neurogenesis and oligodendrogenesis, as well as axonal sprouting from adult neural stem cells [4]. It also became clear that not only resident microglia but also bone marrow-derived blood-borne monocytes can be induced to undergo a switch in phenotype, so that the activity they express is similar to that of transplanted growth-promoting macrophages [7]. Blood-borne innate immune cells that are recruited as a result of a T cell-based vaccination reside mainly at the margins of the lesion site.

Recognition that adaptive immune cells confer local immunity capable of supporting cell renewal by supporting an ectopic stem-cell niche raised another important question: after CNS injury, can the ►local immune response be controlled in a way that allows exogenously applied stem cells to be harnessed for promotion of recovery? Investigation of this possibility disclosed that a T cell-based vaccination given on the day of spinal cord contusion, if supplemented 1 week later by injection of neural stem cells into the CSF, results in significantly better recovery than that attained by vaccination alone. No effect was observed with the

stem-cell injection alone. Moreover, in the vaccinated injured mice (but not in mice that were not vaccinated after injury), stem cells that are injected into the CSF find their way to the lesion site, supporting the contention that the local immune response helps to create a niche which recruits not only stem cells but also additional immune cells for repair. The injected stem cells apparently do not undergo local differentiation into any of the neural lineages; rather, their functions appear to be related to immune activity and creation of a regulatory niche [13].

Taken together, the blood-borne monocytes, play a major role in CNS repair. They can be recruited in various ways, including bone-marrow transplantation, active or passive vaccination, and administration of autologous macrophages.

References

- Bomstein Y, Marder JB, Vitner K, Smirnov I, Lisaey G, Butovsky O, Fulga V, Yoles E (2003) Features of skin-coincubated macrophages that promote recovery from spinal cord injury. *J Neuroimmunol* 142:10–16
- Knoller N, Auerbach G, Fulga V, Zelig G, Attias J, Bakimer R, Marder JB, Yoles E, Belkin M, Schwartz M, Hadani M (2005) Clinical experience using incubated autologous macrophages as a treatment for complete spinal cord injury: phase I study results. *J Neurosurg Spine* 3:173–181
- Rapalino O, Lazarov-Spiegler O, Agranov E, Velan GJ, Yoles E, Fraidakis M, Solomon A, Gepstein R, Katz A, Belkin M, Hadani M, Schwartz M (1998) Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nat Med* 4:814–821
- Butovsky O, Landa G, Kunis G, Ziv Y, Avidan H, Greenberg N, Schwartz A, Smirnov I, Pollack A, Jung S, Schwartz M (2006) Induction and blockage of oligodendrogenesis by differently activated microglia in an animal model of multiple sclerosis. *J Clin Invest* 116:905–915
- Shechter R, London A, Varol C, Cusimano M, Raposo C, Rolls A, Pluchino S, Martino G, Jung S, and Schwartz M unpublished observations
- Yin Y, Cui Q, Li Y, Irwin N, Fischer D, Harvey AR Benowitz LI (2003) Macrophage-derived factors stimulate optic nerve regeneration. *J Neurosci* 23:2284–2293
- Rolls A, Shechter R, London A, Segev Y, Jacob-Hirsch J, Amariglio N, Rechavi G and Schwartz M, unpublished observations
- Simard AR, Soulet D, Gowing G, Julien JP, Rivest S (2006) Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. *Neuron* 49:489–502
- Schwartz M, Yoles E (2006) Immune-based therapy for spinal cord repair: autologous macrophages and beyond. *J. Neurotrauma* 23:360–370
- Hauben E, Agranov E, Gothilf A, Nevo U, Cohen A, Smirnov I, Steinman L, Schwartz M (2001) Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. *J Clin Invest* 108:591–599

11. Moalem G, Leibowitz-Amit R, Yoles E, Mor F, Cohen IR, Schwartz M (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med* 5:49–55
12. Butovsky O, Koronyo-Hamaoui M, Kunis G, Ophir E, Landa G, Cohen H, Schwartz M (2006) From the cover: Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1. *Proc Natl Acad Sci USA* 103:11784–11789
13. Ziv Y, Avidan H, Pluchino S, Martino G, Schwartz M (2006) Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proc Natl Acad Sci USA* 103:13174–13179

Automatic Postural Response

Definition

The automatic postural response is a muscular response to a postural perturbation that is thought to be mediated by brainstem centers. The response can be modulated in amplitude by many factors, including habituation, anticipation, prior experience, etc. However, it is “automatic” because it cannot be completely suppressed and is therefore neither completely fixed nor completely voluntary.

► Postural Synergies

Automatic Ventilation

► Central Integration of Cardiovascular and Respiratory Activity Studied In?Situ

Automatism

► Epiphenomenalism

Automaton Theory

► Epiphenomenalism

Autonomic Control of Sensory Receptors

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Definition

The autonomic nervous system consists of three divisions: sympathetic, parasympathetic and enteric nervous system, however, only the sympathetic system is considered relevant in the context of vegetative-sensory interaction. The sympathetic nervous system (SNS) is activated during states of arousal and, in general, by physical, psychological and psychosocial stress as part of a complex neuro-hormonal body adjustment. In particular SNS governs the so-called ►defense reaction that contributes at rapidly mobilizing body resources for a ►fight or flight response. In addition, or probably within the same adjustment procedures, SNS modulates the discharge of several ►sensory receptors. Among them are several types of cutaneous ►mechanoreceptors, ►muscle spindle receptors, pain receptors, some visceral ►chemo- and mechanoreceptors. As a consequence, also the reflex actions mediated by the affected receptors may be modified.

A list of the ►receptors affected by enhancement of sympathetic flow is presented in Table 1 [see also 1,2]. We will focus on muscle spindle receptors that have been studied more extensively, due to their relevance in control of skeletal muscle function. Pain receptors, which are affected by ►catecholamines only under particular circumstances, are given more extended treatment elsewhere, in chronic pain mechanisms.

Characteristics

General Considerations

Claude Bernard in 1851 first suggested that sensory input can be modulated by the activation of the SNS, on the basis of the observation of changes in cutaneous sensitivity following the extirpation of the cervical ganglion in the cat. A large number of old and recent electrophysiological and pharmacological data show that the SNS modulates the discharge of numerous types of mechanical and chemical receptors, at least in a percentage of them. The electrical stimulation of the relevant sympathetic nerve and local administration of catecholamines affect the firing properties of these receptors, in terms of both resting discharge and excitability, as recorded from ►primary afferents in several animal species [1,2]. The majority of data available in the literature are in fact collected in *acute* experiments performed on animal models, or in *in vitro*

Autonomic Control of Sensory Receptors. Table 1 Sympathetically induced modulation of receptors

Tactile, thermal receptors	+ (frog)	Loewenstein WR (1956) J Physiol 132:40; Chernetski KE (1964) J Neurophysiol 27:493
"Cutaneous mechanoreceptors" slowly adapting	- (frog) + (frog)	Spray DC (1974) J Physiol 237:15; Calof AL et al. (1981) J Physiol 310:481
Cutaneous hair follicles rec.	- (cat vibrissae)	Nilsson BY (1972) Acta Physiol Scand 85:390
Pacinian corpuscle rec.	+ (cat mesentery)	Loewenstein, Altamirano-Orrego (1956) Nature 178:1292; Schiff JD (1974) J Gen Physiol 63:601; Akoev GN et al. (1976) Progr Brain Res 43:187
	- or + (cat skin)	Freeman B, Rowe M (1981) Neurosci Lett 22:145
	+ or 0 (human skin)	Hallin RG, Wiesenfeld Z (1983) J Auton Nerv Syst 7:391
Type I slowly adapting	+ (humans)	Wiesenfeld-Hallin Z, Hallin RG (1984) Hum Neurobiol 3:41
"hairy skin"	+ (cat)	Roberts WJ et al. (1985) Somatosens Res 2:223
Type II slowly adapt. (Ruffini) Guard hair, rapidly adapting	+ or + - (cat) -, few + (cat, skin near joints)	Pierce JP, Roberts WJ (1981) J Physiol 314:411
High-T mechanoreceptors, myelinated	0 (rabbit)	Barasi S, Lynn B (1986) Brain Res 378:21
Hairy skin mechanoreceptors, C fibers	+ (cat)	Roberts WJ, Elardo SM (1985) Brain Res 339:123
	+ - or 0 (rabbit)	Barasi S, Lynn B (1986) Brain Res 378:21
Type I-II, fast -slowly adapting	- or 0 (humans, tactile receptors)	Elam M, Macefield VG (2004) Auton Neurosc 111:116
Periodontal mechanoreceptors	+ (rabbit)	Passatore M, Filippi GM (1983) Arch Ital Biol 121:55
	-/0 (cat)	Cash RM, Linden RWA (1982) J Physiol 329:451
Golgi tendon organs	0 (cat)	Hunt CC (1960) J Physiol 151:332
Muscle spindles	+ - <i>in vitro</i>	Calma I, Kidd GL Arch Ital Biol 100:381
	+ - (cat limb m.)	Eldred E et al. (1960) Exp Neurol 2:13
	+ -/0 (cat limb m.)	Hunt CC (1960) J Physiol 151:332
	+ - (cat)	Francini F et al. (1978) Boll Soc Ital Biol Sper 54:1353
	- (rabbit jaw m.)	Passatore M, Filippi GM (1981) Brain Res 219:162
	0/ - (cat limb m.)	Hunt CC et al. (1982) Arch Ital Biol 120:371
	+ - (rabbit jaw m.)	Passatore M et al. (1996) J Auton Nerv Syst 57:163
	+ - (rabbit jaw reflexes)	Grassi C et al. (1993) Arch Ital Biol 131:213; Grassi C et al. (1993) J Physiol 469:601
	+ - (rabbit jaw m.)	Passatore M et al. (1996) J Auton Nerv Syst 57:163
	- SS (rat jaw m.)	Matsuo R et al. (1995) J Physiol 483:239
	+ - (rabbit jaw m.)	Roatta S et al. (2002) J Physiol 540:237
	+ - (cat neck m.)	Hellström F et al. (2005) Exp Brain Res 165:328
Gustatory receptors	+ (frog)	Chernetski KE (1964) J Neurophysiol 27:493
Olfactory receptors	+ (rabbit)	Tucker D, Beidler LM (1956) Am J Physiol 187:637
Intestinal receptors (perception)	+ (duodenum, humans)	Iovino P et al. (1995) Gastroenterology 108:680

Autonomic Control of Sensory Receptors. Table 1 Sympathetically induced modulation of receptors (Continued)

Carotid sinus baroreceptors	+, or 0 at high carotid sinus pressures (opossum, dog)	Koizumi K, Sato A (1969) Am J Physiol 216:231; Bolter CP, Ledsome JR (1976) Am J Physiol 230:1026
Carotid glomus chemoreceptors	+ (dog)	Eyzaguirre C, Fidone SJ (1980) Am J Physiol 8:C135
	+ (cat)	Acker H, O'Regan RG (1981) J Physiol 315:99
Atrial and ventricular mechanoreceptors	+ (cat)	Nishi K et al. (1974) J Physiol 240:53
		Nishi K et al. (1977) Pflug Arch ger Physiol 372:53
Nociceptors		
Tooth pulp receptors	+ or + - (cat)	Edwall L, Scott DJ (1971) Acta Physiol Scand 82:555; Matthews B (1976) Adv Pain Res Ther 195
Cutaneous A δ fibers	0 (cat)	Roberts WJ, Elardo SM (1985) Somatosensory Res 3:33
	0 (rabbit)	Barasi S, Lynn B (1986) Brain Res 378:21
	0 (rat)	Lang PJ et al. (1990) Psychol Rev 97:377
	0 (humans)	Iovino P et al. (1995) Gastroenterology 108:680
Cutaneous C fibers	+ (rat: <i>in vitro</i> prep)	Kieschke J et al. (1991) Progr Brain Res 74:91
	+ (rat)	Mense S (1986) Prog Sens Physiol 6:139
	0 (rat)	Sanjue H, Jun Z, Pain 38:85; Sato A et al. (1993) Neurosci Lett 164:225
	+ - (rabbit)	Barasi S, Lynn B (1986) Brain Res 378:21
	- rabbit, single fibers, in sural nerve	Shyu BC et al. (1989) Acta Physiol Scand 137:85
	+ (cat)	Roberts WJ, Elardo SM (1985) Brain Res 339:123
	0 (humans)	Elam M et al. (1999) Brain 122:2237
	0 (monkey)	Selig DK et al. (1993) Soc Neurosci Abs 19:326
A δ and C fibers after "precipitating factors" occur, e.g., nerve lesion, inflammatory processes, previous sensitization	0 (rabbit)	Shea VK, Perl ER (1985) J Neurophysiol 54:513; Sato J, Perl ER (1991) Science 251:1608; Bossut DF, Perl ER J Neurophysiol 73:1721
	+ (cat)	Roberts WJ, Elardo SM (1985) Somatosensory Res 3:33
	+ (rabbit, C fibers)	Roberts WJ (1986) Pain 42:297; Shyu BC et al. (1990) Acta Physiol Scand 140:237; Sato J, Perl ER (1991) Science 251:1608
	+ humans (Sympathetically-Maintained Pain)	Walker AE, Nulsen F (1948) Arch Neurol Psych 59:559; Bonica JJ (1979) Adv Pain Res Ther 3:141; Levine JD et al. (1986) Nature 323:158; Bonica JJ 1990; Sanjue H, Jun Z (1989) Pain 38:85; Sato J, Perl ER (1991) Science 251:1608; Koltzenburg M et al. (1994) Brain 117:579; Drummond PD (1995) Pain 60:301; Torebjörk E et al. (1995) Pain 63:11; Drummond PD et al. (2001) Neurology 57:1296

Data obtained following sympathetic activation induced by either electrical stimulation of sympathetic supply (1–10 Hz) or application of catecholamines or through specific manoeuvres, in the species indicated. Effects reported are obtained by recording afferent discharges from primary neurons; symbols indicate the prevalent response: activation of the resting discharge and/or facilitation of the test response (+), inhibition and/or depression (-), diphasic response (+ - or - +), no effect (0).

preparations. Few studies are available on humans based on microneurography during sympathetic activation tests.

The mechanisms responsible for this action are still debated. For some of the reported actions, there is in fact some disagreement on whether they are due to the *direct* effect exerted by catecholamines on the sensory receptors or rather they are *indirect*, i.e., secondary to metabolic, mechanical or thermal changes induced in the receptor-bearing tissue by the concomitant sympathetically induced ►vasoconstriction. For some cutaneous receptors, micromovements induced by contraction of adjacent ►piloerector muscles has been also suggested. An action exerted directly on the sensory receptors, rather than secondary to vasoconstriction, is suggested by: (i) functional studies in which the sympathetic effect on the receptors was not mimicked by ischemia; (ii) morphological studies proving the existence of noradrenergic fibers in close contact with a number of receptors, such as Pacini corpuscles, muscle spindles and cutaneous hair receptors. Conclusive contribution to the debate should be provided by immunohistochemical investigations proving or disproving the presence of specific adrenoceptors on the various sensory receptor terminals. The studies listed in Table 1 attribute the sympathetically induced effect to a direct action on the receptors, except for some of them, i.e., Freeman & Rowe (1981), Edwall & Scott (1971), Eldred et al. (1960), Eyzaguirre & Fidone (1980) and Elam & Macefield (2004).

It must be added that the sympathetically induced action on the same sensory receptors is likely to be different or more pronounced after “sensitization” processes develop in the affected area; this possibility has been particularly investigated for nociception (see below, under *Pain receptors*).

Overview

Increase in sympathetic outflow and locally-applied noradrenaline is reported to elicit or enhance the resting discharge and/or to increase the sensitivity to the relevant stimuli, in various types of cutaneous mechanoreceptor. The effect was shown, in some case, to be mediated by increased amplitude and rate of rise of the generator potential, and possibly by an action at the level of the ►encoding site. In general excitatory actions seem to predominate on slowly adapting mechanoreceptors while depressant actions are more commonly observed in rapidly adapting receptors. Besides characteristics of adaptation, sympathetic effects seem to depend on the ►afferent fiber type (see Table 1).

Sympathetic stimulation enhances ►Pacini corpuscle activity in experimental animal models, although some depressant effect is also reported. In some of these receptors, in humans, Hallin & Wiesenfeld [3] evidence a

clear relationship between extent of stress/sympathetic outflow and spontaneous discharge frequency of the receptor. A similar interaction is reported in their experiments for the discharge of slowly adapting type I receptors in response to light mechanical stimuli (see Table 1).

The two studies performed on periodontal mechanoreceptors show excitatory and depressant sympathetic actions on rabbit and cat models, respectively, while excitation occasionally followed by inhibition is reported for tooth pulp receptors, having nociceptive function.

An increase in visceral perception of intestinal distension is evidenced in humans during increase in sympathetic outflow (Table 1) while, in the same experimental condition, somatic sensitivity (cutaneous) appears scarcely affected. Sympathetic activation was elicited in this study by means of lower body negative pressure that produces venous pooling in lower extremities (which activates the sympathetic nervous system directly via cardiovascular reflexes).

Muscle Spindles

Stimulation of peripheral sympathetic pathways has been shown to profoundly affect the resting discharge rate, as well as the stretch sensitivity of both Ia and II spindle afferents. However the results from different studies performed on various muscles and animal species are not uniform [1,2,4], the mechanisms of such modulator action are still disputed, and so is the functional relevance of the sympathetic action on spindles. In particular, the effects observed in hindlimb muscles of experimental animals were either considered secondary to vasoconstriction or exerted directly on spindles but having small magnitude, therefore scarce functional relevance [2]. By contrast, more recent studies performed on masticatory and neck muscles in several experimental models show that sympathetic activation exerts, in the large majority of muscle spindle afferents, a consistent depression of the response to muscle length changes, possibly preceded by a transient enhancement of variable magnitude. This response consists of a reduction in the ►static and dynamic sensitivity, observed in both Ia and II units innervating bag and chain ►intrafusal muscle fibers. This response was found to be mediated by α_1 -adrenoceptors and to be independent of sympathetically induced vasoconstriction [2,5]. To the action exerted by the sympathetic outflow on muscle spindle afferents is attributed the sympathetically-induced transient enhancement followed by remarkable decrease in the magnitude of both jaw ►jerk and ►tonic vibration reflex in jaw elevator muscles lasting throughout the stimulation and longer [6]. In fact these effects parallel, in relative magnitude and time course, the ones induced by the

sympathetic stimulation on spindle afferent discharge recorded from jaw elevator muscles. Thus the main action induced by the sympathetic stimulation consists of a considerable decrease in the quality of proprioceptive information. This should impair the ability of motor system both to correct perturbations, i.e., decrease the ► feedback control of muscle length, and to tune the motor program according to current constraints (► feed-forward control of movement).

Besides affecting muscle spindle afferents sensitivity to muscle length changes, sympathetic stimulation also affects their resting discharge, such effect ranging from enhancement to strong depression of firing. Even though the origin of this difference is not clarified, such action is of obvious importance since baseline activity is an important excitatory input that may affect ► muscle tone, through spindle support to α-► motoneurons. The different time course exhibited by the effect on spontaneous discharge rate and sensitivity to stretch suggests that more than one mechanism is involved in the sympathetic action on spindles. Recent findings indicate that intrafusal muscle fibers are among the possible targets of sympathetic innervation. Bombardi et al. [7] report, in rabbit masseter muscle, the presence of sympathetic fibers, visualized by immunohistochemical fluorescent labeling of the noradrenaline-synthesizing enzymes tyrosine hydroxylase and dopamine beta-hydroxylase, along the entire length of the spindles, within the capsule wall, in periaxial fluid space and in close apposition to intrafusal fibers, confirming previous findings obtained, using traditional techniques, on limb muscles [8]. In addition α_{1a} -adrenoceptors are detected at the polar region of a large percentage of spindles, both bag and chain intrafusal fibres [7]. Recent work from the same group demonstrates the presence of α_{1a} -adrenoceptors, with the same localization, in spindles of several muscles i.e., trapezius, splenius, triceps (caput longum) and gastrocnemius muscles in rabbits (Bombardi, personal communication). Localization of the α_{1a} -adrenoceptors in the polar regions of the spindles suggests that the sympathetic mediator may modulate the spindle afferent discharge by altering the mechanics of both types of intrafusal fibers.

The functional implications of the sympathetic action on muscle spindle receptors are of considerable interest since this signal contributes to a number of body functions, such as control and coordination of ongoing movements, maintenance of postural control, perception of position and movement of our body (kinaesthesia), and learning of stereotyped movements and motor skills. Therefore, any system able to modulate the spindle receptors is liable to affect those functions. The action of sympathetic innervation on spindle receptors still needs to be confirmed in humans.

Pain Receptors

The large majority of studies agree in showing that, under normal conditions, increase of sympathetic outflow does neither activate nociceptors nor affect their ongoing discharge (see Table 1). However, the sympathetic action may become powerful under pathological conditions, when some “precipitating factor” intervenes, such as peripheral nerve lesions resulting from injury or compression, trauma of soft tissues, inflammatory processes or previous sensitization of the relevant receptors. Under these conditions, in which pain problems are disproportional to the initial injury, some ► nociceptive receptors develop sensitivity to catecholamines, which may initiate or enhance the ongoing discharge [9] (see Table). The reasons suggesting that the SNS system plays a role in certain painful states are the following: (i) the control of the sympathetically innervated structures in the affected area is abnormal (sweating, temperature dysregulation, trophic changes); (ii) pain is exacerbated by emotionally arousing stimuli; (iii) pain is temporarily relieved by sympathetic blockade (α -adrenoreceptors) and is rekindled by injecting small amounts of catecholamines or of α -adrenergic agonists.

It has been hypothesized that this peripheral sympathetic-sensory coupling is one of the mechanisms involved in initiation and maintenance of a symptom defined ► sympathetically-maintained pain, that may be common to several diseases [4,9,10].

Final Remarks

As reported above, the sympathetic nervous system exerts a widespread modulation of several receptors. It is well known that the central nervous system can control the inflow of sensory information at different spinal and supra-spinal levels, the aim being either to amplify or filter out specific signals, thus selecting the ones that are most relevant in a particular context. It is tempting to speculate that the SNS takes part to this aim/action acting directly at the receptor level, thereby constituting the peripheral branch of a general system controlling and processing afferent information.

References

1. Akoev GN (1981) Catecholamines, acetylcholine and excitability of mechanoreceptors. Prog Neurobiol 15:269–294
2. Roatta S, Windhorst U, Ljubisavljevic M, Johansson H, Passatore M (2002) Sympathetic modulation of muscle spindle afferent sensitivity to stretch in rabbit jaw closing muscles. J Physiol Lond 540:237–248
3. Hallin RG, Wiesenfeld Z (1983) Does sympathetic activity modify afferent inflow at the receptor level in man? J Auton nerv Syst 7:391–397

4. Passatore M, Roatta S (2005) Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model. *Eur J Appl Physiol* 98:423–449
5. Hellstrom F, Roatta S, Thunberg J, Passatore M, Djupsjobacka M (2005) Responses of muscle spindles in feline dorsal neck muscles to electrical stimulation of the cervical sympathetic nerve. *Exp Brain Res* 165:328–342
6. Grassi C, Deriu F, Passatore M (1993) Effect of sympathetic nervous system activation on the tonic vibration reflex in rabbit jaw closing muscles. *J Physiol Lond* 469:601–613
7. Bombardi C, Grandis A, Chiochetti R, Bortolami R, Johansson H, Lucchi ML (2006) Immunohistochemical localization of alpha_{1a}-adrenoceptors in muscle spindles of rabbit masseter muscle. *Tissue Cell* 38:121–125
8. Barker D, Saito M (1981) Autonomic innervation of receptors and muscle fibers in cat skeletal muscle. *Proc R Soc Lond B Sci* 212:317–332
9. Koltzenburg M (1997) The sympathetic nervous system and pain. In: Dickenson A, Besson JM (eds) *The pharmacology of pain*. Springer-Verlag, Berlin Heidelberg New York, pp 61–91
10. Bonica JJ (1990) Causalgia and other reflex sympathetic dystrophies. In: Bonica JJ (eds) *The management of pain*, 2nd edn. Lea & Febiger, Philadelphia, PA, pp 220–243

developed by skeletal **►muscle twitches** in the dog. Besides this **►inotropic** action, catecholamines have been shown to affect many other processes at the muscle fiber level that also impact on relevant aspects of muscle function, like fatigability, energy consumption and metabolism. Given that skeletal muscles receive no parasympathetic innervation (with possible exceptions, like the rat masseter muscle in which a vascular parasympathetic innervation is reported), the autonomic effects appear to be exclusively sympathetic in origin, mediated either by the neurally released noradrenaline or indirectly through circulating adrenaline released in the blood by the adrenal medulla. The issue was extensively reviewed by Bowman [1] and is here resumed and updated. The anatomical basis for autonomic effects on skeletal muscles is first introduced, then the different effects are dealt with separately, being grouped in the following categories:

1. Effects on contractility.
2. Effects on excitability.
3. Effects on glucose and protein metabolism.
4. Effects on neuromuscular transmission.

Characteristics

Anatomical Basis

Besides innervating blood vessels, post ganglionic unmyelinated sympathetic fibers have also been reported to lay interspersed and in neuroeffective association with skeletal muscle fibers [2]. However, most effects on the skeletal muscle appear to be mediated by the circulating adrenaline rather than by the noradrenaline released by sympathetic fibers. This results from experiments in which the effects observed by local or systemic injection of adrenaline were not reproduced by stimulation of the relevant sympathetic pathways and is explained by the following considerations: (i) among the increasing list of **►adrenergic receptors** (ARs) (α_1 , α_2 , β_1 , β_2 , β_3 , and relative subtypes), β_2 -ARs mediate most adrenergic effects on skeletal muscle fibers; (ii) at difference from α_1 -ARs, the ubiquitous vascular receptors mediating vasoconstriction, β_2 -ARs are not located in tight correspondence with sympathetic **►varicosities** releasing noradrenaline; (iii) β_2 -ARs are the preferential target of circulating adrenaline, which has for these receptors a much higher affinity than noradrenaline.

β_2 receptor density on the **►sarcolemma** may depend on the **►muscle fiber type** and has been reported to be higher in type-I, as compared to type-II. Conversely, α_1 - and β_1 -ARs have been detected pre-junctionally in the motor endplate (see below) and are usually not found in skeletal muscle fibers. However, exceptions and differences may occur in different muscles and different animal species. For instance α_1 effects have

Autonomic Dysfunction

Definition

Autonomic dysfunction is an impairment of autonomic function which may be caused by disease or degeneration of the central or peripheral nervous system. The effects may be focal or widespread and tend to increase in prevalence with age, affecting the cardiovascular and thermoregulatory systems in particular.

►Autonomic Insufficiency

Autonomic Effects on Skeletal Muscle

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Definition

The autonomic nervous system is generally considered to control “vegetative functions”. However, since the end of nineteenth century catecholamines (“adrenal extracts” at that time) were shown to increase the force

been reported in the rabbit masticatory muscles [3] and in rat muscles, where their expression in the sarcolemma was shown to increase in particular conditions like motor denervation, chronic hypokalemia and aging [1,4]. Finally, cotransmitters of adrenaline like NPY may also play a role [3].

Effect on Contractility (Inotropic Effect)

Catecholamines affect the force developed by skeletal muscle fibers, the effects being different depending on the muscle fiber type. The effects on contractility are classically described through the modification exhibited by the muscle twitch: it generally results increased and longer lasting in fast contracting muscle fibres (type-II) while it is decreased and shorter lasting in slow-contracting fibres (type-I) [1]. The potentiating effect on type-I fibres, that in the masticatory muscles was shown to be partly mediated by the noradrenaline co-transmitter NPY [3], was also observed in limb muscles. However, the fact that in limb muscles such effect was observed at relatively high doses of injected adrenaline or at relatively high frequencies of splanchnic sympathetic nerve stimulation (which stimulates secretion of catecholamines from the adrenal medulla) has cast doubts on its actual physiological significance. On the contrary, the inhibitory effect on slow-twitch muscle fibres could be evoked with much lower doses of injected adrenaline, as well as by stimuli reflexly increasing the sympathetic outflow, and is therefore expected to have an impact in physiological conditions [1].

More recently, an increase in twitch amplitude was also described for type-I muscle fibres, in *in vitro* preparations exposed to β_2 ARs agonists [5]. These experiments led to clarify that the contractility of the muscle fiber can be modulated by controlling the release/reuptake of calcium ions from/into the intracellular calcium store (the sarcoplasmatic reticulum), through the following mechanisms: (i) increased Ca^{++} release from the sarcoplasmatic reticulum mediates the increase in twitch amplitude in both fiber types; (ii) increased Ca^{++} re-uptake in the sarcoplasmatic reticulum decreases the twitch duration (slow fibres only). These effects would be achieved by phosphorylation of both ryanodine receptors and the sarcoplasmic pump regulatory protein *phospholamban*, respectively, via the cAMP-PKA pathway [5]. The same pathway exists in cardiac muscle fibers and contributes to the increase in force and rate of relaxation produced by catecholamines via β_1 ARs.

From the functional point of view, the potentiation of amplitude and/or duration of the twitch occurring in type-II muscle fibers would result in an increase in the force level developed by **►subtetanic contractions**. Interest for these effects has recently emerged in sports physiology where the relevance of the positive inotropic effect and the *anti-fatigue* effect (see below) is

investigated to ascertain any possible improvement in muscle performance or endurance by administration of β_2 agonists. However the most pronounced effect concerns type-I muscle fibers. It generally consists in a weakening of subtetanic contractions, due to the fact that the effect of twitch shortening overcomes the effect of amplitude increase. In response to β_2 -agonists administration the developed force may decrease to less than 40% of the original value, the magnitude of such decrease depending on the experimental setup and on of stimulation frequency of the muscle fibers. The functional implication is not evident in this case. One possible interpretation is that, under the effect of adrenaline, the speed of contraction is privileged, rather than the force, so that slow-twitch (type-I) muscle fibers behave more similarly to the fast-twitch (type-II) fibers. This effect may improve the performance of fast movements in a **►fight or flight response**.

Effect on Excitability

Catecholamines, via β_2 ARs, potentiate the activity of the **►Na/K pump** located in the sarcolemma thus promoting a hyperpolarizing effect. This effect is not consistently observed in resting conditions but may become important in preserving muscle function (force) during exercise. During intense muscle activity a relevant outflow of potassium ions from muscle fibers to the interstitial fluid takes place. The ensuing decrease of concentration gradients across the sarcolemma (particularly at the level of T-tubules) leads to decreased excitability of muscle fibers and impaired force production, and constitutes a major peripheral mechanism of **►muscle fatigue**.

An *anti-fatigue* effect of catecholamines has been demonstrated in several *in-vitro* and *in-vivo* preparations; these experiments show that the force level decreased by hypokalemia or fatigue could be partially restored by infusion of adrenaline or of β_2 -agonists (e.g., salbutamol, terbutaline) [6], as well as by electrical stimulation of the lumbar sympathetic chain (Orbeli effect).

It may be worth considering the adrenergic stimulation of the Na/K pump in a systemic perspective. During exercise, the potassium loss from active fibers generally leads to a substantial increase in plasma potassium concentration that may rise from 4 mM to more than 8 mM, depending on exercise intensity and muscle mass involved. It is interesting to observe that, in steady-state exercising muscles, potassium efflux from active fibers is not affected by pharmacological blockade of β_2 -ARs.

This suggests that the Na/K pump in active fibers cannot be further potentiated by the circulating adrenaline, being already stimulated by the locally altered ionic gradients. However, adrenaline may still effectively operate in all non-exercising muscles,

thereby stimulating a general potassium uptake. This attenuates the exercise-induced rise in plasma potassium concentration, thus preserving excitability of active fibers and delaying fatigue. An increased rise in plasma potassium concentration is in fact observed when this action is prevented by β -blockade.

Through the adrenergic modulation of the Na/K pump activity and the control on blood flow redistribution (via α - and β -ARs) the sympato-adrenergic system operates a central control of plasma potassium concentration in exercise [7].

Effect on Glucose and Protein Metabolism

Adrenaline, again through the β_2 -ARs – cAMP – PKA pathway, modulates important metabolic functions in the skeletal muscle cells, that will be here briefly summarized.

Adrenaline and β_2 -agonists were shown to reduce the release of amino acids (mainly alanine and glutamine) from isolated muscle preparations and to increase muscle mass when orally administered in different animal species. This anabolic effect is specific to striated muscle (smooth muscles are not affected); it appears within two days after β_2 -agonists administration and is attenuated 14 days afterwards, possibly because of β receptors down-regulation. This *protein sparing* was recently shown to be mediated by inhibition of proteolysis (through a mechanisms involving PKA-activation of *calpastatin* which specifically inhibits the proteolytic enzyme *calpain*), although potentiation of protein synthesis may also occur [8].

Catecholamines promote glucose uptake and glycogenolysis in skeletal muscle, however some of the underlying mechanisms remain unclear.

As for glucose uptake, it is potentiated, particularly by noradrenaline, via unspecified β -ARs (it is debated whether β_3 receptors are implicated). Adrenaline instead, via β_2 -ARs, antagonizes the insulin-mediated glucose transport. Again, in antagonism with insulin, adrenaline inhibits glycogen synthesis and promotes glycogenolysis, this latter process appears to be not particularly relevant in resting muscles, being conditioned to the simultaneous occurrence of muscle activity. These actions, however, result in increased lactate outflow from the muscle fibers; lactate diffuses out of the cells and may be then reconverted to glucose by the liver. These effects may contribute to the adrenaline-induced increase in ►glycemia [9].

The sympato-adrenal system plays an important role in the processes of storage and release of energy substrates by coherently modulating the activity of skeletal muscles, liver, pancreas and adipose tissue.

Effects on Neuromuscular Transmission

In addition to the modulation of several intracellular processes, another action of catecholamines may be of interest in this context, i.e., the modulation of

acetylcholine release at the ►motor end plate, through an action exerted on the motor terminal. This pre-synaptic modulation appears to be (i) rather complex, being mediated by both α - and β -ARs; (ii) difficult to study, given the concomitant postsynaptic effects on cell excitability (see above); and (iii) not particularly relevant in physiological condition, given the intrinsically high reliability and effectiveness of neuromuscular transmission. In fact, the effects of ►sympathomimetics were evidenced under partial curarization, i.e. an experimental model in which neuromuscular transmission is weakened in all motor end plates and blocked in some of them. In this condition both adrenaline and noradrenaline improve the efficacy of neuromuscular transmission, to the extent that neuromuscular blockade is overcome in some fibers (so called *anti-curare effect*) [1]. The hypothesized involvement of β -receptors has been confirmed in recent studies indicating that presynaptic β_1 -ARs may potentiate the postsynaptic effect by increasing synchronization of vesicles exocytosis [10].

Function

The autonomic nervous system affects several important functions of the skeletal muscle fiber primarily through the action of adrenaline via β_2 ARs, although other ARs may be implicated in the modulation of neuromuscular transmission and in processes related to glucose uptake. Secretion of adrenaline increases during exercise and most of its actions on muscle fibers can be considered as part of a general strategy aimed at increasing muscle performance in terms of developed force, movement velocity, availability of energy substrates and protection from fatigue. However, it should be taken into account that adrenaline secretion also occurs in stressful conditions, possibly in the absence of relevant muscle activity; in this condition adrenergic effects on skeletal muscle may be inappropriate. A possibly similar situation occurs when β_2 -agonists are systemically administered, e.g., for the treatment of asthma (β_2 -ARs mediate broncho-dilation). No broncho-specific sympathomimetics have been devised, as yet, and a number of side-effects of these drugs, such as ipokalemia (see above), hyperglycemia (see above) and ►tremor, can partly be attributed to activation of β_2 -ARs in skeletal muscles. Increased physiological tremor (in the range 8–12 Hz) due to administration of adrenaline was attributed to its negative inotropic effect on type-I muscle fibers: decreased fusion of subtetanic contractions (see above) implies increased oscillations in force/position in the limbs.

However, the involvement of muscle spindles in physiological tremor was also hypothesized, the oscillations having been attributed to instability of the ►feedback control of muscle length. Catecholamines might also affect this feedback control through their modulating action on muscle spindle receptor activity (►Autonomic control of sensory receptors).

References

- Bowman WC (1980) Effects of arenergic activators and inhibitors on skeletal muscles. In: Szekeres (ed) Handbook of experimental pharmacology, adrenergic activators and inhibitors, vol 54/2. Springer-Verlag, Berlin New York Heidelberg, pp 47–128
- Barker D, Saito M (1981) Autonomic innervation of receptors and muscle fibres in cat skeletal muscle. Proc R Soc Lond B Biol Sci 212:317–332
- Grassi C, Deriu F, Roatta S, Santarelli R, Azzena GB, Passatore M (1996) Sympathetic control of skeletal muscle function: possible co-operation between noradrenaline and neuropeptide Y in rabbit jaw muscles. Neurosci Lett 212:204–208
- Akaike N (1981) Sodium pump in skeletal muscle: central nervous system-induced suppression by α -adrenoreceptors. Science 213:1252–1254
- Ha TN, Posterino GS, Fryer MW (1999) Effects of terbutaline on force and intracellular calcium in slow-twitch skeletal muscle fibres of the rat. Br J Pharmacol 126:1717–1724
- Clausen T, Andersen SL, Flatman JA (1993) Na(+)–K⁺ pump stimulation elicits recovery of contractility in K(+)-paralysed rat muscle. J Physiol (Lond) 472:521–536
- Hallen J (1996) K⁺ balance in humans during exercise. Acta Physiol Scand 156:279–286
- Navegantes LC, Migliorini RH, Do Carmo Kettelhut I (2002) Adrenergic control of protein metabolism in skeletal muscle. Curr Opin Clin Nutr Metab Care 5:281–286
- Nonogaki K (2000) New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 43:533–549
- Bukharaeva EA, Gainulov RKh, Nikol'skii EE (2002) The effects of noradrenaline on the amplitude-time characteristics of multiquantum endplate currents and the kinetics of induced secretion of transmitter quanta. Neurosci Behav Physiol 32:549–554

Autonomic Failure

► Autonomic Insufficiency

Autonomic Function and Exercise

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Synonyms

Terms sometimes used to describe exercise and related phenomena include muscle contraction, muscular work, and physical activity

Definition

Exercise can be defined as the voluntary activation of skeletal muscles for recreation, rehabilitation, or participation in sport. Since it is possible to evoke muscle contraction via electrical stimulation or segmental reflexes, this definition emphasizes the voluntary component of exercise and CNS involvement in the contractions. Terms like physical activity include exercise as defined above but also voluntary muscular contractions directed toward occupational and other activities of daily living.

Exercise has been categorized as “static,” “dynamic,” or “intermittent.” Static exercise refers to exercise associated with limited muscle shortening, and is the human analog to “isometric” contractions in isolated muscle preparations. Dynamic exercise describes rhythmic shortening and/or lengthening contractions and is exemplified by running or cycling. Intermittent exercise describes things like ball games where variable bursts of activity with varying muscle mass and forces are used. The basic mechanisms that govern the autonomic responses to static, dynamic and intermittent exercise are similar. In this chapter only “static” and “dynamic” exercise will be discussed further.

Characteristics

Quantitative Description

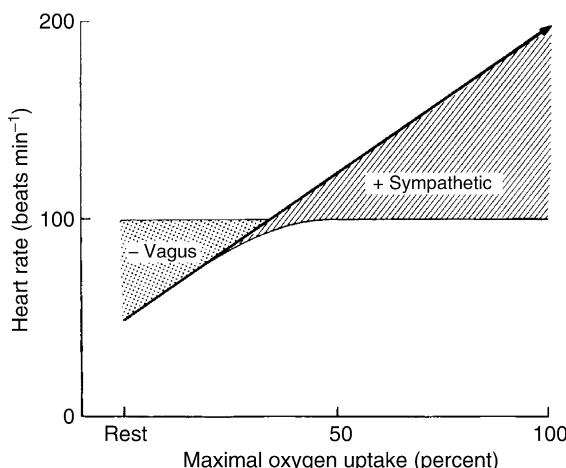
Exercise of all types is associated with several physiological responses governed by the autonomic nervous system:

- An increase in heart rate.
- An increase in blood pressure, especially systolic blood pressure.
- An increase in ventilation.
- Exercise lasting more than a few minutes also evokes autonomic responses directed at metabolism and thermoregulation.

The magnitude of these responses can be highly variable depending on the intensity and duration of the exercise along with subject specific variables. However, the direction of change across conditions is similar.

At the onset of exercise, heart rate (HR) rises instantaneously [1,2]. During heavy or maximal dynamic exercise in the young, values increase from around 60 beats/min at rest to about 200 beats/min. With a static handgrip, heart rate usually rises 10–20 beats per minute (depending on the fraction of maximal voluntary contraction), but with prolonged or fatiguing contractions larger increases occur. The rise in HR from rest to 100 beats/min is mainly due to withdrawal of vagal tone to the heart. As HR increases to values above 100 beats/min, the cardiac sympathetic nerves become increasingly engaged (Fig. 1).

At the onset of exercise there is also an instantaneous rise in arterial blood pressure [1,2]. During dynamic



Autonomic Function and Exercise.

Figure 1 Schematic showing the contributions of vagal withdrawal and sympathetic activation to the rise in heart rate (HR) with exercise. At rest, vagal control of heart rate predominates. As exercise intensity increases to 30–40% of maximal, vagal tone is withdrawn and HR increases to about 100 beats per minute. At this exercise intensity, sympathetic traffic to the heart increases and is responsible for the further rise in HR as exercise intensity increases. (Figure from Rowell, LB: “Human Cardiovascular Control,” Oxford 1993.)

exercise, systolic pressure rises due to increases in stroke volume and heart rate that eject more blood into the aorta and large conducting vessels. The effects of dynamic exercise on diastolic pressure are more variable due to vasodilation in the active skeletal muscles. In young healthy subjects and trained athletes diastolic blood pressure does not change or falls. In older subjects and those with conditions like hypertension diastolic pressure can rise with exercise. The net effect of these changes is a modest to marked increase in mean arterial pressure.

During static exercise both systolic and diastolic pressure rise. The rise in systolic pressure is due to increased cardiac output (due primarily to an increased HR) and peripheral vasoconstriction caused by the sympathetic nervous system. Static muscle contractions also compress blood vessels in the active muscles [2,3]. With large muscle mass exercise this causes diastolic pressure to rise. In severe forms of large muscle mass static exercise or during very heavy weight lifting, systolic arterial pressure can rise to values above 300 mmHg.

Like heart rate and blood pressure, ventilation increases instantaneously at the onset of exercise. During heavy dynamic exercise values in excess of 100 L/min can be seen, and in some elite athletes values

in excess of 150–200 L/min are common. With static exercise, the rise in ventilation is usually much less.

The autonomic nervous system also maintains metabolic homeostasis during exercise (especially prolonged dynamic exercise), when the metabolic rate can increase by 10-fold or more. This is accomplished by mobilizing fuel from the liver and fat cells via the sympathetic nerves and release of epinephrine and other hormones [4]. During prolonged dynamic exercise core temperature can rise several degrees and engage autonomic thermoregulatory responses that evoke sweating and can cause skin blood flow to rise from very low levels to as much as 5–7 L/min [2].

The main structures that regulate the cardiovascular and respiratory responses are in or near the nucleus of the solitary tract, and for metabolic and thermoregulatory control they reside in the hypothalamus [1–3,5]. These structures receive descending commands from CNS centers (especially the sub-thalamic locomotor center) that are involved in the planning and execution of the contractions.

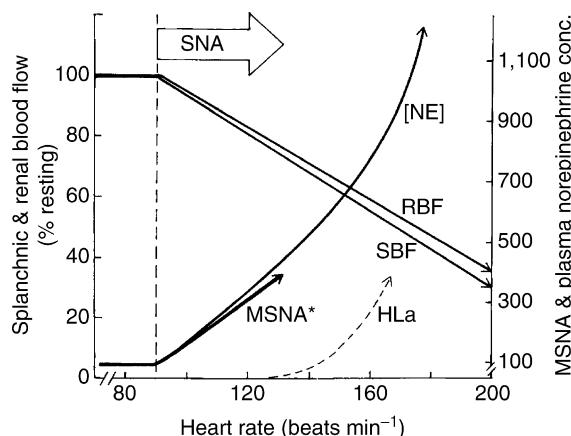
Lower Level Components

The cardiovascular and respiratory centers receive continuous input from afferents located throughout the body. The primary afferent information affecting cardiovascular function during exercise comes from arterial baroreceptors and chemoreceptors located in the aortic arch and carotid sinus, and carotid body along with group 3 and 4 afferents in the active skeletal muscles [1–3,6,7]. There are also thermal sensors located throughout the body (but most notably in the hypothalamus), and sensory neurons in the hypothalamus also monitor blood glucose [2,4].

Higher Level Processes

In general, a signal proportional to the central motor command provides “feed-forward” information to the brainstem cardiovascular and respiratory centers (and probably the centers that govern metabolism and thermoregulation). This “central command” evokes the instantaneous increase in heart rate, blood pressure and ventilation seen at the onset of exercise [1,2]. It permits substantial physiological adjustments to be made before there are vast increases in muscle metabolism that might overwhelm traditional feedback regulatory mechanisms. Central command clearly causes:

- Vagal withdrawal from the heart and a rapid increase in heart rate
- An increase in renal sympathetic nerve activity
- An increase in ventilation prior to any changes in arterial blood gases that might be sensed by chemoreceptors
- A resetting of arterial baroreflexes so that blood pressure and heart rate can rise with exercise [7]



Autonomic Function and Exercise.

Figure 2 Schematic representation of how various indices of sympathetic outflow change with exercise intensity. Splanchnic and renal blood flow are 100% at rest and as exercise intensity increases vasoconstrictor outflow to these vascular beds can reduce blood flow to ~30% of resting values. The curvilinear line shows the rise in plasma norepinephrine, (NE) an index of whole body sympathetic activation. The rise NE does not start until exercise intensities become moderate. Muscle sympathetic nerve activity (MSNA) also rises during moderate and heavy exercise. Vasoconstriction in the visceral beds permits a higher fraction of the cardiac output to perfuse the contracting muscles. The rise in MSNA limits blood flow to inactive muscle and restrains metabolic vasodilation to maintain blood pressure. (Figure from [1].)

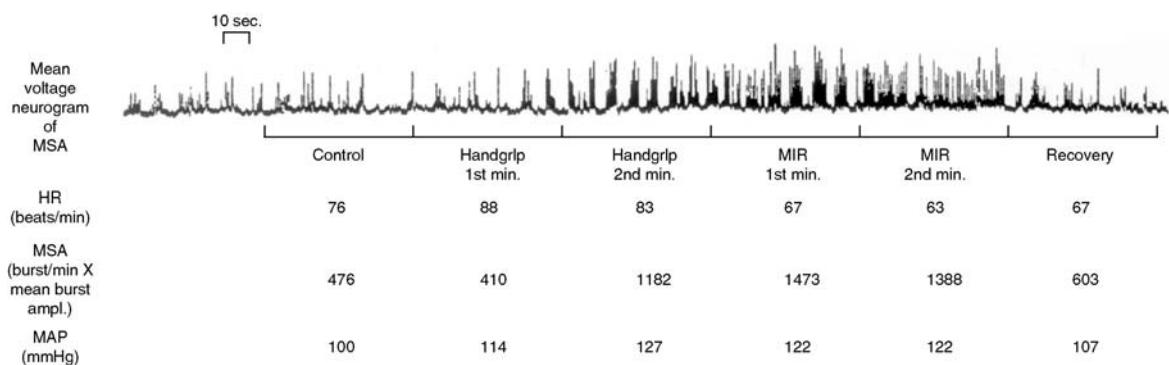
However, central command does not evoke “mass sympathetic” discharge to most organ systems, but provides discrete and targeted changes in autonomic outflow [Figure 2](#) [1–3,5].

Lower Level Processes

Arterial baroreceptors respond to mechanical deformation in the aortic arch and carotid sinus. Increased deformation results in increased afferent firing and is related to changes in arterial pressure. Changes in arterial blood pCO_2 and pO_2 are sensed by the aortic and carotid chemoreceptors that are close to the baroreceptors. During mild and moderate dynamic exercise changes in any of the variables sensed by the arterial chemoreceptors are minimal, and it is unclear if these receptors are obligatory for the regulation of ventilation during exercise under most circumstances.

In skeletal muscle group III and IV afferents evoke cardiovascular and respiratory responses based on exercise-induced changes in the skeletal muscle, and thus provide the autonomic nervous system with information about the contracting skeletal muscle [1–3,5,6]. At rest the group III afferents are primarily mechanosensitive and the group IV afferents respond primarily to metabolic stimuli, especially acidosis. However, during exercise chemosensitive afferents can respond to mechanical stimuli and vice versa ([Fig. 3](#)).

As blood glucose declines, epinephrine is released from the adrenal medulla and (in conjunction with other hormonal adaptations) mobilizes glucose from liver glycogen and liberates free fatty acids from adipocytes



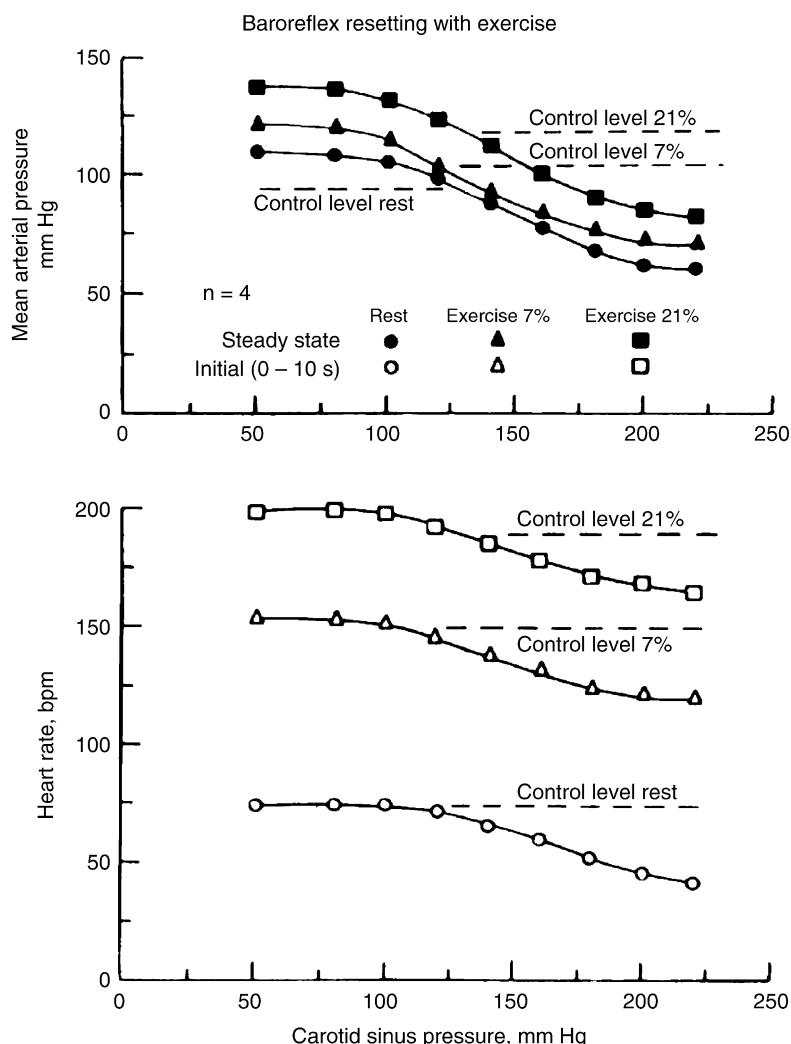
Autonomic Function and Exercise. Figure 3 Change in Muscle Sympathetic Nerve Activity (MSNA) during a forceful handgrip lasting several minutes followed by muscle ischemia produced by inflation of an arm cuff to supersystolic levels. From rest to exercise there is a rapid rise in HR and blood pressure, however, MSNA does not rise for about a minute. Additionally, blood pressure and MSNA, but not heart rate, remains elevated during the muscle ischemic response (MIR). These data show that central command can cause HR and blood pressure to rise before MSNA is increased. During handgripping, the rise in MSNA is thought to occur when muscle acidosis acts locally to stimulate chemosensitive muscle afferents. This stimulation continues during the MIR when the acidotic metabolites are trapped in the previously active muscles. Experimental paradigms like this have been used to study the interplay between central command and feedback from muscle in regulating the autonomic responses to exercise. (Figure from [3].)

to support muscle metabolism during prolonged heavy dynamic exercise like marathon running.

Temperature sensitive neurons located in the preoptic/anterior hypothalamus monitor central temperature. This area also receives feedback from temperature sensitive afferents throughout the body. When core temperature falls there is an increase in vasoconstrictor activity to skin to conserve heat. When core temperature rises there is a withdrawal of vasoconstrictor activity, followed by activation of sympathetic cholinergic nerves to sweat glands and cutaneous blood vessels [2].

Process Regulation

The current concept is that central command evokes changes in autonomic outflow that prepare the organism for exercise. However, the old idea of “mass sympathetic discharge” at the onset of exercise has been superseded. In this context, central command is thought to operate in two basic ways [1–3,6,7]. First, central command directly influences the cardiovascular and respiratory centers. Second, it is also thought to re-set feedback mechanisms so that the “operating point” and gain of the response facilitates the physiological



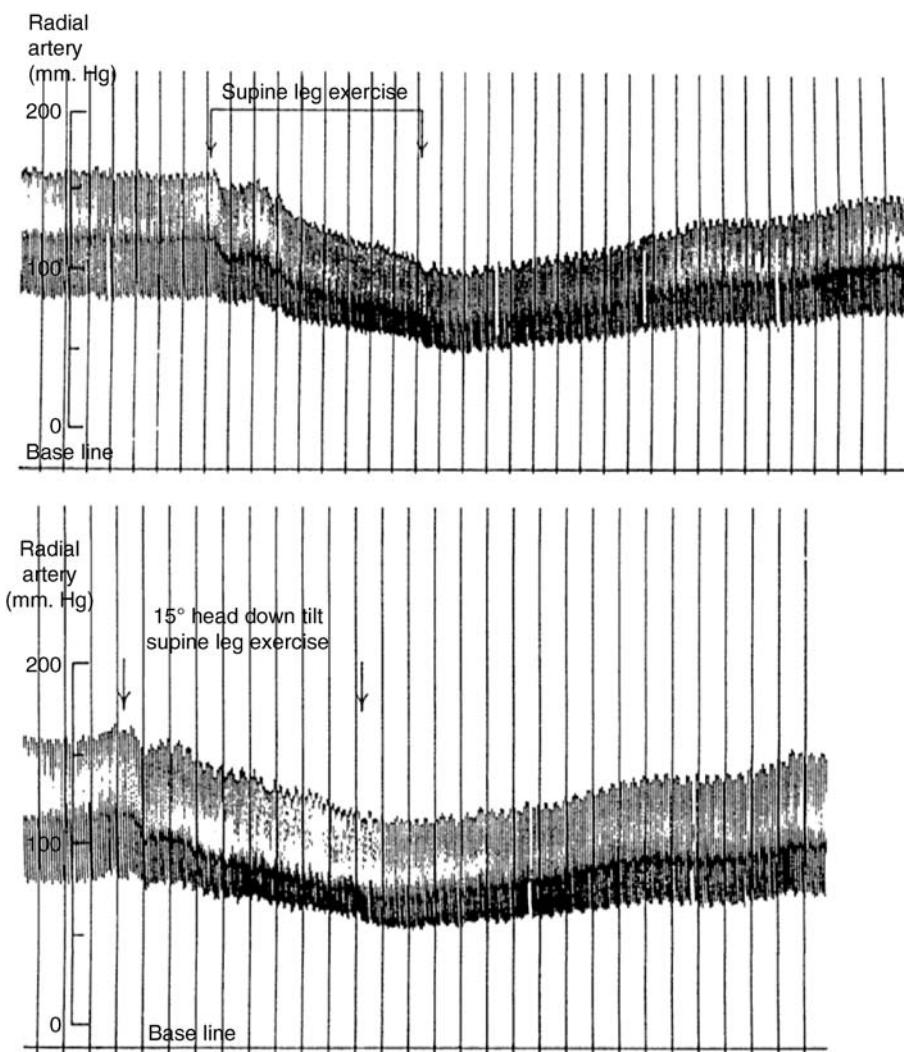
Autonomic Function and Exercise. Figure 4 Effects of altering pressure in a surgically isolated carotid sinus preparation in a conscious dog during rest and several levels of exercise. This preparation permits manipulation of pressure in the carotid sinus and measurement of systemic responses. A rise in carotid sinus pressure will evoke a baroreflex mediated fall in systemic pressure and HR. By contrast, a fall in carotid sinus pressure will evoke a baroreflex mediated rise in systemic pressure and HR. During exercise, the ability of baroreflexes to regulate arterial pressure and heart rate are maintained, but their operating point is shifted upward so that a rise in BP and HR are permitted. Central command is thought to cause baroreceptor “resetting” in the brainstem cardiovascular centers. (Figure from [7].)

adjustments needed for exercise. For example, blood pressure and heart rate rise during exercise, but recent evidence suggests that baroreflexes operate normally but are re-set to defend a higher blood pressure during exercise [7] (Fig. 4).

The group III and IV afferents contribute to overall blood pressure and respiratory regulation by providing the brain with information about the metabolic and contractile state of the active muscles. When skeletal muscle becomes acidotic, Group IV afferents can evoke a robust pressor (and modest ventilatory) response and signal a “mismatch” between blood flow and

metabolism so that blood pressure rises to increase blood flow to the active skeletal muscles [1–3,5,6].

Normally, when core temperature increases by 0.5–1°C there is withdrawal of vasoconstrictor tone to the skin, and then activation of sudomotor (and vasodilator) nerves to the skin. The sudomotor nerves evoke sweating which increases evaporative heat loss and cools the skin. At about the same time there is marked neurally-mediated cutaneous vasodilation which transports heat from the core to the periphery. With exercise, the threshold for sweating and cutaneous dilation is shifted to a higher temperature [1].



Autonomic Function and Exercise. Figure 5 Total failure of arterial pressure regulation during exercise in a patient with autonomic failure. This patient had undergone extensive surgical sympathectomies for malignant hypertension before antihypertensive drugs were available. In the upper panel blood pressure falls as soon as supine exercise starts and continues to fall as it continues. A second trial of exercise was then attempted with a 15% head down tilt to augment venous return. However, blood pressure also fell during this trial. This demonstrates the essential role of the sympathetic nervous system in redistributing cardiac output and restraining vasodilation in the active muscles to regulate blood pressure during exercise. (Figure from [9].)

With the onset of exercise there is an increase in sympathetic outflow to visceral organs to mobilize glucose from the liver and suppress the release of insulin [4]. Additionally, with heavy, large-muscle-mass exercise, epinephrine is released from the adrenal medulla and also contributes to these and related responses. During prolonged, moderate exercise, these responses are more modest, and are important after one or two hours of exercise when glucose homeostasis is threatened by depletion of liver and intramuscular glycogen.

Function

The overall function of the autonomic nervous system during exercise is to maintain whole body homeostasis in the face of potentially huge increases in skeletal muscle metabolism. With static exercise fuel for skeletal muscle and temperature regulation are not major problems, and the respiratory consequences are generally not limiting. The main problem is that high skeletal muscle forces compress blood vessels to the active muscles and contribute to skeletal muscle acidosis. A combination of relative or absolute skeletal muscle underperfusion and high levels of metabolic demand lead to autonomic responses designed to increase arterial blood pressure, and hence blood flow to the active muscles.

With large muscle mass dynamic exercise, skeletal muscle metabolic activity can increase to 10-fold in untrained healthy subjects and up to 20-fold in trained athletes. The first physiological “problem” is that there is a marked (up to 50- to 100-fold) vasodilation in the active skeletal muscles and without vasoconstriction of visceral organs, increases in heart rate, and some sympathetic restraint of metabolic vasodilation in the active skeletal muscles blood pressure will fall [1,2,8]. Additionally, if there is not a prompt and adequate increase in minute ventilation, potentially lethal changes in blood gases might occur. So, the increase in minute ventilation (probably evoked largely by central command) is essential to avoid exercise-induced asphyxia. A third main problem posed by dynamic exercise to homeostasis is thermoregulation.

However, when a large increase in skin blood flow is superimposed on the rise in skeletal muscle blood flow with exercise the vasodilation can threaten arterial pressure regulation [2].

Pathology

There are many pathophysiological conditions associated with the autonomic nervous system that influence the physiological adjustments to exercise. Figure 5 shows the fall in blood pressure seen in patients with autonomic failure [9]. In these patients the sympathetic nerves do not restrain blood flow to the active muscles and visceral organs and exercise tolerance is severely limited. By contrast, in congestive heart failure, there

is augmented sympathetic outflow to muscle at rest and during exercise, contributing to skeletal muscle underperfusion and limiting exercise tolerance.

Therapy

Endurance exercise is a common and effective therapy for a variety of “lifestyle” related diseases including: hypertension, diabetes, dyslipidemia, obesity, and rehabilitation from heart attack. Exercise is also a key anti-aging strategy. While there are many beneficial effects of regular exercise, at least some are likely to relate to improved autonomic control of heart rate and blood pressure.

References

- Rowell LB, O’Leary DS (1990) Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol* 69:407–418
- Rowell LB, O’Leary DS, Kellogg DLJ (1996) Integration of cardiovascular control systems in dynamic exercise. In: Rowell LB, Shepherd JT (eds) *Handbook of physiology*, sect. 12, exercise: regulation and integration of multiple systems. Oxford University Press, New York, pp 772–783
- Mark AL, Victor RG, Nerhed C, Wallin BG (1985) Microneurographic studies of the mechanisms of sympathetic nerve responses to static exercise in humans. *Circ Res* 57:461–469
- Richter EA (1996) Glucose utilization. In: Rowell LB, Shepherd JT (eds) *Handbook of physiology*, sect. 12, exercise: regulation and integration of multiple systems. Oxford University Press, New York, pp 912–951
- Mitchell JH, Victor RG (1996) Neural control of the cardiovascular system: insights from muscle sympathetic nerve recordings in humans. *Med Sci Sports Exerc* 28: S60–S69
- McCloskey DI, Mitchell JH (1972) Reflex cardiovascular and respiratory responses originating in exercising muscle. *J Physiol* 224:173–186
- Melcher A, Donald DE (1981) Maintained ability of carotid baroreflex to regulate arterial pressure during exercise. *Am J Physiol* 241:H838–H849
- Joyner MJ, Proctor DN (1999) Muscle blood flow during exercise: the limits of reductionism. *Med Sci Sports Exerc* 31:1036–1040
- Marshall RJ, Schirger A, Shepherd JT (1961) Blood pressure during supine exercise in idiopathic orthostatic hypotension. *Circulation* 24:76–81

Autonomic Function in Space

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Synonyms

Neurovegetative function in outer space; Sympathetic and parasympathetic nerve activity in microgravity

Definition

Autonomic function, also called neurovegetative function, is essentially important to regulate vital functions in humans and animals. This function is mainly dependent on the autonomic nervous system being composed of the sympathetic and parasympathetic nervous system. The autonomic nervous system regulates different kinds of vital organs and organ systems in the living body, including heart, blood vessels, sweat glands, adrenal gland and other hormone secretory organs, gastrointestinal tract, genitourinary organs, etc., by automatically and involuntarily using complex central commands and reflex mechanisms. This system plays indispensable roles in maintaining the homeostasis of blood pressure, blood glucose level, body temperature, and body fluid volume. Some of the autonomic functions are important for the maintenance of homeostasis of blood pressure and body fluid volume against terrestrial gravity. Gravity-dependent autonomic function should be altered in ►microgravity in space to adapt to this unusual condition. Autonomic function in space has been studied in Skylab, Spacelab, and more recently in ►Neurolab, using the space shuttle Columbia launched by NASA in USA [1–3], as well as in the Russian space station Mir [4]. This function is going to be investigated in the International Space Station, and also in interplanetary flights, for example to Mars, in the future. The same function has also been studied using various ground-based simulations of microgravity including ►parabolic flight [5], lower body positive pressure [6], head-out water immersion [7], dry immersion [8] and head-down bed rest [9].

Characteristics

Quantitative Description

Autonomic function has been evaluated in the living body using several different methods. Indirect and direct methods have been used for the quantitative evaluation of autonomic function. One of the indirect methods is to determine the plasma level of noradrenaline that is secreted at ►sympathetic nerve terminals. The plasma level of noradrenaline has been used as a good index of overall sympathetic nerve activity. More recently, noradrenaline spillover measurement became available to assess sympathetic nerve function in the organ levels. Another method often used is power spectral analysis of heart rate and blood pressure variabilities. Heart rate and blood pressure are modulated depending on sympathetic and parasympathetic neural regulation. Power spectral analysis of the heart rate reveals low (around 0.1 Hz) and high frequency (around 0.25 Hz) peaks. High frequency peaks in the power spectrum of heart rate variations is dependent on respiration and is considered to represent cardiac parasympathetic (vagal) nerve activity. The value of

high frequency power divided by low frequency power is considered to represent cardiac sympathetic nerve activity; however, the assessment of this value is still under discussion. On the other hand, low frequency peaks in the power spectrum of blood pressure is related to so-called Mayer rhythm, and is considered to represent vasomotor sympathetic nerve activity. Based on these power spectral analyses of heart rate and blood pressure, quantitative analysis of autonomic functions has been possible in human subjects. In animals, direct recordings of sympathetic and ►parasympathetic nerve activity allows us a more precise and quantitative evaluation of autonomic function. Direct measurement of sympathetic nerve activity has also become possible in humans using a technique called ►microneurography. Microneurography has enabled us to record sympathetic nerve activity leading to muscle (►muscle sympathetic nerve activity; MSNA) and skin (skin sympathetic nerve activity; SSNA) from human peripheral nerves. Unfortunately, direct evaluation of parasympathetic nerve activity is not yet possible in humans. Autonomic function in space has been analyzed in humans using these different methods including measurement of the plasma level of noradrenaline, noradrenaline spillover measurement, power spectral analysis of heart rate and blood pressure, as well as microneurography.

Higher Level Structures

The autonomic nervous system is composed of higher and lower level structures. Higher level structures include cerebral cortex, hypothalamus and brainstem. Hypothalamus plays a particularly important role in central control of autonomic function. Functions of these higher structures have been studied on earth, but poorly in space. These problems are expected to be resolved by future research under microgravity conditions in space.

Lower Level Components

Lower level components of the autonomic nervous system include spinal cord, peripheral nerve, ►peripheral receptors and target effector organs. The descending commands from upper structures descend through brainstem and spinal cord to control target effector organs through peripheral sympathetic nerve with adrenergic α and β receptors, as well as parasympathetic nerves with cholinergic receptors. Peripheral ►target organs, also called effector organs, include pupils, heart, blood vessels, sweat glands, hormone secretory glands, gastrointestinal tracts, and genitourinary organs, etc., and react to efferent neural signals through peripheral receptors to maintain functional homeostasis against changes in environmental condition. Changes in efferent neural signals in peripheral sympathetic nerve leading to skeletal muscle (muscle sympathetic

nerve activity; MSNA) in humans have been studied using microneurography in ►simulated microgravity on the ground and also in space. MSNA was suppressed during exposure to short-term simulation of microgravity (parabolic flight [5], lower body positive pressure [6], and head-out water immersion [7]), but was enhanced after exposure to long-term simulation of microgravity (dry immersion [8], ►head-down bed rest [9]) and also after spaceflight of 17 days [1]. A lack of enhanced MSNA response after head-down bed rest of two weeks induced orthostatic hypotension.

Structural Regulation

Structural regulation of the autonomic nervous system depends not only on descending commands from central structures, but also on different kinds of autonomic reflexes being composed of peripheral afferent (vagal and somatosensory) and efferent (sympathetic and parasympathetic) nerves, as well as reflex centers in spinal cord, brainstem and/or cerebral cortex. Autonomic reflexes play essential roles in maintaining homeostasis in the living body against changes in environmental conditions, including gravitational stress. For example, ►baroreflex is essentially important to maintain blood pressure homeostasis against terrestrial gravity. Changes in baroreflex and its components were studied in rats after exposure to spaceflight (Neurolab). The baroreflex sensitivity became lower with fewer unmyelinated nerve fibers, lower contraction ability and tension of the aorta, and a reduced number of smooth muscle cells in the aorta compared to preflight controls [3].

Function

The function of the autonomic nervous system is highly complicated. Some of the autonomic functions are gravity-dependent. Gravity-dependent functions are more influenced by changes in gravitational loading and unloading. Some functional changes of the autonomic nervous system in space are comparable to age-related changes in autonomic function. For example, increases in basal MSNA after exposure to simulated (head-down bed rest) and real microgravity in space is similar to age-related changes in MSNA [10]. The MSNA increase induced by exposure to microgravity and aging may be related to similar compensatory mechanisms for changes in fluid volume, baroreflex, blood vessel and/or its receptors.

Pathology

Different kinds of autonomic dysfunction occur in space. The autonomic disorder that appears at the early phase of spaceflight is ►space motion sickness. This disorder resembles motion sickness on earth, with symptoms such as nausea, vomiting, loss of appetite, vertiginous sensation, head heaviness, etc. Space motion sickness

is caused by abnormal vestibulo-autonomic reflex related to brainward fluid shift and/or mismatching among sensations of different modalities, i.e., visual, vestibular and somatosensory information. Another important autonomic disorder is cardiovascular deconditioning in space. This deconditioning is induced by many factors including ►headward fluid shift, loss of blood volume, changes in baroreflex, changes in blood vessels and its receptor, loss of muscle pumping due to leg muscle atrophy and so on. Cardiovascular deconditioning is a kind of adapted condition to microgravity. The problem occurs when astronauts return to the earth. They often experience ►orthostatic intolerance with hypotension when standing. Orthostatic hypotension is one of important post-spaceflight dysfunctions in the human body that maintains upright posture against terrestrial gravity. The cause of post-flight orthostatic intolerance has been discussed and several hypotheses have been proposed; (i) reduced circulatory plasma volume due to fluid shift, (ii) reduced vascular responsiveness to sympathetic stimulation, (iii) cardiac hypofunction, and (iv) altered baroreflex and cardiopulmonary reflex.

Therapy

For the therapy of space motion sickness, drugs used for motion sickness on earth such as antihistamine can be administered. Biofeedback treatment is also applicable for this disorder. To prevent post-spaceflight orthostatic intolerance, in-flight exercise and lower body negative pressure loading have been recommended. Water and salt intake before landing is also effective to prevent orthostatic intolerance. Artificial gravity applying short radius centrifuge is being developed to prevent orthostatic intolerance after long-term spaceflight. As medical therapy, a selective α -adrenoreceptor agonist midodrine hydrochloride and a peripheral noradrenaline competitor amezinium metilsulfate can be used for the treatment of orthostatic hypotension.

References

- Levine BD, Pawelczyk JA, Ertl AC, Cox JF, Zuckerman JH, Dietrich A, Biaggioni J, Ray CA, Smith MI, Iwase S, Saito M, Sugiyama Y, Mano T, Zhang R, Iwasaki K, Lane LD, Buckey JC, Cook WH, Baisch FJ, Robertson D, Eckberg DL, Blomqvist CG (2002) Muscle sympathetic neural and haemodynamic responses to tilt following spaceflight. *J Physiol* 538:331–340
- Cox JF, Tahvanainen KUO, Kuusela TA, Levine BD, Cook WH, Mano T, Iwase S, Saito M, Sugiyama Y, Ertl AC, Biaggioni I, Dietrich A, Robertson MR, Zuckerman JH, Lane LD, Ray DA, White RJ, Pawelczyk JA, Buckey JC, Baisch FJ, Blomqvist CG, Robertson D, Eckberg DL (2002) Influence of microgravity on sympathetic and vagal responses to Valsalva's manoeuvre. *J Physiol* 538:309–320

3. Shimizu T, Yamasaki M, Waki H, Katsuda S, Oishi H, Katahira K, Nagayama T, Miyake M, Miyamoto Y (2002) Development of the aortic baroreflex in microgravity. In: Buckey JC, Homick JL (eds) The Neurolab Spacelab mission: neuroscience research in space. Lyndon B Johnson Space Center, Houston, TX, NASA SP-2003-535, pp 151–159
4. Cooke WH, Ames JEIV, Crossman AA, Cox JF, Kuusela TA, Tavanainen KUO, Moon LB, Drescher J, Baisch FI, Mano T, Levine BD, Blomqvist GC, Eckberg DL (2000) Nine months in space: effects on human autonomic cardiovascular regulation. *J Appl Physiol* 89:1039–1045
5. Iwase S, Mano T, Cui J, Kitazawa H, Kamiya A, Miyazaki S, Sugiyama Y, Mukai C, Nagaoka S (1999) Sympathetic outflow in humans during short period of microgravity produced by parabolic flight. *Am J Physiol* 266:R419–R426
6. Fu Q, Iwase S, Niimi Y, Kamiya A, Kawanokuchi J, Cui J, Mano T, Suzumura A (2001) Effects of lower body positive pressure on muscle sympathetic nerve activity response to head-up tilt. *Am J Physiol* 281:R1134–R1139
7. Miwa C, Mano T, Saito M, Iwase S, Matsukawa T, Sugiyama Y, Koga K (1996) Aging reduces sympatho-suppressive response to head-out water immersion in humans. *Acta Physiol Scand* 58:15–20
8. Iwase S, Sugiyama Y, Miwa C, Kamiya A, Mano T, Ohira Y, Shenkman B, Egorov A, Kozlovskaya IB (2000) Effects of three days of dry immersion on muscle sympathetic nerve activity and arterial blood pressure in humans. *J Auton Nerv Syst* 9:156–164
9. Kamiya A, Iwase S, Kitazawa H, Mano T, Vinogradova OL, Kharchenko IB (2000) Baroreflex control of muscle sympathetic nerve activity after 120 days of 6 head-down bed rest. *Am J Physiol* 278:R445–R452
10. Iwase S, Mano T, Watanabe T, Saito M, Kobayashi F (1991) Age-related changes of sympathetic outflow to muscles in humans. *J Gerontol Med Sci* 46:M1–M5

Autonomic Ganglia

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Synonyms

Sympathetic ganglia; parasympathetic ganglia

Definition

Signals from the CNS to all peripheral tissues except skeletal muscle are transmitted, and in some cases modulated, within autonomic ganglia. Autonomic ganglia are aggregations of neurones that lie along peripheral

nerve trunks where synapses are made by the axons of preganglionic neurones projecting from the brainstem and spinal cord.

Characteristics

General Description

The autonomic (Cross Ref) and somatomotor (Cross Ref) systems differ in that there is at least one autonomic synapse between the outflow from the central nervous system and the target organ. These synapses occur in swellings (“ganglia”) along peripheral nerve trunks where the cell bodies of autonomic neurones aggregate during development. The ganglia differ somewhat between the divisions of the autonomic nervous system. These divisions were defined by John Langley at the end of the nineteenth century, primarily on anatomical grounds. Sympathetic preganglionic neurones lie in the intermediate zone of the thoracic and upper lumbar spinal cord, whereas ▶parasympathetic preganglionic neurones lie in the cranial nerve nuclei and in the intermediate zone of the sacral spinal cord. ▶Ganglia of the ▶enteric nervous system are located within nerve plexuses in the gastrointestinal tract (cross ref to Enteric NS): the effects of the central nervous system on the gut are mediated via axons of sympathetic and parasympathetic origin, i.e., the enteric nervous system is a target of the other divisions.

Sympathetic and parasympathetic ganglia are mainly located separately. Preganglionic neurones project their axons in a segmental ventral root or in a cranial nerve to reach their target ganglia. Neurones within the ganglia (“ganglion cells,” “postganglionic neurones”) have axons projecting to specific functional targets, largely without any somatotopic organization. In a few cases, as in the pelvic ganglion of the male rat [1], sympathetic and parasympathetic ganglion cells intermingle in a single ganglion. The postganglionic axons project to their target organs in the peripheral nerve trunks.

Autonomic and sensory ganglia have a common origin in the neural crest, and share dependence on nerve growth factor(s) for survival during development and for maintenance in the adult [2]. Axotomy without regeneration leads to significant loss of both sympathetic and small sensory neurones. (Cross Ref to Neurotrophins and Degeneration/regeneration) The capillaries of these ganglia lack a significant barrier from the blood so that circulating hormones and toxins have ready access to modify neurones and synaptic behavior.

Quantitative Description

The innervation of all peripheral tissues except skeletal muscle fibers is provided by autonomic pathways. There are many hundreds of thousands of autonomic neurones located in peripheral ganglia, which amplify spatially the signals emanating from the central nervous

system and, in some cases, modify the signals via feedback from the target tissue. Many of the properties of ganglia have been summarized previously [3] and only newer information is referenced here.

Higher Level Structures

Sympathetic paravertebral chain, sympathetic prevertebral ganglia, parasympathetic ganglia.

Lower Level components

Functional Anatomy of Autonomic Pathways

Sympathetic ganglia are organized in two ways:

1. Bilateral paravertebral “chains” dorsal to the aorta extend to the base of the skull rostrally (to the superior cervical ganglion, SCG) and to the fused coccygeal ganglia (the ganglion impar) caudally. The segmental ganglia form beaded structures on either side that are more or less separate but often fuse at lumbar and sacral levels. Adjacent segmental ganglia may be fused (e.g., SCGs represent all cervical segments). Paravertebral ganglia are primarily involved with the innervation of blood vessels, sweat glands and erector pili in the trunk and limbs.

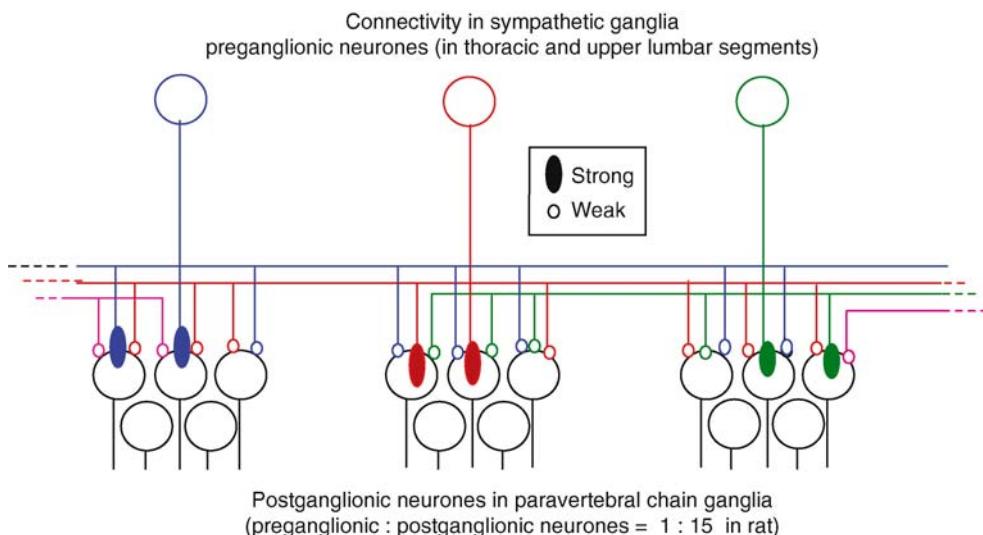
The neurones in each segmental ganglion project their axons to peripheral nerves via a grey ramus (reflecting the lack of myelination of postganglionic axons) or to the viscera via the splanchnic nerves. Each segmental ganglion between T1 and the most caudal sympathetic output for that species receives preganglionic axons via a white ramus (most preganglionic

axons are myelinated). The preganglionic axons branch rostrally and/or caudally along the chain at thoracolumbar levels, so that each preganglionic axon forms synapses in several adjacent chain ganglia (Fig. 1), whereas cervical and lumbar chain ganglia receive axons arising from the rostral and caudal ends of the spinal outflow, respectively.

2. The preganglionic axons to the abdominal viscera cross the paravertebral chain in the splanchnic nerves which project to the prevertebral ganglia (e.g., coeliac-superior mesenteric and hypogastric ganglia). Postganglionic axons from these large ganglia project along the visceral nerves to the gastrointestinal tract and other viscera.

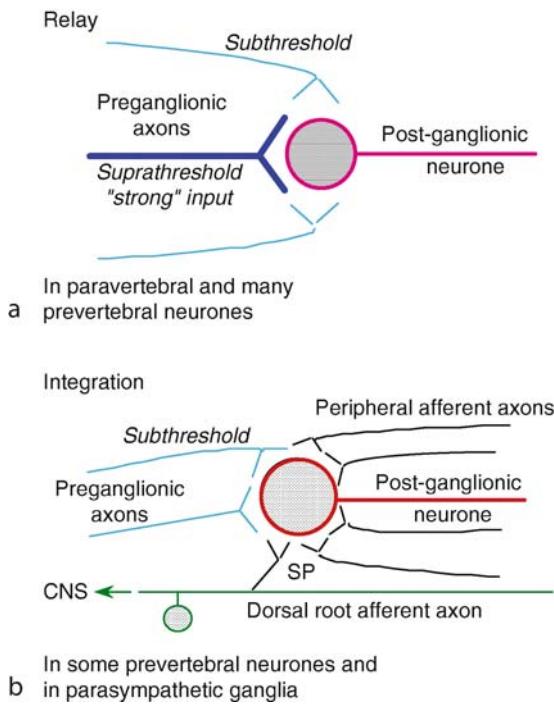
Paravertebral ganglia contain only preganglionic terminals, postganglionic neurones and associated supporting glia, with occasional “paraganglion cells” (small intensely fluorescent (SIF) cells) which have no axon but may release catecholamines into the vasculature. In contrast, prevertebral ganglia also contain the terminals of axons from enteric afferent neurons. Together with collateral branches of peptidergic primary afferent axons, these inputs excite ganglion cells involved with the inhibition of motility and secretion (Fig. 2, [4]). Finally, the sympathetic innervation of the enteric nervous system involves presynaptic modulation of enteric synapses rather than direct synapses on enteric neurones.

The *parasympathetic* ganglia project largely to cranial and visceral organs (not the limbs) and are less



Autonomic Ganglia. Figure 1 Connectivity in sympathetic ganglia of the thoracic paravertebral chain.

Preganglionic axons arising in each spinal segment pass into the chain where they form synapses with postganglionic neurones. Synapses are either suprathreshold (“strong”) or subthreshold (“weak”). Preganglionic axons tend to form strong synapses in the corresponding segmental ganglion. They send collateral branches to adjacent segmental ganglia where they generally form weak synapses. The weak synapses hardly ever contribute to the postganglionic discharge, but they can grow and take over the connection if the strong axon disappears (after e.g., injury to the spinal cord).



Autonomic Ganglia. Figure 2 Function of synaptic transmission in ganglia. Transmission is by one of two mechanisms: (a) In most sympathetic ganglia, only one (occasionally two) of many preganglionic inputs activate the postganglionic cell, acting to relay precisely the CNS command via a suprathreshold cholinergic input. (b) In some prevertebral neurones and in parasympathetic ganglia, the postganglionic neurone integrates subthreshold information from many cholinergic inputs that arise both centrally and peripherally. Peptides such as Substance P (SP) released from collaterals of primary afferents act to potentiate the effects of the cholinergic inputs from other pathways by decreasing the conductance of the postganglionic cell.

organized. They resemble enteric ganglia in consisting of small clusters of neurones adhering to or lying within the walls of the viscera, e.g., salivary gland, heart, pancreas, bladder. Most of these ganglia contain sensory somata and interneurons as well as the postganglionic neurones that project to the target tissue. Thus, they have all the necessary components for reflex activity, although the precise function of the reflexes is largely unknown. The signals in parasympathetic pathways are more likely to be modified before they reach their targets than those in the sympathetic paravertebral chain (Fig. 2). Finally, parasympathetic neurones supplying the gastrointestinal tract directly innervate enteric neurones.

Structure of Autonomic Ganglion Cells and their Synapses

Sympathetic neurones have large somata ($\sim 20\text{--}50 \mu\text{m}$ in diameter) and 0 to >20 dendrites that are relatively

thin and sometimes varicose. The dendrites extend up to $500 \mu\text{m}$ from the soma (Fig. 3). The number of dendrites is proportional to the number of inputs that the neurone receives. Synaptic contacts ($<1 \mu\text{m}^2$) are made randomly by the varicosities of input neurones at a low density ($<1/100 \mu\text{m}^2$) over the soma, and dendrites and adjacent synapses can arise from distinct inputs [5]. About 50% of varicosities do not contact a ganglion cell, even with an intervening glial process. The number of synaptic contacts on a single guinea pig sympathetic paravertebral ganglion cell with ~ 10 dendrites is ~ 100 . In contrast, parasympathetic neurones are usually monopolar and tend to be small with synapses that arise from one preganglionic axon, sometimes together with other peripheral inputs.

Higher Level Processes

Connectivity

In both autonomic divisions, each preganglionic axon innervates a number of ganglion cells (divergence), while most ganglion cells receive synaptic inputs from multiple preganglionic axons (convergence).

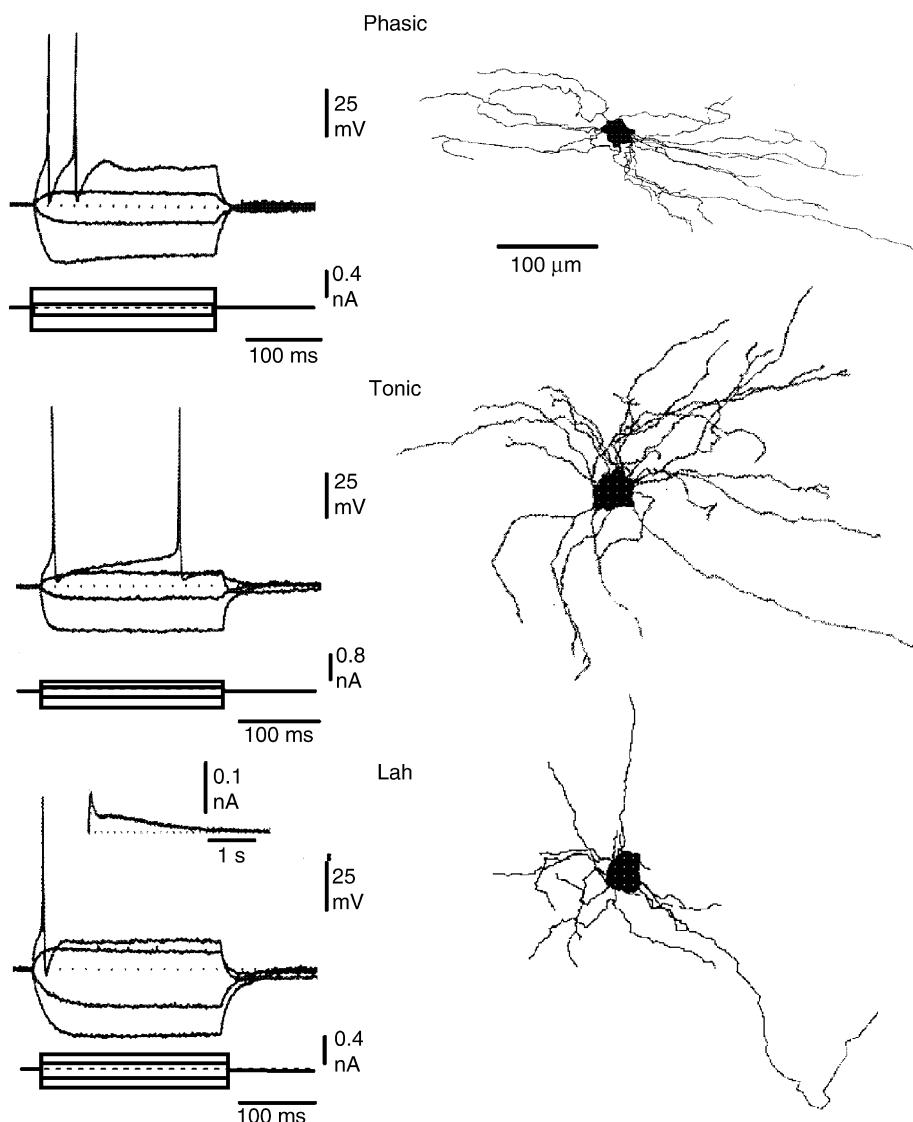
1. *Divergence* is probably more important, at least in paravertebral ganglia, as only one (rarely two) of the several inputs is involved in discharging the postganglionic neurone. This “strong” input has a large safety factor for transmission, like the skeletal neuromuscular junction. The remaining inputs rarely summate due to the low firing frequencies of individual preganglionic axon. Thus, activity in each sympathetic preganglionic neurone discharges many postganglionic neurones (up to >200 or more in humans), amplifying the signal spatially and distributing it widely to the multiple innervated target tissues. Divergence is much less in parasympathetic ganglia (1: <10).

2. *Convergence* is essential for ganglion cells that integrate information from sensory and interneurons with preganglionic signals within sympathetic prevertebral and parasympathetic ganglia. The synaptic events must summate before these neurones discharge.

Lower Level Processes

Synaptic Transmission

Transmission in autonomic ganglia occurs via the ▶quantal release of ▶acetylcholine (ACh) from the preganglionic axons. These interact with nicotinic receptor channels (nAChR) composed of five subunits ($\alpha_3, \alpha_5, \alpha_7, \beta_2, \beta_4$ in different combinations), as at the skeletal neuromuscular junction. The α_3/β_4 heteromultimer is the main ganglionic nAChR, and various specific drugs antagonize the synaptic channels by both competitive and open-channel block. Single quanta produce $\sim 0.1 \text{ nA}$ peak inward postsynaptic current, whereas the strong input generates a synaptic current of 1 to $>10 \text{ nA}$, reflecting the action of between



Autonomic Ganglia. Figure 3 Three major classes of sympathetic ganglion cell can be distinguished in guinea pig ganglia by their discharge pattern when depolarized just above suprathreshold and by their distinctive morphology. The discharge depends primarily on the predominant expression and voltage-dependence of M-type K⁺ channels (phasic neurones), A-type K⁺ channels (tonic neurones) and a slow Ca-activated K⁺ conductance (LAH or long-after hyperpolarizing neurones; the conductance takes the time course of the current shown in the inset). The neurones shown are examples close to the average morphologies in terms of soma size, numbers and length of dendrites. Modified from Boyd et al., *Journal of Comparative Neurology* 369:372–387 (1996).

10 and >100 quanta. As this is similar to the number of synaptic contacts, it is likely that each contact releases at most one quantum and that there is a high probability of release. Subthreshold “weak” inputs release only a few quanta, although these also arise with a relatively high probability (>0.5), presumably from a limited number of varicosities. The synaptic current decay reflects average channel lifetimes of ~5 ms and ~25 ms, arising from the average duration of bursts of openings of two groups of nAChR channels.

The subtypes of voltage-dependent Ca²⁺ channel that are involved in ACh release from preganglionic terminals vary between species, but are usually multiple. They also vary between inputs to the same neurone. For example, in the guinea pig, ~40% of transmitters released from a strong preganglionic input results from Ca²⁺ influx through N-type channels, while the rest involves another channel (R-type, resistant to blockade by known antagonists). However, weak inputs to the same cell utilize N-type (35%), R-type (25%) and P-type (40%) channels

[6]. Sympathetic and parasympathetic inputs impinge on some guinea-pig pelvic neurones, but only the parasympathetic pathway is sensitive to N-type antagonists [7]. Across all ganglia, a major part of ganglionic transmission is resistant to selective Ca^{2+} channel antagonists.

The postsynaptic nAChR channels permit the entry of both Na^+ and Ca^{2+} ions, depolarizing the neurone to a threshold within a few ms. In the case of strong synapses, this leads to a postganglionic action potential. The weak post-synaptic potential lasts 30–100 ms because of the large input time constant of the ganglion cells (20–80 ms). Although this should assist the temporal summation of weak inputs, this rarely occurs as individual preganglionic axons discharge at <1.5 Hz. Even though axons in e.g., vasoconstrictor pathways fire with cardiac and respiratory rhythms, the low average frequency means that they rarely fire in consecutive cycles, so that the opportunity for summation is limited. Thus, the strong inputs dominate in firing the postganglionic cell, and the ganglia simply relay signals without modification in e.g., vasoconstrictor, pilomotor and sudomotor pathways but not in prevertebral ganglia (*see below*).

Evidence that synapses formed between cultured sympathetic neurones use adenosine 5'-triphosphate (ATP) has led to the idea that ATP contributes to synaptic transmission in normal autonomic ganglia. However, the evidence is against this at normal connections between preganglionic and postganglionic neurones [8], although it appears to be true for a subset of synapses in the enteric nervous system.

In addition to the preganglionic inputs, the synapses formed by peripheral afferent terminals in sympathetic prevertebral and parasympathetic ganglia are also ►cholinergic and utilize nAChRs, but these synapses release only a few quanta with a very low probability. Thus, individual axons release intermittently during repetitive stimulation, possibly due to a limited expression of synaptic proteins [9]. However, a barrage of weak synaptic potentials is generated during gut distension. At the same time, peptidergic primary afferents release Substance P within the ganglion. The activation of a variant NK-1 receptor on some ganglion cells decreases K^+ conductance, depolarizing the membrane, enhancing the concurrent weak synaptic potentials and triggering action potentials. This integrative function of ganglia occurs only in the extrinsic control of visceral motility and secretion.

Neuronal Excitability and the AHP

The postganglionic action potential is readily blocked by tetrodotoxin leaving a residual inward Ca^{2+} current. Ca^{2+} entry during the action potential produces an afterhyperpolarization (AHP) lasting several hundred ms, which may be enhanced by Ca^{2+} entry through nAChRs. The source of Ca^{2+} to activate the underlying

K^+ channels appears very localized. Ca^{2+} entry through L-type channels activates Ca-dependent ►BK channels to determine the early peak of the AHP, while Ca^{2+} entry through N-type channels activates ►SK channels that underlie the prolonged phase [10]. A small proportion of neurones also have a very slow Ca-dependent K^+ conductance dependent on Ca-induced Ca^{2+} release. The long AHP limits the ability of the postganglionic neurone to fire at high frequency and may block inputs that are just suprathreshold at resting potential.

Phenotypes of Autonomic Neurone

Sympathetic ganglion cells have been differentiated on the basis of their discharge pattern (phasic or tonic or with a long AHP), their expression of neuropeptides and of K^+ , Na^+ and Ca^{2+} channels and their morphology (Fig. 3).

Different sympathetic phenotypes have distinct distributions between ganglia and targets and have been identified in several species. Similarly, postganglionic neurones in parasympathetic ganglia can be distinguished from their companion neurones. The full range of this diversity has yet to be described, but clearly reflects the expression of distinct functional autonomic phenotypes.

Function

Autonomic ganglia contain cholinergic synapses that either relay the central (preganglionic) signal directly to the target organ or, in other pathways, integrate central and peripheral inputs to provide control of visceral targets. The characteristics of synaptic transmission have been well defined, showing species, strain and pathway diversity in the subtypes of Ca^{2+} channel and the subunit composition of nAChRs involved. Distinct neuronal phenotypes characterize different functional pathways.

References

- Keast JR (2000) Unusual autonomic ganglia: connections, chemistry, and plasticity of pelvic ganglia. *Int Rev Cytol* 193:1–69
- Rush RA, Chie E, Liu D, Tafreshi A, Zettler C, Zhou XF (1997) Neurotrophic factors are required by mature sympathetic neurons for survival, transmission and connectivity. *Clin Exp Pharmacol Physiol* 24:549–555
- McLachlan EM (1995) Autonomic ganglia In: Burnstock G (ed) *The autonomic nervous system*, vol 6. Harwood Academic Publishers, Luxembourg, p 518
- Szurszewski JH, Ermilov LG, Miller SM (2002) Prevertebral ganglia and intestinofugal afferent neurones. *Gut* 51 (Suppl 1):6–10
- Gibbins IL, Jobling P, Messenger JP, Teo EH, Morris JL (2000) Neuronal morphology and the synaptic organisation of sympathetic ganglia. *J Auton Nerv Syst* 81:104–109
- Ireland DR, Davies PJ, McLachlan EM (1999) Calcium channel subtypes differ at two types of cholinergic synapse in lumbar sympathetic neurones of guinea-pigs. *J Physiol* 514:59–69

7. Jobling P, Gibbins IL, Lewis RJ, Morris JL (2004) Differential expression of calcium channels in sympathetic and parasympathetic preganglionic inputs to neurons in paracervical ganglia of guinea-pigs. *Neuroscience* 127:455–466
8. Inokuchi H, McLachlan EM (1995) Lack of evidence for P2X-purinoceptor involvement in fast synaptic responses in intact sympathetic ganglia isolated from guinea-pigs. *Neuroscience* 69:651–659
9. Gibbins IL, Jobling P, Teo EH, Matthew SE, Morris JL (2003) Heterogeneous expression of SNAP-25 and synaptic vesicle proteins by central and peripheral inputs to sympathetic neurons. *J Comp Neurol* 459:25–43
10. Davies PJ, Ireland DR, McLachlan EM (1996) Sources of Ca^{2+} for different Ca^{2+} -activated K^+ conductances in neurones of the rat superior cervical ganglion. *J Physiol* 495:353–366

Autonomic Hyperactivity

Definition

Autonomic hyperactivity may manifest as sympathetic hyperactivity, parasympathetic hyperactivity or both.

These most often occur in the context of acute brain injury resulting in loss of inhibition or irritation of excitatory foci within the central autonomic network.

Centrally mediated sympathetic hyperactivity is also seen in chronic spinal cord injury (Autonomic dysreflexia).

Sympathetic or parasympathetic hyperactivity are also occasional features of Guillain-Barré syndrome.

Patients may present with extraordinarily high blood pressure and heart rate – even a doubling of normal values – or conversely hypotension and bradycardia where vagal hyperactivity predominates.

These and other symptoms, such as salivary and bronchial hypersecretion, may place patients at immediate risk of cardiac or respiratory failure.

- Autonomic Insufficiency
- Guillain-Barré Syndrome

Autonomic Insufficiency

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Synonyms

Autonomic failure

Definition

Autonomic insufficiency refers to autonomic output which is not adequate to meet homeostatic needs. In clinical practice, this most often refers to syndromes in which there is widespread failure of autonomic output due either to central or peripheral disease.

Characteristics

Autonomic insufficiency occurs in a great many disorders and so the spectrum of dysfunction is broad and individual presentations are varied. Some diseases cause symptoms throughout the body, while others appear restricted to particular organs [1]. Autonomic insufficiency may appear as a congenital disorder, and a number of inherited syndromes have been identified [2]. These include the hereditary sensory and autonomic neuropathies (HSANs), such as familial dysautonomia (FD). While such disorders are relatively uncommon, in later life attenuation of autonomic output occurs with increasing prevalence, either as a component of senescence (► Ageing) or secondary to other disease processes. Most often, autonomic insufficiency presents clinically as orthostatic intolerance (► Orthostatic intolerance) associated with syncope or presyncope. Other common complaints are anhidrosis (► Sweating disorders), impaired thermoregulation, impaired gastrointestinal motility, urinary dysfunction and impotence.

Quantitative Description

The impact of autonomic diseases cannot be quantified in broad statements. In part, this is due to the insidious nature of many of these disorders which makes diagnosis problematic. Additionally, autonomic insufficiency is most often secondary to other disorders whose own prevalences may be changing rapidly due to the evolution of preventative and management strategies. Nonetheless, a few examples will serve to illustrate the importance of autonomic insufficiency from a global perspective. Orthostatic hypotension (orthostatic intolerance), the most common clinical presentation in autonomic insufficiency is defined as a fall of at least 20 mmHg in systolic blood pressure or at least 10 mmHg in diastolic blood pressure within 3 min of assuming an upright posture. The prevalence of this complaint increases with age such that, depending upon the population surveyed, it may be so common as to be the norm. Furthermore, its occurrence correlates with multiple drug use [3], another phenomenon which is on the rise, especially in more developed nations with aging populations. Similarly, in diabetes mellitus, estimates of the prevalence of autonomic abnormalities range from a few percent to the overwhelming majority of patients tested [4]. While there is great variation in the prevalence of diabetes mellitus, worldwide it is increasing so that autonomic complications may be

expected to be quite common in many societies in the near future. This contrasts with Chagas disease, which is largely restricted to Central and South America and has historically been a very important cause of disability and death [5]. At the beginning of the 1990s, Chagas disease, caused by the parasite *Trypanosoma cruzi* and spread by a number of insects, effected millions of people in endemic areas, with new cases numbering in the hundreds of thousands each year, and deaths in the tens of thousands. In some areas with vigorous vector control the incidence has dropped in a logarithmic fashion in recent years. In other areas, however, Chagas disease remains a common cause of gastrointestinal and cardiac disease among adults in their working years. A final example to illustrate the spectrum of autonomic insufficiency will be provided by Portuguese-type amyloidosis, also called familial amyloid polyneuropathy type 1 (FAP-1). This inherited, autosomal dominant disorder is rare globally, but common in restricted areas [6], with a few percent of the population effected in some localities. Hence, in summary, autonomic insufficiency may be important both globally and locally as a cause of disability and death. Furthermore, the stage seems to be set for increased prevalence of some already common causes of this affliction.

Higher Level Structures

Autonomic insufficiency may arise from disease of the central autonomic network (CAN), including stroke, trauma, infection and neoplasia ([►Central regulation of autonomic function](#)). However, since various components of the CAN also perform inhibitory functions, lesions to these areas may also result in disinhibition and consequent overactivity of the autonomic nervous system ([►Autonomic/enteric dysreflexia](#)). In many instances it is still not known which components of the CAN are involved or are most important in specific syndromes of autonomic insufficiency. Furthermore, as various diseases with autonomic involvement also result in impairment of cerebral circulation, it may be difficult to determine whether pathology in any given component of the CAN is primary or secondary. Notwithstanding these caveats, a few examples will serve to demonstrate the importance of particular higher level structures in representative disorders with autonomic involvement. A relatively common neurodegenerative disorder associated with autonomic insufficiency is Parkinson's disease [7], which is marked by degeneration of a number of nuclei including not only the substantia nigra but also the locus ceruleus ([►Periaqueductal gray matter](#)), the principle source of norepinephrine in the brain. Additionally, in both Parkinsonism and multiple system atrophy (MSA), loss of particular cell populations has been noted in the ventrolateral medulla [8]. With MSA, which normally develops insidiously late in life, there is also marked

degeneration in the intermediolateral (sympathetic preganglionic) cell columns of the spinal cord. Hence, in addition to motor and sensory symptoms, patients with CAN disorders may experience a range of localized or generalized autonomic deficits.

Lower Level Structures

In truth, many disorders defy classification as strictly central versus peripheral, or preganglionic ([►Preganglionic neurons](#)) versus postganglionic ([►Postganglionic](#)). However, pure autonomic failure (PAF), which like MSA most often effects older adults, is representative of those disorders which are primarily postganglionic. Outwardly, the patients may appear very much like those suffering from MSA, often demonstrating orthostatic hypotension and disorders of urinary or gastrointestinal function. However, the CAN is largely unaffected in PAF, while there is loss of postganglionic sympathetic function [9]. In a number of clinically similar syndromes manifesting as postganglionic autonomic failure, patients have been shown to possess antibodies to postganglionic neurons, including antibodies to ganglionic neurotransmitter receptors. Autoimmune damage is, in fact, one of the mechanisms responsible for peripheral nerve damage in diabetic [►autonomic neuropathy](#), the most common cause of postganglionic autonomic insufficiency in developed nations. There are, not surprisingly, many varieties of diabetic autonomic neuropathy, just as there are many varieties of diabetes mellitus. These autonomic neuropathies are most often accompanied by sensory and motor neuropathies which may demand more attention clinically. Nonetheless, the autonomic components of diabetic neuropathies are responsible for significant morbidity, and perhaps mortality. Signs and symptoms attributed to autonomic insufficiency include cold, discolored hands and feet due to loss of peripheral vascular tone. There is often asymmetrical loss of sweating, initially affecting the limbs. With loss of postganglionic vagal fibers, gastrointestinal motility is impaired and patients may experience complaints such as achalasia and constipation. Loss of autonomic, and particularly vagal, cardiac output may contribute to the increased risk of silent myocardial infarctions and sudden cardiac death in diabetic patients. Thus, diabetic autonomic neuropathies are commanding more attention, particularly as primary care increases the life expectancy of patients and allows autonomic dysfunction to manifest.

Management

As autonomic insufficiency most often occurs as a secondary disorder, management commonly focuses on prevention or amelioration of the underlying disease. Additionally, autonomic insufficiency is sometimes successfully managed by supportive measures focusing

on strategies to minimize symptoms. These include modifying behaviors such as using supportive stockings, or altering eating and drinking patterns to control orthostatic hypotension. More recently, a number of neuroprotective drugs have appeared, and strategies such as stem cell transplantation show great promise in certain disorders. As the stage is set for an increase in autonomic insufficiency in more developed nations, it is most likely that there will be increasing research effort in these fields.

References

- Mathias C (2003) Autonomic diseases: clinical features and laboratory evaluation. *J Neurol Neurosurg Psychiatr* 74 (Suppl 3):iii31–iii41
- Axelrod F, Chelimsky G, Weese-Mayer D (2006) Pediatric autonomic disorders. *Pediatrics* 118:309–321
- Poon I, Braun U (2005) High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Ther* 30:173–178
- Hilsted J, Low P (1997) Diabetic autonomic neuropathy. In: Low P (ed) *Clinical autonomic disorders*, 2nd edn. Lippincott-Raven, Philadelphia, pp 487–507
- Moncayo A (2003) Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the southern cone countries. *Mem Inst Oswaldo Cruz* 98(5):577–591
- Labato L (2003) Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). *J Nephrol* 16:438–442
- Magerkurth C, Schnitzer R, Braune S (2004) Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. *Clin Auton Res* 15:76–82
- Benarroch E, Schmeichel A, Parisi J (2000) Involvement of the ventrolateral medulla in parkinsonism with autonomic failure. *Neurology* 54(4):965–968
- Young T, Asahina M, Nicotra A, Mathias C (2006) Skin vasomotor reflex responses in two contrasting groups of autonomic failure; multiple system atrophy and pure autonomic failure. *J Neurol* 253:846–850

Autonomic Interneurons

Definition

Interneurons in the spinal cord or brain stem that form synapses with preganglionic neurons. These interneurons are segmental or intersegmental (propriospinal) interneurons in the spinal cord or equivalent in the brain stem (e.g., second-order neurons in the nucleus tractus solitarius receiving synaptic input from vagal visceral afferents).

►Autonomic Reflexes

Autonomic Nervous System

Definition

The autonomic nervous system is that part of the nervous system that regulates basic visceral processes, usually independently of voluntary control. The executing part of the autonomic nervous system is divided into a parasympathetic and a sympathetic branch. In many organs, these two branches have antagonistic effects, while in others (e.g. salivary glands), they act synergistically (even though not giving identical responses), and thereby enhance the effect of each system. In addition information about the functional condition of our organs is transmitted back to the brain via these two branches.

- Central Integration of Cardiovascular and Respiratory Activity Studied In Situ
- Neuroendocrine Regulation and the Autonomic
- Nervous System
- Sympathetic Nervous System
- Sympathetic Pathways
- Parasympathetic Nervous System
- Parasympathetic Pathways

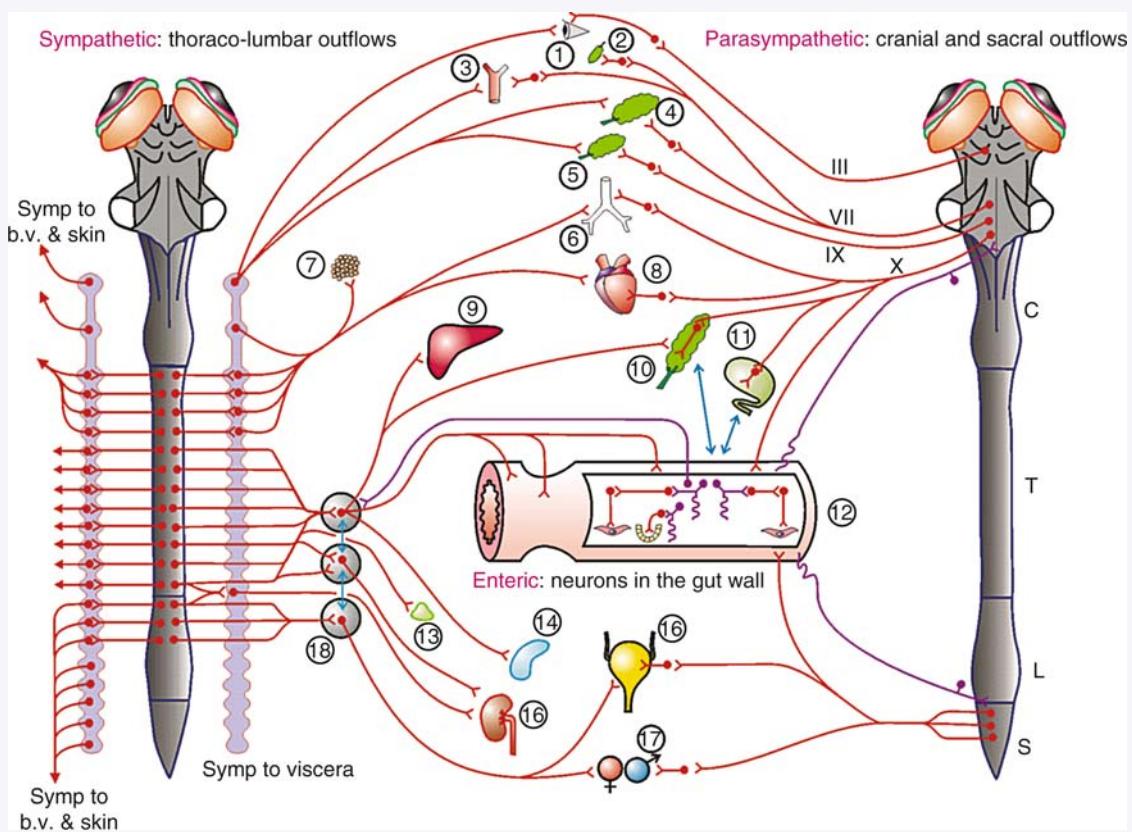
Autonomic Nervous System and Its Divisions: Sympathetic, Parasympathetic and Enteric

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Introduction

The autonomic nervous system (ANS) is that system of nerves that controls peripheral organs, other than striated muscle that is under voluntary control (Fig. 1). Thus it controls the visceral organs of the thoracic, abdominal and pelvic cavities, including the lungs, heart, digestive organs, kidneys, urinary bladder and internal generative organs. The autonomic nervous system also controls endocrine and exocrine glands throughout the body, the blood vessels that supply all organs, and, within the eye, ►neural regulation of the pupil. More recently, it has also become obvious that the autonomic nervous system can modulate the function of sensory receptors (see ►autonomic control



Autonomic Nervous System and Its Divisions: Sympathetic, Parasympathetic and Enteric. **Figure 1** Depiction of the organization of the peripheral pathways of the autonomic nervous system, showing its three parts, sympathetic, parasympathetic and enteric. The spinal cord and brainstem are pictured twice, at the left to show their sympathetic outflows and at the right to show parasympathetic outflows. Major organs that are supplied are numbered: 1 Eye; 2 Lacrimal gland; 3 Intracranial arteries; 4, 5 Salivary glands; 6 Respiratory tract; 7 Adipose tissue; 8 Heart; 9 Liver; 10 Pancreas; 11 Gallbladder and biliary tree; 12 Gastrointestinal tract; 13 Adrenal gland; 14 Spleen; 15 Urinary bladder; 16 Kidney; 17 Genital organs. 18 indicates prevertebral ganglia. Motor pathways are in red. The ANS also has associated afferent neurons. Some of these are shown in purple. Visceral afferents in fact supply all organs, but these are not shown, in order to simplify the diagram. Double-ended arrows indicate that there are neural connections between the pancreas and the gastrointestinal tract and between the biliary system and the gastrointestinal tract, as well as between pre-vertebral ganglia. Levels of the spinal cord are indicated, C, T, L and S.

of sensory receptors) and skeletal muscle (see ▶autonomic effects on skeletal muscle).

Autonomic Function

The functions of the autonomic nervous system are all related to ▶homeostasis (Table 1), adjusting the activities of these organs so that the organs function at levels that are most favorable to the state of the body and to its environment (see [1]). This is achieved most often through reflex mechanisms which are largely involuntary. These ▶autonomic/enteric reflexes particularly involve viscero-visceral reflexes. However, recently there has been a growing awareness that much autonomic function is also influenced by ▶somato-autonomic reflexes [2] and entrained to circadian rhythms (see ▶circadian rhythms of autonomic function). Thus, for

example, physiological parameters such as blood pressure show daily rhythms appropriate to the sleep-wake cycle [3]. Furthermore, it is apparent that humans may exert varying degrees of voluntary control over autonomic function (see ▶biofeedback of autonomic function). Thus, while ▶tonic activity of autonomic nerves is always present to some degree, there are substantial adjustments to homeostatic challenges, such as those presented by exertion (see ▶autonomic function and exercise) [4]. Additionally, information from visceral autonomic afferents may, via ▶viscero-somatic reflexes, such as the ▶Hering-Breuer reflex, modulate musculoskeletal function. The autonomic nervous system is thus one of two systems, the other being the endocrine system, that control the functions of the internal and surface organs (the skin is included as an organ). The two systems

Autonomic Nervous System and Its Divisions: Sympathetic, Parasympathetic and Enteric. Table 1 A summary of major autonomically controlled functions

Heart rate and force
Arterial diameter (all vascular beds)
Mesenteric venous capacity
Pupillary diameter, accommodation of lens
Exocrine gland secretion: lacrimal gland, salivary glands, gastric glands, exocrine pancreas, sweat glands
Secretion into organs: intestinal water and electrolyte secretion, pulmonary secretion, nasal secretion
Gastrointestinal wall movement
Gall bladder contraction, and biliary tract regulation
Regulation of the urinary bladder and control of micturition
Tracheal and bronchial diameter
Contraction of vas deferens
Penile erection, clitoral and labial engorgement
Fat mobilization
Secretion of adrenal medullary hormones
Piloerection

would be better thought of as one, because they act in synergy to control the organs (see ►autonomic regulation of endocrine system). However, largely due to the history and pattern of basic and clinical investigation, autonomic and endocrine control are often separated in text-books.

Autonomic control of organs is through reflexes and through cortical control centers [5]. To elicit a reflex, the relevant states of organs must be detected. This detection is through ►visceral afferents that are properly regarded as part of the autonomic nervous system. Many visceral afferent neurons also communicate other information, for example pain from the viscera, satiety from the digestive tract or temperature. Thus visceral afferent neurons, while part of the autonomic nervous system, carry signals to the central nervous system that serve other functions [6].

Structural Organization of the Autonomic Nervous System

Since the nineteenth century or early twentieth century, it has been common to divide the autonomic nervous system into three divisions, the sympathetic, parasympathetic and enteric divisions (see ►enteric nervous system). There were pragmatic reasons for this separation of parts of what is essentially one control system. The efferent (motor) autonomic outflows from the central nervous system are not distributed uniformly in the peripheral nerves; rather there are gaps. More precisely, there are some cranial, cervical and lumbosacral nerves that do not carry autonomic motor pathways (Fig. 1). Autonomic fibers are absent from the first two cranial nerves – the olfactory and optic nerves, they are then present in cranial nerves III, VII, IX and X. Then a gap in outflow occurs, with no autonomic contribution

to cranial nerves XI and XII or the cervical nerves (there can rarely be a contribution from C7). The next group of nerve roots, T1 to L2 or 3 (the thoraco-lumbar outflows), all have autonomic components, and then there is a small gap where there are few autonomic fibers, which become prominent again in sacral roots 2–4. The outputs are thus considered as cranial, thoraco-lumbar and sacral.

Early studies of autonomic nervous system function particularly focused on ►cardiovascular reflexes, including ►blood volume regulation. It was noted that there are pathways that emerge from the cranial autonomies that slow the heart and dilate blood vessels, and that there are also dilator nerves in the sacral outflows. Thus, these were grouped together and called the crano-sacral nerves. Conversely, there are cardio-accelerator and vasoconstrictor pathways in the thoraco-lumbar outflows. Furthermore, early investigations indicated that these opposite effects on cardiovascular function were elicited by two different ►postganglionic neurotransmitters, acetylcholine and norepinephrine. Because of the opposite effects on the cardiovascular system, and the thoraco-lumbar effects being “sympathetic” (in sympathy with the body) the two anatomical divisions became known as sympathetic and parasympathetic (the latter being associated with slowing or lowering cardiovascular function).

The division of the ANS into sympathetic and parasympathetic systems has led to enormous misconceptions, the most serious being the concept that the two divisions are somehow in opposition to each other. Thus it may be envisioned that, for example, an increase in sympathetic outflow to a particular organ is necessarily linked to a decrease in parasympathetic outflow. This

is quite a wrong idea. Autonomic nerves, whatever their anatomical origin, act in concert to control visceral organs and the vasculature [7].

The third division of the ANS is the enteric division, which is the system of autonomic ganglia and nerve fibers that is contained within the walls of the digestive organs [8]. This is given the status of a separate division because it contains complete reflex circuits which can operate in the absence of connections with the central nervous system. In terms of numbers of neurons, the enteric is the largest autonomic division. In humans, it contains 200–600 million neurons.

The motor pathways of the ANS that arise in the central nervous system pass through ►autonomic ganglia and generally make synapses on the way to the organs that they innervate [9]. The adrenal glands are exceptional in that they are innervated by preganglionic neurons with cell bodies within the spinal cord. Synaptic transmission in autonomic ganglia is mediated primarily by acetylcholine (ACh) that acts on nicotinic receptors. The use of nicotine and other drugs that block these receptors has been important in analyzing the nerve pathways. Neurons with cell bodies in the central nervous system that make synapses in peripheral ganglia are known as autonomic (sympathetic or parasympathetic) pre-ganglionic neurons. The neurons with which they connect are called post-ganglionic neurons; most of those of the sympathetic nervous system producing the classical neurotransmitter norepinephrine and those of the parasympathetic nervous system producing acetylcholine. Both classes of post-ganglionic neurons also produce a range of other neuroactive substances which modulate the effects of their primary neurotransmitters (see [10]). Enteric neurons are innervated by both parasympathetic pre-ganglionic neurons and sympathetic post-ganglionic neurons.

►Central regulation of autonomic function involves higher integrating centers but depends most immediately on a series of nuclei in the brain-stem (including the Edinger-Westfall nucleus, the nucleus of the facial nerve, the salivatory nuclei, the dorsal motor nucleus of vagus and the nucleus ambiguus) which contain the cell bodies of preganglionic neurons [11]. Within the spinal cord, autonomic cell groups are arranged in columns in the lateral funiculus, intermediolateral nuclei, intermedio-medial nuclei and central autonomic nuclei. The central autonomic motor nuclei of the brain stem and spinal cord receive inputs from autonomic integrative cell groups, including the nucleus of the tractus solitarius, the Bezhold-Jarisch complex, the autonomic cell groups of the rostral ventro-lateral medulla, the paraventricular nucleus and other cell groups. At higher levels, important autonomic control is exerted through the amygdala and the cingulate cortex. At these higher levels, it is no longer possible to distinguish the centers as simply autonomic. They are

also involved in endocrine control and affective behavior, both of which are closely related to autonomic function.

Disorders of the Autonomic Nervous System

As homeostatic mechanisms normally manifest as subtle adjustments in physiology, the importance of the autonomic nervous system to human health is easily underestimated until we subject ourselves to extreme environments (see ►autonomic function in space) or encounter frank disease. In fact, disorders of the autonomic nervous system are numerous and diverse in their presentations (see [12]). ►Complex regional pain syndromes were recognized early in the evolution of our understanding of autonomic pathology. More recently, and especially with improvements in ►autonomic testing, it has been possible to differentiate disorders which, while similar in their presentations, actually have distinct etiologies and pathologies, and so warrant distinct treatment approaches [13]. Importantly, aging is associated with senescence of the autonomic nervous system [14] (see ►aging of autonomic/enteric function), although ►autonomic insufficiency is also a component of a range of disorders seen across the life cycle. Autonomic insufficiency is most apparent in its effects on cardiovascular function and frequently associated with orthostatic hypotension. However, insufficiency also has clinically important effects on digestive function (see ►salivary secretion control and ►bowel disorders), urogenital function (see ►micturition – neurogenic control and ►sexual reflexes) and sweating (see ►sweat gland control).

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References

1. Jänig W (2006) The autonomic nervous system. Cambridge University Press, Cambridge
2. Sato A, Sato Y, Schmidt R (1997) The impact of somatosensory input on autonomic functions. Rev Physiol Biochem Pharmacol 130:1–328
3. Giles TD (2006) Circadian rhythm of blood pressure and the relation to cardiovascular events. J Hypertens Suppl 24:S11–S16
4. Joyner MJ, Coyle EF (2007) Endurance exercise performance: the physiology of champions. J Physiol: Epub ahead of print
5. Jordan B (1997) Central nervous control of autonomic function. CRC Press, Baton Rouge
6. Grundy D (2002) Neuroanatomy of visceral nociception: vagal and splanchnic afferent. Gut 51 Suppl 1:i2–i5

7. Malliani A (1997) The autonomic nervous system: a Sherringtonian revision of its integrated properties in the control of circulation. *J Auton Nerv Syst* 64:158–161
8. Furness JB (2006) The enteric nervous system. Blackwell, Oxford
9. McLachlan EM (2003) Transmission of signals through sympathetic ganglia – modulation, integration or simply distribution? *Acta Physiol Scand* 177:227–235
10. Burnstock G (2007) Physiology and pathophysiology of purinergic neurotransmission. *Physiol Rev* 87:659–797
11. Blessing WW (1997) The lower brainstem and bodily homeostasis. Oxford University Press, Oxford
12. Mathias CJ (2006) Multiple system atrophy and autonomic failure. *J Neural Transm Suppl* 70:343–347
13. Low PA (2003) Testing the autonomic nervous system. *Semin Neurol* 23:407–421
14. Schmidt RE (2002) Age-related sympathetic ganglionic neuropathology: human pathology and animal models. *Auton Neurosci* 96:63–72

Autonomic Neuropathy

Definition

The autonomic neuropathies are disorders of peripheral autonomic function, and may manifest as autonomic hyperactivity, autonomic failure, or a mixture of both.

An exemplar of autonomic neuropathy is acute panautonomic neuropathy (pandysautonomia) in which there is often widespread and severe loss of sympathetic and parasympathetic function, but virtually no involvement of somatic fibers. At the other end of the spectrum is Guillain-Barré syndrome in which somatic nervous system dysfunction usually dominates, and there may be hypoactivity or hyperactivity of peripheral autonomic fibers.

- Autonomic Insufficiency
- Guillain-Barré Syndrome

Autonomic Neurotransmitter

- Postganglionic Neurotransmitter

Autonomic Premotor Neurons

Definition

Neurons in brain stem, hypothalamus or even cerebral hemispheres that project to preganglionic neurons or

autonomic interneurons associated with the preganglionic neurons and form synapses with these neurons are called autonomic (parasympathetic, sympathetic) pre-motor neurons.

► Autonomic Reflexes

Autonomic Reflexes

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Definition

Reflexes are functionally defined by an efferent (motor) output system leading to a distinct effector response when activated and by the population of afferent neurons stimulated. They are fragments of more complex somatomotor behaviors and are used in the laboratory as tools to study experimentally the central organization of neural regulation of movement. In this isolated context they are experimental artifacts or fictions [1]. The same applies to ►autonomic reflexes when seen in this restricted experimental context. Systematic experimental studies of autonomic reflexes using measurements of effector responses, recording from functionally identified autonomic neurons, pharmacological interventions, histological techniques, tracer methods etc. have given and will continue to give invaluable insight into the central and peripheral neural mechanisms underlying regulations in which the autonomic nervous system is involved. The functions of many individual autonomic reflexes mediated by the spinal cord, brain stem or hypothalamus or by the peripheral nervous system may not always be obvious at first sight. This does not mean that these reflexes have no function or are left-overs from development. As in the somatomotor system, the function of most autonomic reflexes cannot be considered in isolation but becomes obvious when looked at in the context of neural regulations in which these reflexes are integrated.

In the somatomotor system, reflexes are the basic building blocks of the initiation and maintenance of movements whether occurring automatically, e.g., during locomotion or in posture, or being initiated by the telencephalon [2,3]. In the autonomic nervous system reflexes are the basic building blocks of autonomic regulations. Coordinated responses generated by the somatomotor, autonomic and neuroendocrine

systems constitute behaviors of the organism. In this sense autonomic reflexes are also fragments of behavior (see the interesting discussion in [4] “What do *reflex* and *voluntary* mean? Modern views on an ancient debate.”) For the autonomic nervous system this may be rephrased “What do *reflex* and autonomic *regulation* mean?”).

Characteristics

Autonomic reflexes mediated by the spinal cord, brain stem or hypothalamus are functionally defined by their afferent input and efferent output. They are di- or polysynaptic, organized at the segmental or propriospinal (propriobulbar) level and form the building blocks of ►autonomic regulations. The interneurons of the autonomic reflex pathways are important for the integration and coordination of different autonomic systems as well as of autonomic and somatomotor systems. Command signals from higher centers act primarily via these interneurons rather than directly with the final autonomic pathways in autonomic regulations.

Categories of Autonomic Reflexes

Autonomic reflexes can be divided into three categories:

1. Autonomic reflexes mediated by CNS structures: spinal cord, brain stem or hypothalamus. These reflex pathways are either segmental (spinal, bulbar), intersegmental (propriospinal, propriobulbar) or supraspinal reflex loops (spino-bulbo-spinal, spino-hypothalamo-spinal, bulbo-hypothalamo-bulbar etc.).
2. Autonomic reflexes mediated by autonomic (non-enteric) ganglia outside the spinal cord (i.e., “extra-central”). For example, reflexes involved in regulation of motility or secretion of the ►gastrointestinal tract (GIT) are mediated by sympathetic postganglionic neurons of prevertebral ganglia. These neurons are physiologically activated by intestino-fugal neurons during distension of or other processes in the GIT leading to inhibition of motility and/or secretion ([5]; Chaps. 5 and 6 in [6]). Other extracentral reflexes may be mediated by parasympathetic postganglionic neurons in cardiac ganglia, by sympathetic postganglionic neurons in the stellate ganglion innervating the heart or by postganglionic neurons in the inferior mesenteric ganglion projecting to pelvic organs. However, the nature of the peripheral afferent synaptic input to these postganglionic neurons as well as the function of these peripheral reflexes during autonomic regulation of the respective target organs are unclear. Sympathetic postganglionic neurons in the paravertebral ganglia innervating target cells in the somatic tissues (blood vessels, glands, non-vascular smooth muscle cells) do not mediate peripheral autonomic reflexes (Chap. 6 in [6]).

3. Autonomic reflexes mediated by the enteric nervous system (ENS) are related to regulation of motility and secretion of the GIT involving smooth (non-vascular, vascular) muscle cells, secretory epithelia and endocrine cells. Several enteric reflexes can be defined by their intrinsic primary afferent neurons and their enteric motor neurons (defined by the target cells). These reflexes are monosynaptic, disynaptic or polysynaptic. They are the building blocks of the autonomic regulation of the GIT by the ENS and of its control by the brain ([5]; Chap. 5 in [6]).

I will concentrate on the first category of autonomic reflexes and here in particular on segmental spinal and propriospinal as well as autonomic reflexes in the brain stem. **Table 1** lists characteristics of several basic autonomic reflexes related to autonomic regulation of pelvic organs, the cardiovascular system, functions of skin, gastrointestinal tract, airways, eye and pineal gland.

The Autonomic Reflex Pathway in Spinal Cord and Brain Stem

The peripheral parasympathetic and sympathetic systems consist of many functionally discrete pathways that transmit impulse activity generated in the CNS to autonomic effector cells. The pre- and postganglionic neurons of each pathway exhibit a distinct reflex pattern to physiological stimulation of somatic or visceral afferents that is dependent on the central circuits connected to this peripheral autonomic pathway ([7]; Chap. 4 in [6]). The centrally generated signals are faithfully transmitted from the preganglionic neurons through autonomic ganglia to the postganglionic neurons and from the postganglionic axons to the effector cells at the neuroeffector junctions ([7]; Chaps. 6 and 7 in [6]). Thus these pathways are anatomically and physiologically separate from each other and functionally distinct with respect to the effector cells (e.g., vasoconstrictor neurons, vasodilator neurons, secretomotor neurons etc.).

Each peripheral autonomic pathway is connected to several basic reflex pathways organized in spinal cord or brain stem (**Table 1**). The common theme of the structure of practically all of these reflex pathways is shown for ►spinal reflexes in **Fig. 1**. Primary afferent neurons, most of them innervating visceral organs, but some also somatic tissues (skin, deep somatic), form reflex circuits with the preganglionic neurons. These reflex circuits are di-, tri- or polysynaptic. Each reflex circuit is primarily characterized by the type of afferent input and by the response elicited in the neurons of the autonomic pathways and therefore by the effector response. This basic structure of the autonomic spinal reflex applies to most autonomic reflexes in spinal cord. The reflexes are either spinal

Autonomic Reflexes. Table 1 Autonomic reflexes mediated by spinal cord and brain stem^a

Organ, target cells	Reflex ^b	Afferents ^c	Efferent pathway	Central reflex pathway	Effector response to stim afferents	Integrated in regulation of ...
Pelvic organs						
Urinary bladder	Spinal segmental (micturition reflex)	Sacral urinary bladder	Sacral to detrusor	Sacral spinal cord	Contraction	Micturition, continence
	Spinal segmental	Sacral colon-rectum	Sacral to urethra	Sacral spinal cord	Relaxation	Micturition
Colon-rectum	Proprio-spinal	Sacral colon-rectum	Sacral to urinary bladder	Sacral spinal cord	Relaxation of urinary bladder	Continence of urinary bladder
	Spinal segmental (defecation reflex)	Sacral colon-rectum	Lumbar to pelvic organs	Sacro-lumbar spinal cord	Relax./contract. sphincters	Continence urinary bladder and colon-rectum
Proprio-spinal	Spinal segmental	Sacral urinary bladder	Sacral to colon-rectum	Sacral spinal cord	Contraction	Defecation, continence
	Spinal segmental	Sacral urinary bladder	Lumbar to pelvic organs	Sacro-lumbar spinal cord	Relaxation of colon-rectum	Continence colon-rectum
Genital organs	Spinal segmental (genito-genital reflex)	Somat sacral pudendal	Sacral to erect tissue	Sacral spinal cord	Relax./contract. sphincters	Continence Urinary Bladder and colon-rectum
	Proprio-spinal (genito-genital reflex)	Somat sacral pudendal	Lumbar to internal genital organs	Sacro-lumbar spinal cord	Vasodilation	Erection
Kidney	Spinal segmental (reno-renal reflex)	Thoracic kidney	Thoraco-lumbar to kidney	Thoraco-lumbar spinal cord	Contraction, secretion	Emission, ejaculation
					Vasoconstriction, renin release, tubular Na ⁺ reabsorption	Electrolyte and fluid balance
Cardiovascular system						
Heart ^d	Spinal segmental (cardio-cardial reflex)	Thoracic heart	Thoracic cardiometer	Thoracic spinal cord	Increase of heart rate and contractility	Cardiac output
	Lower BS (baroreceptor reflex)	Arterial baroreceptor	Parasymp cardiometer	NTS, ncl ambiguus	Decrease of heart rate and contractility of atria	Blood pressure, cardiac output
	Lower BS, bulbo-sp (baroreceptor reflex)	Arterial baroreceptor	Thoracic cardiometer	NTS, CVLM, RVLM, thoracic spinal cord	Decrease of heart rate and contractility	Blood pressure, cardiac output
	Lower BS, bulbo-sp (part of diving reflex)	Trigem (face, nasopharyngeal), art. chemorec	Parasymp cardiometer	NTS, trigeminal ncl, ncl ambiguus	Decrease of heart rate and contractility	Cardiovascular system during diving
	Resistance vessels	sp segm, proprio-sp	Noxiousptive	MVC/VVC	Thoraco-lumbar sp c	Body Protection

(Skeletal muscle, viscera)	Lower BS, bulbo-sp (baroreceptor reflex)	Arterial baroreceptor	MVC/VVC	NTS, CVLM, RVLM, thoraco-lumbar sp	Vasodilation	Blood pressure, peripheral resistance
	Lower BS, bulbo-sp (chemoreceptor reflex)	Arterial chemoreceptor	MVC/VVC	NTS, ?, RVLM, thoraco-lumbar sp c	Vasoconstriction	Blood pressure, peripheral resistance
	Lower BS, bulbo-sp (part of diving reflex)	Trigem (face, nasopharyngeal), art chemorec	MVC/VVC	NTS, trigem, ?, RVLM thoraco-lumbar sp c	Vasoconstriction	Cardiovascular system during diving
Skin						
Blood vessels skin	sp segm, proprio-sp (Lövén reflex)	Nociceptive skin	CVC acral skin	Thoraco-lumbar sp c	Vasodilation, vasoconstriction	Body protection
	sp segm, proprio-sp	Mech skin (low threshold)	CVC acral skin?	Thoraco-lumbar sp c	Vasodilation	Body protection
	sp segm, proprio-sp	Warm spinal cord	CVC	Thoraco-lumbar sp c	Vasodilation	Thermoregulation
Spinal segmental (viscero-cut reflex)	Thoraco-lumbar	CVC body trunk	Thoraco-lumbar sp c	Vasodilation, vasoconstriction	Referred zone, body protection?	
Lower BS, bulbo-sp (part of diving reflex)	Trigem (face, nasopharyngeal), art chemorec	CVC to arterio-venous anastomoses	NTS, trigem, ?, RVLM thoraco-lumb sp c	Vasodilation	Cardiovascular system during diving.	
Sweat glands	sp segm, proprio-sp	Nociceptive skin	SM	Thoraco-lumbar sp c	Sweating	Friction of skin (sensory discrim.)
	sp segm, proprio-sp (vibration reflex)	Vibration receptor (paw/ hand)	SM acral (paw/ hand)	Thoraco-lumbar sp c	SWEATING	Friction of skin (sensory discrim.), territory marking (cat)?
Spinal segmental (viscero-cut reflex)	Thoraco-lumbar	SM body trunk	Thoraco-lumbar sp c	Sweating	Referred zone, body protection?	
Organ, target cells	Reflex ^b	Afferents ^c	Efferent pathway	Central reflex pathway	Effectors response to stim afferents	Integrated in regulation of ...
Gastrointestinal tract^e						
Stomach smooth m.	Lower BS	Vagal stomach	Gastromotor	NTS, DMNX	Contraction	Motility GIT
	Lower BS	Vagal duodenum	Gastromotor	NTS, DMNX	Inhibition	Motility GIT
	lower BS (receptive relaxation r)	Vagal esophagus	Gastromotor	NTS, DMNX	Inhibition	Motility GIT
Salivary glands	Lower BS	Oropharyngeal	Salivomotor	Trigeminal, ncl salivatori	Salivation	Food intake

Autonomic Reflexes. Table 1 Autonomic reflexes mediated by spinal cord and brain stem^a (Continued)

Organ, target cells	Reflex ^b	Afferents ^c	Efferent pathway	Central reflex pathway	Effector response to stim afferents	Integrated in regulation of ...
Smooth m., glands	sp segm, proprio-sp	Thoraco-lumbar	MR, secretomotor	Thoraco-lumbar spinal cord	Inhibition	Protection of GIT
Airways						
Smooth muscle	Lower BS	Vagal mucosa airways	Bronchomotor	NTS, ncl ambiguus	Contraction	Airway resistance
	Lower BS	Vagal mucosa airways	Bronchomotor	NTS, ncl ambiguus	Relaxation	Airway resistance
Mucosal glands	Lower BS	Vagal mucosa airways	Secretomotor	NTS, ncl ambiguus?	Secretion	Airway protection
Eye						
Iris	Mesencepalon (pupillary light reflex)	Retino-tectal tract (area pretectalis)	Pupilloconstrictor	Edinger-Westphal nucleus, lateral	Constriction of pupil	Pupil diameter
	Hypothal, spinal	Retino-hypothalamic tract	Pupillodilator thoracic T1/T2	Hypothalamo-spinal	Dilation of pupil	Pupil diameter, defense
Pineal gland	Hypothal, spinal	Retino-hypothalamic tract	Thoracic T1/T2	SCN, PVN, spinal cord	Inhibition of melatonin synthesis	Circadian rhythms of hypothalamic functions

^a(i) Only spinal segmental and propriospinal (and equivalent reflexes in the brain stem and hypothalamus related to the iris or pineal gland and the retino-hypothalamic/tectal tract) are listed. For references see [3]. (ii) No autonomic long-loop reflexes are listed (e.g., spinobulbo-► spinal reflexes related to pelvic organs, resistance vessels, cutaneous blood vessels, sweat glands etc; long-loop reflexes related to peripheral autonomic [parasympathetic] pathways (the brain stem). (iii) No autonomic reflexes are listed related to excitation or inhibition of hypothalamic neurons by osmotic stimuli (autonomic reflexes related to electrolyte-fluid balance), warm stimuli (thermoregulatory reflexes) or nutritive signals (glucose, lipids in the blood) and hormonal signals to neurons of the arcuate nucleus that are important in regulation of food intake and metabolism (leptin from adipocytes, insulin from B-cells of the endocrine pancreas, ghrelin from endocrine cells of the stomach, peptide YY from endocrine mucosa cells of ileum and colon-rectum).

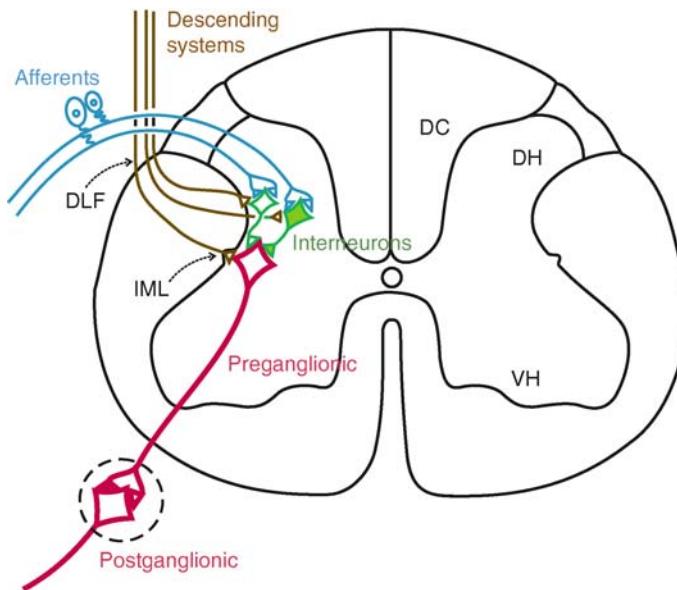
^bSome reflexes are listed by their genuine names as reported in the literature.

^cMost afferent neurons are visceral (spinal or vagal); some afferent inputs are somatic (indicated) or central.

^dReflexes related to vagal afferents from atria and ventricles of the heart have not been listed.

^eThere must exist other reflexes mediated by the dorsal vagal complex (NTS, DMNX) that are related to regulation of secretion and transmural transport by the mucosa and to regulation of the endocrine cells of the mucosa (secreting e.g., cholecystokinin, gastrin, secretin, ghrelin, glucagon-like peptide, peptide YY or other hormones) or of the endocrine pancreas (secreting insulin, glucagon or pancreatic polypeptide). However, these reflex pathways have so far not been investigated (see [3] and Travagli RA, Hermann GE, Browning KN, Rogers RC (2006) Brainstem circuits regulating gastric function. *Annu Rev Physiol* 68:279–305).

List of Abbreviations *a*: arterial; *B*: brain stem; *CM* cardiomotor; *bulbo-spinal*; *CVC*cutaneous vasoconstrictor; *CVLM*; caudal ventrolateral medulla; *DMNX*; dorsal motor nucleus of the vagus *GIT* gastrointestinal tract; *MVC* muscle vasomotor; *ncl*NTS nucleus solitarius; *proprio-spinal* *PVN*paraventricular nucleus (hypothalamus); *rRVL*rostral ventrolateral medulla; *SCN*suprachiasmatic nucleus; *segm*segmental somatosomatic; *som*somatic; *segm*segmental somatosomatic; *sp*spinal cord; *trig*trigeminal; *U*urinary bladder; *V*visceral vasocconstrictor; *Vc*viscero-cutaneous.



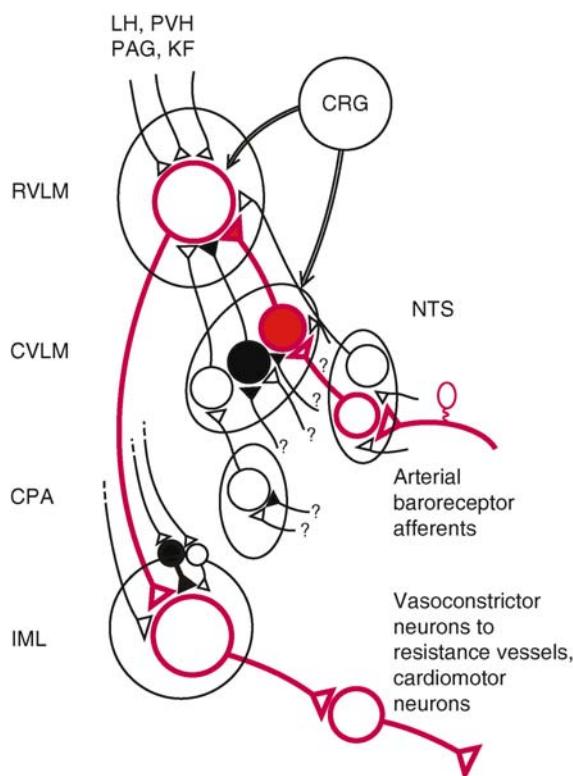
Autonomic Reflexes. Figure 1 The spinal autonomic reflex pathway as building block between supraspinal centers and final autonomic pathways. There is usually at least one (excitatory or inhibitory [filled in]) interneuron (green) between (visceral or somatic) primary afferent neurons (blue) and preganglionic neurons (red). Supraspinal centers in brain stem and forebrain (hypothalamus and cerebral hemispheres) project mainly through the dorsolateral funiculus (DLF, brown) of the spinal cord and connect synaptically to the autonomic interneurons and the preganglionic neurons. DC, dorsal column. DH, dorsal horn. IML, intermediolateral nucleus. VH, ventral horn. Modified from [6].

segmental, in which afferent input and efferent output are located in the same spinal segment or neighboring spinal segments, or proprio-spinal in which afferent input and efferent output are located in different (separate) spinal segments (e.g., sacro-lumbar reflexes related to pelvic organs (see Fig. 4); muscle vasoconstrictor reflexes, cutaneous vasoconstrictor reflexes or sudomotor reflexes mediated by neurons innervating the hindlimb and elicited by stimulation of cutaneous afferents from the hindlimb).

The corresponding situation exists for autonomic reflexes mediated by the brain stem. Basic reflexes associated with the gastrointestinal tract (including salivary glands and mucosa of the oropharyngeal cavity), airways and eye mediated by the lower brain stem (nucleus tractus solitarius [NTS], trigeminal nuclei, nucleus ambiguus, dorsal motor nucleus of the vagus [DMNX], salivary nuclei) or the mesencephalon (nucleus Edinger-Westphal) correspond to segmental spinal reflexes, whereas other reflexes including the bulbo-spinal pathways (e.g., ►baroreceptor (see Fig. 2), chemoreceptor, diving reflexes) involving afferent inputs to the NTS [10] or trigeminal nuclei and sympathetic pathways to resistance blood vessels (in skeletal muscle and viscera, including kidney), to the heart, to cutaneous blood vessels (in particular arterio-venous anastomoses) or to other targets correspond to propriospinal reflexes.

Function of Interneurons in Autonomic Reflex Pathways

It is generally assumed that reflexes are hard-wired components of the nervous system that can be inhibited or enhanced by higher centers. However, this ►concept may be misleading and too narrow. In analogy to the reflex pathways in the somato-motor system, the important components of the autonomic reflexes mediated by the spinal cord or the brain stem are the excitatory glutaminergic interneurons or GABA-ergic and/or glycinergic inhibitory interneurons interposed between afferent input and efferent output. These interneurons outnumber the preganglionic output neurons probably by an order of magnitude. With a few exceptions, notably baroreceptor reflexes (Fig. 2), reflexes represented in the dorsal vagal complex (Fig. 3) and reflexes related to the urinary bladder (Fig. 4), most autonomic interneurons have not been identified physiologically and anatomically. However, many functionally distinct types of interneurons are needed to explain the many distinct types of autonomic reflexes demonstrated in neurophysiological and other experimental investigations (Table 1). These pools of interneurons represent neural autonomic subroutines or “neural autonomic motor programs.” Command signals from higher autonomic centers may target the neural autonomic subroutines via the interneurons leading in this way to a spatially and temporally coordinated smooth regulation of autonomic target



Autonomic Reflexes. Figure 2 The baroreceptor reflex pathway to sympathetic cardiovascular neurons is modulated at all synapses in the brain stem and spinal cord. The neurons of the baroreceptor reflex pathway are outlined in red. Excitatory neurons/synapses, open symbols. Inhibitory neurons/synapses, closed symbols. CVLM, caudal ventrolateral medulla. CPA, caudal pressure area. CRG, central respiratory generator. IML, intermediolateral cell column. LH, lateral hypothalamus. KF, Kölliker-Fuse nucleus. NTS, nucleus tractus solitarii. PAG, periaqueductal gray. PVH, paraventricular nucleus of the hypothalamus. RVLM, rostral ventrolateral medulla. From [6].

organs. This principle of organization is probably responsible for the adaptability and flexibility of all autonomic regulations operating during behavioral changes of the organism. It applies to all levels of the central organization of the autonomic nervous system:

- At the most basic level in spinal cord and lower brain stem the interneuron pools are responsible for the coordination and integration of different but functionally related autonomic systems (e.g., cutaneous vasoconstrictor and sudomotor systems; autonomic systems involved in regulation of pelvic organs) and of somatic and autonomic systems (e.g., sphincters and autonomic components of urinary tract (Fig. 4) or hindgut; cardiovascular and respiratory systems;

cardiovascular, thermoregulatory and somatomotor systems during muscular efforts; see Chap. 10 in [6]).

- Sympathetic premotor neurons (e.g., in the rostral ventrolateral medulla, in the raphe nuclei of the medulla and in the hypothalamus) may not primarily target preganglionic sympathetic neurons but rather, spinal autonomic circuits via their interneurons. The same may apply to parasympathetic premotor neurons targeting the autonomic reflex circuits in the sacral and sacro-lumbar spinal cord, the dorsal vagal complex related to the GIT (Fig. 3) or the circuits in the nucleus ambiguus related to heart and airways.
- Signals from the cerebral hemispheres (e.g., the anterior cingulate cortex and the medial and lateral prefrontal cortex) may equally target, for example by way of the hypothalamus or the periaqueductal grey, these autonomic reflex circuits via their interneurons. This would lead to a smooth adaptation of the body during exercise, defense, diving, digestion and food intake, thermoregulation, reproduction etc.; Chap. 11 in [6]).

Examples of Autonomic Reflexes and Their Integration in Autonomic Regulations

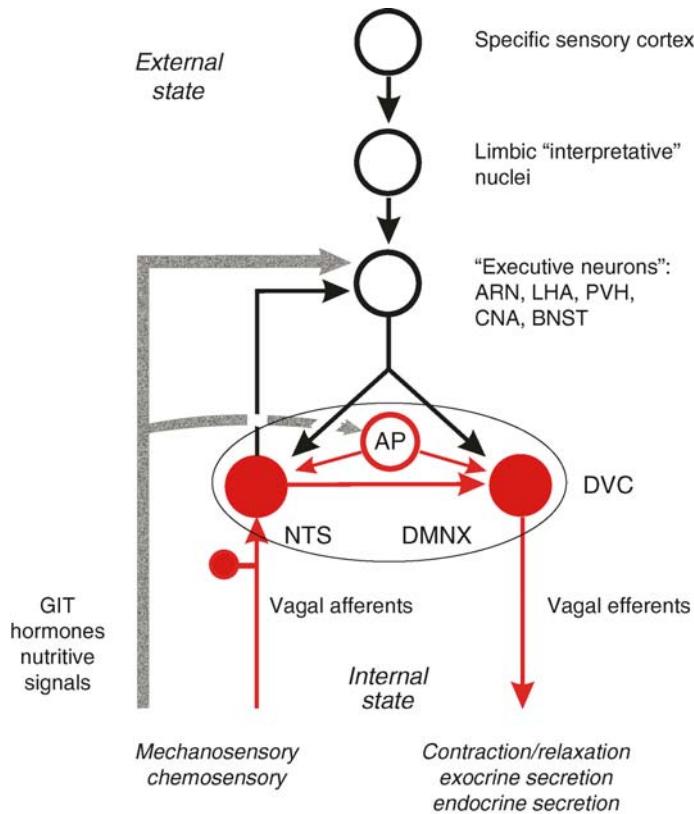
The concept of the functioning of autonomic reflexes during regulation of autonomic target organs as outlined above is exemplified by three examples.

Arterial Baroreceptor Reflexes Mediated by Sympathetic Cardiomotor Neurons

The main components of the baroreceptor reflex pathways mediated by sympathetic cardiovascular neurons and parasympathetic cardiomotor neurons have been worked out in the last 20 years (Fig. 2; [6]). Every relay of this reflex pathway (red in Fig. 2 for the sympathetic cardiovascular neurons) in the lower brain stem (NTS, CVLM, RVLM) and spinal cord (IML) is under multiple synaptic excitatory and inhibitory controls from other centers in spinal cord, brain stem and forebrain. This (together with the structure of the baroreceptor pathway to the parasympathetic cardiomotor neurons) is one basis for the acute and chronic adaptation and plastic changes of the regulation of cardiovascular targets (heart, resistance blood vessels) under various behavioral conditions.

Vago-vagal Reflexes of the Gastrointestinal Tract in the Dorsal Vagal Complex (DVC)

The functionally distinct reflex circuits formed in the DVC between the afferents from the GIT [10] and the preganglionic neurons to the GIT are the *basic building blocks* used by the brain to control GI functions (Fig. 3). Anatomical studies have shown that several nuclei in

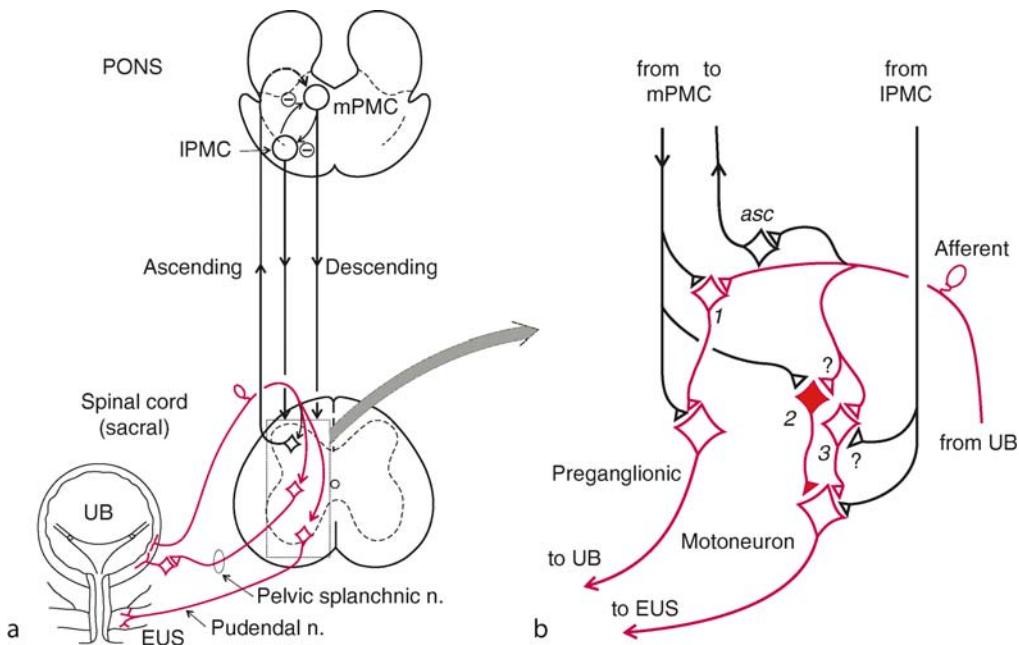


Autonomic Reflexes. Figure 3 Gastrointestinal vago-vagal reflex pathways in the dorsal vagal complex (DVC) and their modulation by centers in the hypothalamus and cerebral hemispheres. Several functionally specific vago-vagal reflex pathways organized in the dorsal vagal complex (nucleus tractus solitarii [NTS], dorsal motor nucleus of the vagus [DMNX], area postrema [AP]) of the medulla oblongata are the *basic neuronal building blocks* of the control of the gastrointestinal tract (GIT) by the brain. Vagal afferents measure mechanical, chemical and other sensory events and project to the NTS [10]; vagal preganglionic neurons are located in the DMNX and are involved in regulation of motility, exocrine secretion and endocrine secretion of the GIT. Second-order neurons in the NTS project to the preganglionic neurons in the DMNX, the synaptic connection being either inhibitory (transmitter noradrenaline or gamma-amino-butyric acid) or excitatory (transmitter glutamate). Multiple hormonal afferent inputs from the GIT and nutritive inputs (glucose, lipids) occur to the DVC (via the area postrema [AP]) and to the hypothalamus (mostly via the arcuate nucleus [ARN]). Neurons of the "executive" centers (e.g., ARN, lateral hypothalamic and paraventricular area [LHA], paraventricular nucleus of the hypothalamus [PVN], central nucleus of the amygdala [CNA], bed nucleus of the stria terminalis [BNST]) evaluate the state of the internal milieu (by way of inputs from visceral afferents, hormonal inputs and nutritive signals) as well as the current or anticipated behavioral state (via input from limbic nuclei that evaluate the significance of exteroceptive signals). These executive centers adapt the internal state (e.g., the functions of the GIT) to the behavioral state of the organism. Modified from Rogers RC and Hermann G (1992) Central regulation of brainstem gastric vago-vagal control circuits. In *Neuroanatomy and Physiology of Abdominal Vagal Afferents* (Ritter S, Ritter RC & Barnes CD eds), pp 99–134 and Travagli RA, Hermann GE, Browning KN, Rogers RC (2006) Brainstem circuits regulating gastric function. *Annu Rev Physiol* 68:279–305.

the brain stem, hypothalamus and telencephalon have *reciprocal connections* with the circuits of the DVC. The functions of most of these neural connections are poorly understood. Thus, the reflex pathways of the DVC are under modulatory control of neurons in the medulla oblongata and supramedullary brain centers, including the insula, the anterior cingulate cortex and medial prefrontal cortex (so-called "executive" neurons) which also receive detailed afferent information

from the GIT (via the NTS), from other visceral organs and from somatic body domains. Executive neurons and basic autonomic circuits in the DVC associated with the GIT represent the *internal state of the organism* as far as the GIT is concerned (Fig. 3).

An essential component of this internal state of the organism is the feedback by hormonal and nutritive signals from the GIT to the DVC via the area postrema and to the hypothalamus (mainly via the arcuate



Autonomic Reflexes. Figure 4 The spinal micturition reflexes and their supraspinal control. (a) Sacral visceral afferents from the urinary bladder (UB) project to interneurons involved in micturition and continence and to ascending tract neurons (asc) which project (probably via the periaqueductal gray) to the pontine micturition center (PMC) consisting of the lateral PMC (IPMC) and the medial PMC (mPMC). Activation of mPMC Barringtons nucleus enhances/initiates micturition and activation of IPMC continence; both inhibit each other reciprocally. Neurons in the PMC project to the sacral spinal cord (descending). Sacral preganglionic neurons project to the bladder body inducing contraction of the urinary bladder. Other sacral preganglionic neurons project to urethra and bladder neck inducing relaxation (not shown). Motoneurons project to the external urethral sphincter (EUS) that is activated during continence and inhibited during micturition. (b) Afferents from the urinary bladder form reflex circuits to preganglionic neurons and motoneurons in the sacral spinal cord via interneurons 1, 2 and 3 (red). Neurons in the mPMC project to sacral preganglionic parasympathetic neurons and interneurons; they activate the preganglionic neurons to the UB (directly and via interneuron 1) and inhibit motoneurons to the EUS (via interneuron 2). Neurons in the lateral pontine micturition center (IPMC) activate motoneurons during continence (directly and possibly also via interneuron 3). It is a matter of debate whether the micturition center acts mainly at the interneurons or at the preganglionic neurons and somatomotor neurons in the adult. Modified from [6] (see [8,9]).

nucleus: ARN). This hormonal feedback consists of several components and is integrated into the homeostatic regulation of metabolism (nutrition), body temperature, electrolyte balance, reproduction and protection of the body by the brain involving lower brain stem and hypothalamus. These homeostatic regulations are adapted to the behavior of the organism by cortical and limbic system structures that monitor and represent the *external state of the organism* (Fig. 3), e.g., during strong exercise, large environmental temperature changes, food and fluid deprivation, invasion of toxic compounds or bacteria (sepsis, toxemia). This concept shows that there is a close integration between the homeostatic regulation of GIT functions and higher nervous system functions related to body perception, emotions and adaptation of behavior. The highly specific autonomic reflex pathways in the DVC are at the basis of this integration.

Micturition Reflexes in the Sacral Spinal Cord

In the adult under physiological conditions, the urinary bladder slowly fills and accommodates to the increasing intravesical volume. Depending on the degree of filling of the urinary bladder and the central (cortical) command signals, micturition is initiated. The detrusor muscle contracts and bladder neck, urethra and external urethral sphincter relax, resulting in the voiding of urine. These coordinated actions are initiated by activation of sacral afferents from the bladder dome and generated by (i) reflex activation of parasympathetic neurons to the detrusor muscle, (ii) reflex activation of inhibitory parasympathetic neurons to the urethra and bladder neck (leading to active relaxation of the outlet of the urinary bladder (not shown in Fig. 4) and (iii) inhibition of pudendal motoneurons.

Figure 4 outlines schematically the central reflex circuits involved in micturition:

1. Activity in sacral vesical afferents activates via an ascending pathway (*ascending* in Fig. 4b) neurons in the medial pontine micturition center (mPMC; Barrington's nucleus). The output neurons of Barrington's nucleus project to the sacral spinal cord and activate the preganglionic neurons mediating bladder contraction both directly and indirectly via interneurons (interneuron 1 Figure 4B) and at the same time, inhibit the motoneurons projecting to the external urethral sphincter via inhibitory interneurons (interneuron 2). The lateral pontine micturition center (IPMC) is inhibited by the mPMC.
2. It is a matter of debate whether the spinal circuits represented by the interneurons 1, 2 and 3 are important during normal micturition when the spinal cord is intact. De Groat and his coworkers believe that the spinobulbospinal reflex pathway involving the mPMC mediates micturition in the adult and that the spinal reflex pathways are unimportant during normal micturition [8]. Others favor the idea that these spinal reflex pathways are involved in the normal micturition reflexes [6,9]. It is suggested for example that the signals from the pontine micturition center are gated by spinal interneurons activated by afferents from the urinary bladder.
3. Motoneurons to the external urethral sphincter are activated by neurons in the lateral pontine micturition center (IPMC) projecting to the sacral spinal cord during continence. This activation occurs by direct synaptic activation of the motoneurons or by synaptic activation of excitatory interneurons antecedent to the motoneurons (interneuron 3 in Fig. 4b). The neurons in the IPMC are inhibited during micturition, probably from the mPMC.

Acknowledgments

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References

1. Sherrington C (1906) The Integrative action of the nervous system. Yale University Press, New Haven
2. Baldissera F, Hultborn H, Illert M (1981) Integration in spinal neuronal systems. In: Brooks VB (ed) Motor control, Part I (Handbook of physiology, Section 1, The nervous system), Bethesda, Maryland: American Physiological Society, pp 509–595
3. Jankowska E (2001) Spinal interneuronal systems: identification, multifunctional character and reconfigurations in mammals. *J Physiol (Lond)* 533:31–40
4. Prochazka A, Clarac F, Loeb GE, Rothwell JC, Wolpaw JR (2000) What do reflex and voluntary mean? Modern views on an ancient debate. *Exp Brain Res* 130:417–432
5. Furness JB (2006) The enteric nervous system. Blackwell, Oxford
6. Jänig W (2006) The integrative action of the autonomic nervous system. Neurobiology of homeostasis. Cambridge University Press, Cambridge, New York
7. Jänig W, McLachlan EM (2002) Neurobiology of the autonomic nervous system. In: Mathias CJ, Bannister R (eds) Autonomic failure. Oxford University Press, New York, Oxford, pp 3–15
8. De Groat WC (2002) Neural control of the urinary bladder and sexual organs. In: Mathias CJ, Bannister R (eds) Autonomic failure. Oxford University Press, New York Oxford, pp 151–165
9. Shefchyk SJ (2001) Sacral spinal interneurones and the control of urinary bladder and urethral striated sphincter muscle function. *J Physiol (Lond)* 533:57–63
10. Undem B, Weinreich D (2005) Advances in Vagal Afferent Neurobiology. CRC Press, Boca Raton

Autonomic Regulation

Definition

Altering visceral processes including those associated with the cardiovascular system, digestion, respiration, metabolism and thermoregulation through the nervous system, mainly via innervation of smooth and cardiac muscle.

Autonomic Regulation of the Endocrine System

Definition

Both sympathetic and parasympathetic nerves regulate secretion of some hormones. Hormones secreted in response to stimulation by sympathetic nerves include catecholamines from the adrenal medulla, glucagon from the pancreas and renin from the kidney. Stimulation by sympathetic nerves inhibits insulin secretion from the pancreas. Hormones secreted in response to stimulation by parasympathetic nerves include gastrins from the stomach and insulin from the pancreas.

Secretion of these various hormones can be elicited by either direct stimulation of the central nervous system, or by visceral and somatic afferent stimulation whereby autonomic nerves serve as the efferent limbs of the respective reflex arcs.

Autonomic Testing: The Clinical Laboratory

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Advantages and Disadvantages

The autonomic nervous system (ANS) regulates such important functions as blood pressure (BP), heart rate (HR), respiration, and bowel, bladder, sexual, thermoregulatory and pupillary functions. Autonomic disorders affecting the brain, spinal cord, or peripheral nerves could cause damage to autonomic pathways and result in autonomic dysfunction. Testing can be done to evaluate the integrity of autonomic pathways and structures, and to detect deviations from normal. Such testing can be done as part of clinical laboratory evaluation or as research into ANS function and dysfunction. Autonomic tests can be divided into two broad categories, “Routine Tests” and “Research Studies.”

Routine Laboratory Tests of Autonomic Function

The goal in clinical autonomic testing is to detect the presence of autonomic failure in patients with suspected autonomic disorders, using a panel of tests that meet certain criteria. Thus, since these tests are to be widely used on many patients, they need to be straightforward to perform, comprehensive, reliable, and based on sound autonomic physiology. One set of routine tests comprises a study of the integrity of autonomic nerves that regulate sudomotor, cardiovagal, and adrenergic function. The aims are to detect the presence of autonomic failure, to quantify the severity, to apportion the type (sudomotor, adrenergic, cardiovagal) and distribution of deficits, and to determine the site (preganglionic versus postganglionic) of the lesion [1].

Postganglionic sudomotor function is evaluated using the quantitative sudomotor axon reflex test (QSART). QSART utilizes an axon-reflex pathway and tests the integrity of the postganglionic sympathetic sudomotor axon [2]. The stimulus is iontophoresed acetylcholine and the evoked sweat response is recorded in a different site. Typically, recording sites are the forearm, proximal leg, distal leg, and foot. In normal subjects, sweat volumes for all sites are similar and women have volumes that are approximately one-half those of males. The distribution of abnormalities is particularly useful in monitoring a length-dependent neuropathy; sweat volumes undergo a progressive decrease from proximal to distal sites. The test is also useful in monitoring the course of a neurologic disorder

over time since the test is highly reproducible. Volumes from the same subjects on two different days correlate well ($R = 0.9$) with a coefficient of variation of 14.7%. QSART can be supplemented by the thermoregulatory sweat test (TST). Sweating in TST, in response to raising core temperature using ambient heat, is detected by an indicator powder. This test provides information on the distribution of sweat loss. The percent of anterior body surface anhidrosis can be quantified [3]. Taken with QSART, the site of the lesion can be defined. For instance, if a patient were anhidrotic at a site but had normal QSART, the lesion would likely be preganglionic.

Cardiovagal function is relatively straightforward to evaluate. Both cardiac afferent and efferent nerve fibers that are activated by maneuvers such as deep breathing, standing up, or the Valsalva maneuver are carried in the vagus nerve. Hence, tests in the time domain, such as those measuring heart rate response to deep breathing or to the Valsalva maneuver, evaluate vagal pathways to the heart. An alternative approach is to evaluate cardiovagal function in the frequency domain. Tests of cardiovagal function, especially the response to deep breathing, are reliable and reproducible, provided that the end organ is healthy [4].

Adrenergic function controls blood pressure (and heart rate) by regulating tone to the microvessels (mainly arterioles) and cardiac contractility. The major reflex is the baroreflex, which responds instantaneously to changes in blood pressure and volume by an increase or decrease in sympathetic nerve traffic [5]. We evaluate adrenergic function by measuring beat-to-beat BP responses to maneuvers that change BP in a standardized way. Two useful maneuvers are the Valsalva maneuver and head-up tilt (HUT) [1]. The Valsalva maneuver is performed by maintaining expiratory pressure at 40 mm Hg for 15 seconds, and results in changes in venous return to the heart resulting in a transient reduction in stroke volume and BP. This, in turn, results in unloading of baroreflexes. The ensuing vasoconstriction and resultant pressor response provide an index of baroreflex function. The phases of the Valsalva maneuver are under adrenergic control [6]. In HUT, orthostatic stress results in volume shift to the dependent parts of the body, and whether BP is maintained or falls depends on the integrity of baroreflexes. An angle of tilt of 60 or 70° is recommended.

Plasma catecholamines measured with the patient supine and then upright provide a profile of the humoral (mainly noradrenergic) response to standing. In a normal subject standing values are approximately double those with the subject supine. The results of this test correlate well with muscle sympathetic nerve activity [7]. When widespread postganglionic adrenergic failure is present, as in pure autonomic failure,

supine norepinephrine is markedly reduced (70 pg/ml) and fails to increase on standing. With a preganglionic lesion, as in multiple system atrophy, supine values are normal but on standing norepinephrine fails to increase.

The effects of age and gender have significant effects on these autonomic responses, so that an autonomic laboratory must generate a large normative data set in order that percentiles and normal variations for age and gender can be determined.

Laboratory evaluation is useful in a number of circumstances. It is useful in detecting the severity and distribution of autonomic failure. It is valuable in monitoring the course of autonomic failure and evaluating the response to therapy. It is also helpful in differentiating benign disorders (such as syncope) from more serious disorders (such as neurogenic orthostatic hypotension).

Autonomic Testing: Research Studies

There are numerous tests of autonomic function for use in the research laboratory. The selection of tests depends on the research question at hand. Below is a selection of some tests that are in relatively wide use. This description is by necessity selective. For instance, we will not describe the extensive molecular studies of a whole range of autonomic receptors.

Microneurography

Muscle sympathetic neural discharges from unmyelinated axons can be recorded in awake human subjects via tungsten microelectrodes inserted percutaneously into an accessible peripheral nerve [8]. This technique has provided important insights into normal autonomic physiology and aging. Recently, the technique is increasingly applied to gain insights into the pathophysiology of sympathetic dysfunction in the autonomic neuropathies, and pre- and post-ganglionic autonomic disorders.

Baroreflex Analysis

A fall in BP leads to unloading of baroreceptors located in the carotid sinus and aortic arch. This results in activation of sympathetic outflow and inhibition of cardiovagal neurons, and so an increase in heart rate. The converse occurs with a rise in BP. The most reliable method to estimate baroreflex sensitivity is to relate changes in heart period to changes in SBP induced first by intravenous sodium nitroprusside. This is followed by a bolus injection of phenylephrine hydrochloride, thus inducing first a fall and then a subsequent rise in arterial blood pressure – a modification of the Oxford method [9]. Noninvasive approaches that omit vasoactive drugs have been adapted using BP and heart

rate alterations that occur in response to autonomic maneuvers or even spontaneously. The sequence technique [10] is a time-domain method that relates spontaneous sequences of BP fluctuations to the associated heart rate fluctuations. The spectral technique is a frequency domain method, and the cross-spectral technique estimates the gain of the transfer function between changes in blood pressure and heart period [10]. Induced BP changes secondary to neck suction or the Valsalva maneuver can also be used.

Cerebral Vasoregulation

Cerebral autoregulation refers to the maintenance of constant cerebral blood flow in spite of changes in cerebral perfusion pressure [11]. Patients with autonomic baroreflex failure develop both orthostatic hypotension and supine hypertension. Cerebral autoregulation is especially important in these patients and indeed compensation is apparently sometimes augmented by an expansion of the range of autoregulation. The availability of transcranial Doppler methodology to measure blood flow velocity in the middle cerebral artery provides ready access to these measurements. Autoregulation can be studied by changing the steady-state BP (static method) or by rapidly altering BP (dynamic method). Both methods have yielded similar estimates of autoregulation in normal human subjects [12]. One concern with these methods is that the induced BP alterations cause rapid changes in critical closing pressure, rendering estimates of autoregulation inaccurate. Thus, a transfer function method has been proposed, and this is unaffected by changes in critical closing pressure. Cerebral autoregulation has been studied in orthostatic hypotension and intolerance [13].

Splanchnic-Mesenteric Vasoregulation

The splanchnic-mesenteric vascular bed is unique in that it is a baroreflex-responsive capacitance bed. It is of large volume containing up to 20–25% of blood volume. The blood volume increases by 200–300% after a meal. Not surprisingly orthostatic hypotension develops or is aggravated post-prandially. Recent advances in duplex ultrasound technology have allowed reliable noninvasive evaluation of the mesenteric circulation. Superior mesenteric artery (SMA) blood flow can be measured by a real-time Doppler ultrasound transducer [14]. The cross-sectional area of the SMA (SMA-area) and time-average velocity (SMA-TAV) are measured using dedicated software, and blood flow and vascular resistance are calculated. The post-prandial fall in BP is linearly related to the increase in SMA flow. It is possible to define the effects of tilt and vasoconstrictors.

Cardiac Innervation

Cardiac postganglionic sympathetic adrenergic innervation can be studied using isotopes and SPECT, or positron-emission tomography (PET) scanning. Cardiac uptake of [123 I]iodine-123 meta-iodobenzylguanidine, an analogue of norepinephrine which traces the functioning of postganglionic sympathetic adrenergic neurons [15], can be imaged using SPECT. PET scanning and 6-[18 F]fluorodopamine provide better resolution [16]. This test has been useful in differentiating MSA (normal uptake) and Parkinson's disease (reduced uptake when autonomic failure is present [17]). Uptake is also reduced in diabetic autonomic neuropathy. Interestingly, PET scanning has been reported to show hyperinnervated adrenergic islands in rostral segments in these patients, raising the possibility that these might be conducive to arrhythmias.

References

1. Low PA (1993) Autonomic nervous system function. *J Clin Neurophysiol* 10:1427
2. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ (1983) Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 14:573–580
3. Fealey RD, Low PA, Thomas JE (1989) Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 64:617–628
4. Wieling W, van Brederode JF, de Rijk LG, Borst C, Dunning AI (1982) Reflex control of heart rate in normal subjects in relation to age: a data base for cardiac vagal neuropathy. *Diabetologia* 22:163–166
5. deBoer RW, Karemker JM, Strackee J (1987) Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol* 253:H680–H689
6. Sandroni P, Benarroch EE, Low PA (1991) Pharmacological dissection of components of the Valsalva maneuver in adrenergic failure. *J Appl Physiol* 71:1563–1567
7. Wallin BG, Sundlof G, Eriksson BM, Dominiak P, Grobecker H, Lindblad LE (1981) Plasma noradrenaline correlates to sympathetic muscle nerve activity in normotensive man. *Acta Physiol Scand* 111:69–73
8. Wallin BG, Elam M (1997) Microneurography and autonomic dysfunction. In: Low PA (ed) *Clinical autonomic disorders: Evaluation and management*. Lippincott-Raven, Philadelphia, pp 233–243
9. Smyth HS, Sleight P, Pickering GW (1969) Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. *Circ Res* 24:109–121
10. Eckberg DL, Sleight P (1992) *Human baroreflexes in health and disease*. Clarendon, Oxford
11. Strandgaard S, Paulson OB (1984) Cerebral autoregulation. *Stroke* 15:413–416
12. Tiecks FP, Lam AM, Aaslid R, Newell DW (1995) Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 26:1014–1019
13. Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, Low PA (1998) Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. *Stroke* 29:1876–1881
14. Fujimura J, Camilleri M, Low PA, Novak V, Novak P, Opfer-Gehrking TL (1997) Effect of perturbations and a meal on superior mesenteric artery flow in patients with orthostatic hypotension. *J Auton Nerv Syst* 67:15–23
15. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH (1999) Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. *Neurology* 53:1020–1025
16. Goldstein DS, Holmes C, Eisenhofer G, Kopin H (1997) Sympathetic cardioneuropathy in dysautonomias. *N Engl J Med* 336:696–702
17. Goldstein DS, Holmes C, Li ST, Bruce S, Metman LV, Cannon III RO (2000) Cardiac sympathetic denervation in Parkinson disease. *Ann Intern Med* 133:338–347

Autonomic/Enteric Dysreflexia

Definition

Autonomic dysreflexia is a clinical syndrome occurring in patients with severe cervical or upper thoracic spinal cord lesions. It normally appears several months following injury and manifests as exuberant reflex autonomic discharges in response to what might otherwise be relatively trivial stimuli. A classical presentation is paroxysmal hypertension, mediated via excessive splanchnic sympathetic output, triggered by bowel or bladder distension.

- Autonomic/Enteric Reflexes
- Autonomic Insufficiency

Autonomic/Enteric Reflexes

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Definition

Enteric reflexes are fundamental mechanisms in the autonomic neural control of motility up and down the digestive tract, starting with swallowing at the oral end and terminating with defecation at the anal end. With the exception of the control of the striated musculature in the pharynx during swallowing and control of the skeletal musculature of the pelvic floor during maintenance of fecal continence and defecation, most

enteric reflexes are mediated by the autonomic nervous system. The three divisions of the autonomic nervous system (i.e. the parasympathetic, sympathetic and enteric divisions) interact with each another in mediating involuntary control of motor behavior of the smooth musculature of the digestive tract, secretory behavior of the glands and gastrointestinal blood flow.

Reflex circuits were also called “reflex arcs” in earlier literature. A reflex circuit consists of a minimum of a sensory neuron that synapses with and excites a motor neuron, which in turn innervates an effector (e.g. muscle or gland). Reflex behavior evoked by a circuit consisting only of a sensory and motor neuron is a monosynaptic reflex. Reflex circuits in which interneurons are synaptically interposed between the sensory and motor neuronal components are polysynaptic reflex circuits. Enteric reflexes are generally polysynaptic with internuncial circuitry located in the brainstem, the spinal cord and within the **►enteric nervous system** (ENS) positioned inside the walls of the digestive tract.

Characteristics

Brain-Stem Reflexes and ENS Reflexes

Reflex Control of the Stomach

Internuncial circuitry in both the brainstem and the gastric ENS is involved in reflex control of secretory and motor functions of the stomach. Motor functions in the stomach are more complex than in the intestines, and require the more sophisticated circuitry of the brainstem to achieve full moment-to-moment control during filling, grinding movements and emptying. Motor functions of the small and large intestines are less complex and are mainly organized by the ENS independent of the central nervous system (CNS).

Functionally, the stomach is divided into a proximal reservoir and distal antral pump on the basis of distinct differences in motility between the two regions. The differences in motility between the reservoir and antral pump reflect adaptations for different functions [8]. The muscles of the proximal stomach are adapted for maintaining continuous contractile tone (tonic contraction) and do not contract phasically. In contrast, the muscles of the antral pump contract phasically. The spread of strong phasic contractions in the region of the antral pump propels the gastric contents toward the gastroduodenal junction. Strong propulsive waves of this nature do not occur in the proximal stomach.

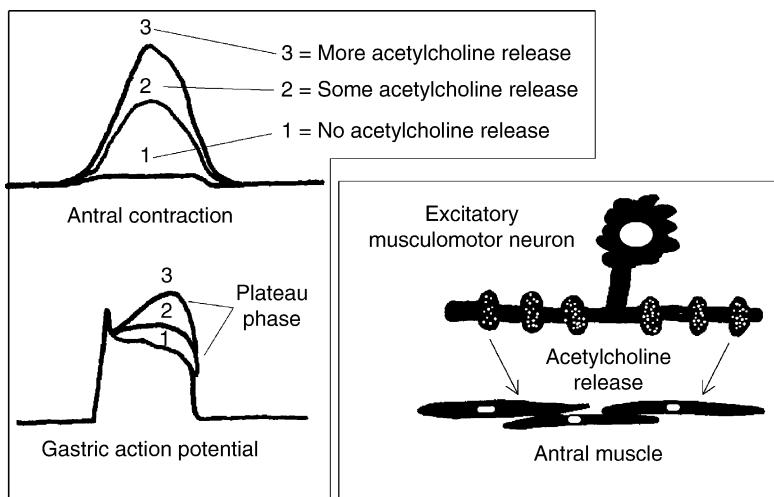
Antral Pump

Gastric action potentials determine the duration, strength and aboral direction of travel of the phasic contractions in the antral pump. Gastric action potentials are initiated by a dominant pacemaker located approximately in the mid-region of the stomach. After

starting at the pacemaker site, an action potential propagates rapidly around the gastric circumference and triggers a ring-like contraction. The action potential and associated ring-like contraction then travel more slowly until they reach the gastroduodenal junction where they stop [8]. ►Electrical syncytial properties of the myogenic gastric musculature (►myogenic musculature) account for the propagation of the action potentials from muscle fiber to muscle fiber away from the pacemaker site toward the gastroduodenal junction. Gastric action potentials are generated at 3 min^{-1} in humans, have durations of about 5 s and have a rising depolarization phase, a plateau phase, and a repolarization falling phase (Fig. 1).

The action potentials trigger propulsive contractions when the plateau phase is above a threshold voltage and the strength of the contraction increases in direct relation to increases in the amplitude of the plateau potential beyond threshold.

The action potentials in the gastric reservoir are myogenic (i.e. an inherent property of the muscle) and occur in the absence of any neurotransmitters or other chemical messengers. The myogenic characteristics of the action potential are modulated by musculomotor neurons in the gastric ENS. Neurotransmitters released by enteric musculomotor neurons determine the amplitude of the plateau phase of the action potential, and thereby control the strength of the contractile event triggered by the plateau phase. Neurotransmitters (e.g. acetylcholine) released from excitatory motor neurons in the ENS increase the amplitude of the plateau phase and of the contraction initiated by the plateau (Fig. 1). Inhibitory neurotransmitters including norepinephrine, vasoactive intestinal peptide and nitric oxide decrease the amplitude of the plateau and the strength of the associated contraction. Postganglionic neurons projecting to the stomach from prevertebral ganglia of the sympathetic nervous system are the source of norepinephrine. The sources of vasoactive intestinal peptide and nitric oxide are inhibitory musculomotor neurons (►enteric inhibitory musculomotor neurons) in the ENS. The magnitude of the excitatory or inhibitory actions of neurotransmitters is related directly to the concentration of the transmitter substance at receptors on the gastric musculature. Progressively higher frequencies of impulse discharge by ►enteric excitatory musculomotor neurons progressively release greater amounts of neurotransmitter. In this way, motor neurons determine, through the actions of their neurotransmitters on the plateau phase, whether or not a propagating contraction occurs in the antral pump. With sufficient release of transmitter, the plateau exceeds the threshold and a contraction occurs. Beyond threshold, the strength of contraction is determined by the amount of neurotransmitter released and present at excitatory receptors on the musculature.



Autonomic/Enteric Reflexes. Figure 1 Firing frequency and therefore the amount of acetylcholine released from excitatory musculomotor neurons in the myenteric plexus of the gastric antrum determine the amplitude of the plateau phase of the gastric action potential. The amplitude of the plateau phase determines the amplitude of antral contractions.

Gastric Reservoir

The gastric reservoir functions in two ways. One is to accommodate the arrival of a meal without a significant increase in intragastric pressure and intramural tension. Failure of accommodation leads to the uncomfortable sensations of bloating, epigastric pain, and nausea in humans. The second function sustains a constant compressive force on the contents of the reservoir that “pushes” the contents into the 3-cycles min⁻¹ motor activity of the antral pump. Drug-induced relaxation of the musculature of the gastric reservoir (e.g. by insulin or glucagon) neutralizes this function and suppresses gastric emptying.

The musculature of the gastric reservoir is innervated by enteric excitatory and inhibitory musculomotor neurons. Vagal efferent nerves and neural networks in the gastric ENS control the firing frequencies of the musculomotor neurons. Changes in the firing frequencies of the musculomotor neurons, and coordination of the activity in excitatory and inhibitory enteric musculomotor neuronal populations, function to adjust the volume and pressure of the reservoir to the amount of solid and/or liquid present, while maintaining constant compressive forces on the contents. Neural control mechanisms continuously readjust the volume and pressure within the reservoir as required during both ingestion and emptying of a meal.

Increased activity of excitatory musculomotor neurons coordinated with decreased activity of inhibitory musculomotor neurons, results in increased contractile tone in the reservoir, a decrease in its volume, and an increase in intraluminal pressure. Increased firing of inhibitory musculomotor neurons, coordinated with decreased activity of excitatory musculomotor neurons,

results in decreased contractile tone in the reservoir, expansion of its volume, and a decrease in intraluminal pressure.

Neurally mediated decreases in tonic contracture of the musculature are responsible for relaxation in the gastric reservoir (i.e. increased volume). Three kinds of relaxation are recognized: (i) Receptive relaxation is initiated by the act of swallowing. It is a reflex triggered by stimulation of mechanoreceptors in the oropharynx, followed by transmission over spinal and cranial afferents to the **dorsal vagal complex** in the medulla oblongata of the brainstem and activation of efferent vagal fibers to inhibititory musculomotor neurons in the gastric ENS. (ii) Adaptive relaxation is triggered by distension of the gastric reservoir. It is a **vago-vagal reflex** consisting of activation of stretch receptors in the gastric wall, transmission over vagal afferents to the brainstem, central processing of the afferent information and return transmission in efferent vagal fibers to stimulate inhibitory musculomotor neurons in the gastric ENS. (iii) Feedback relaxation is triggered by the presence of nutrients in the small intestine. This form of reservoir relaxation can involve both local reflex connections between receptors in the small intestine and the gastric ENS, or hormones (e.g. cholecystokinin) that are released from endocrine cells in the small intestine and transported by the blood to signal the gastric ENS.

Pathology

Adaptive relaxation is impaired in patients who have suffered injury to the vagus nerves during laparoscopic fundoplication surgery or have undergone gastric vagotomy for treatment of an acid-related disorder.

Following a vagotomy, increased tone in the musculature of the reservoir decreases the wall compliance, which in turn affects the responses of gastric stretch receptors to distension of the reservoir. The loss of adaptive relaxation following vagotomy is associated with a lowered threshold for sensations of fullness and pain during a meal and filling of the gastric reservoir. Increased sensitivity to gastric distension in these cases is explained by excessive stimulation of the gastric mechanoreceptors that sense distension of the gastric wall. These effects of vagotomy underscore the importance of sensory detection in the gastric wall and processing of the sensory information in the dorsal vagal complex (see next section), and help to understand disordered gastric sensations in diseases that have a component of vagal nerve pathology (e.g. autonomic neuropathy in diabetes mellitus).

Vago-Vagal Reflexes

Sensory nerve fibers in the afferent arm of ►vago-vagal reflexes involved in control of gastric functions enter the brainstem and form synaptic connections with cell bodies of efferent vagal neurons that project efferent information back to the stomach. The cell bodies of efferent vagal neurons to the stomach are located in the dorsal motor nucleus of the vagus (DMNV). The vagal afferents also form synapses with second order neurons in the brainstem that distribute visceral information throughout the CNS. Fifty thousand vagal afferent fibers are estimated to supply the gastrointestinal tract. The number of vagal afferent fibers exceeds the number of efferent vagal fibers by about 10:1. Vagal afferent fibers are unmyelinated C-fibers that transmit different modalities of sensory information at low conduction velocity. Vagal afferents generally transmit physiological information on the nature and composition of the luminal contents, on shearing forces occurring at the mucosal surface and on contractile tension in the gastric musculature.

Some vagal afferents connect monosynaptically with vagal efferent neurons and thus become the sensory arm of monosynaptic vago-vagal reflex arcs. Nevertheless, the majority of gastrointestinal vagal afferents project to second order neurons in the nucleus tractus solitarius, and much of the afferent information from the upper gut is therefore processed in polysynaptic pathways through the brainstem. The nucleus tractus solitarius and DMNV combine to form the dorsal vagal complex. Various subnuclei form the nucleus tractus solitarius. Of these, the subnucleus gelatinosus and the medial and commissural nuclei are the principal targets for sensory information in gastric afferents. Gastric afferents also project to the area postrema in the medulla oblongata and transmit input that triggers nausea and emesis. Projections of neurons in the nucleus tractus solitarius to the DMVN complete the vago-vagal reflex

arcs involved in regulation of gastric function. Additional sensory pathways ascend through the mid-brain and reticular nuclei to innervate higher brain centers, and in particular to hypothalamic nuclei involved in mechanisms of satiety and regulation of food intake.

Vagal efferent neurons form the cephalic component of the parasympathetic division of the autonomic nervous system. The cell bodies of the vagal efferents are centered in the DMVN, which is a spindle-shaped nucleus running rostro-caudally through the medulla oblongata on either side of the central canal as it emerges into the fourth ventricle. The DMVN is organized anatomically into longitudinal columns of neurons that ultimately give rise to the branches of the vagal nerves that supply the various abdominal organs.

Vagal efferent nerve fibers transmit CNS input to the ENS. A relatively small number of efferent vagal fibers supply synaptic input to a much larger number of neurons in the ENS. Vagal efferent fibers branch extensively within the gastric ENS where they make synaptic contact with the excitatory and inhibitory musculomotor neurons that innervate the gastric musculature. Most of the vagal efferents release acetylcholine to stimulate nicotinic excitatory receptors on the postsynaptic neurons.

Experimental electrical stimulation of efferent fibers in the vagus nerves evokes a mixture of muscular contraction and relaxation as a consequence of activating parallel pathways to excitatory and inhibitory musculomotor neurons. Contractile responses to vagal stimulation are largely cholinergic and are suppressed by drugs that block nicotinic receptors on enteric neurons or muscarinic receptors on the musculature. Vagally-evoked relaxation is mediated by release of nitric oxide, ATP and vasoactive intestinal peptide from the inhibitory motor innervation of the musculature. Vagally-mediated excitatory or inhibitory gastric reflexes therefore arise from selective activation or suppression of populations of efferent vagal neurons in the DMVN, which project either to inhibitory or excitatory musculomotor neurons in the gastric ENS.

Spontaneously discharged impulses, which reflect ongoing generation of neural activity in the DVMN, can be detected by electrodes on vagal efferent fibers. The spontaneous activity may be generated by DVMN neurons themselves or result from activity in circuitry elsewhere in the brainstem or in higher brain centers that supply excitatory synaptic input to the DVMN neurons. A diverse array of neurotransmitters, including glutamate, serotonin and gamma aminobutyric acid, is expressed in the synaptic neuropil surrounding the DVMN neurons. Brain regions with a prominent input to the DVMN include the medullary raphe nuclei, the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala. These connections underlie emotional and behavioral influences on vagal

outflow to the gut, and in particular, the effects of physical and psychological stress on gastrointestinal function.

As vagal efferents connect to both excitatory and inhibitory motor neurons in the ENS, these pathways are suggested to be reciprocally controlled in the brainstem such that contraction of the gastric musculature arises from activation of cholinergic pathways and simultaneous inhibition of inhibitory pathways [4]. Accordingly, vagally-evoked relaxation of the musculature in the gastric reservoir would involve simultaneous activation of inhibitory pathways and suppression of excitatory pathways. The reflex circuits in the brainstem may therefore be “hardwired” for reciprocal control.

Lower Level Components

Reflexes Mediated by the ENS

The ENS division of the autonomic nervous system is embedded inside the walls of the digestive tract (Fig. 2).

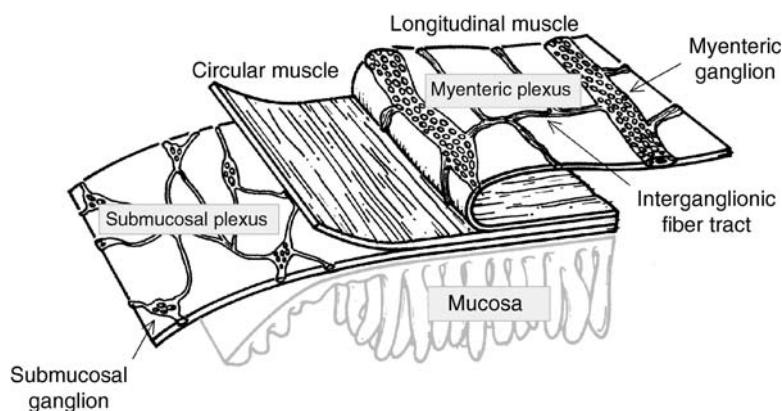
It consists of ganglia, primary interganglionic fiber tracts and secondary and tertiary fiber projections to the musculature, glands and blood vessels. Two ganglionated plexuses are the most obvious gross morphological feature of the ENS. The ►myenteric plexus, also called Auerbach’s plexus, is located between the longitudinal and circular muscle layers of most of the digestive tract. The ►submucosal plexus consists of Meissner’s and Schabadasch’s plexuses and is situated in the submucosal region between the circular muscle and mucosa. The submucosal plexus is most prominent as a ganglionated network in the small and large intestine. It does not exist as a ganglionated plexus in the esophagus and is sparse in the submucosal space of the stomach. Neurons in submucosal ganglia project fibers to the myenteric plexus and also receive synaptic input from axons projecting from the myenteric plexus. The interconnections link the two networks into a functionally integrated nervous system.

The heuristic model for the ENS is the same as for the brain and spinal cord. Like the brain and spinal cord, the ENS develops with the neural elements and integrated circuitry necessary for independent processing of sensory information and programming of organized behavior of effector systems. The ENS controls the intestinal effector systems (i.e. musculature, secretory glands and blood vasculature) in the minute-to-minute regulation of the intraluminal environment of the gut. The population of neurons in the ENS, like the neurons in the brain and spinal cord, is divided into a subpopulation of sensory neurons, a subpopulation of interneurons and a subpopulation of motor neurons. The sensory neurons, interneurons and motor neurons are synaptically interconnected into integrated circuits that process sensory information, and program the variety of digestive functions found in the specialized compartments of the digestive tract during ever changing demands of the ingestive/digestive states of the functioning bowel.

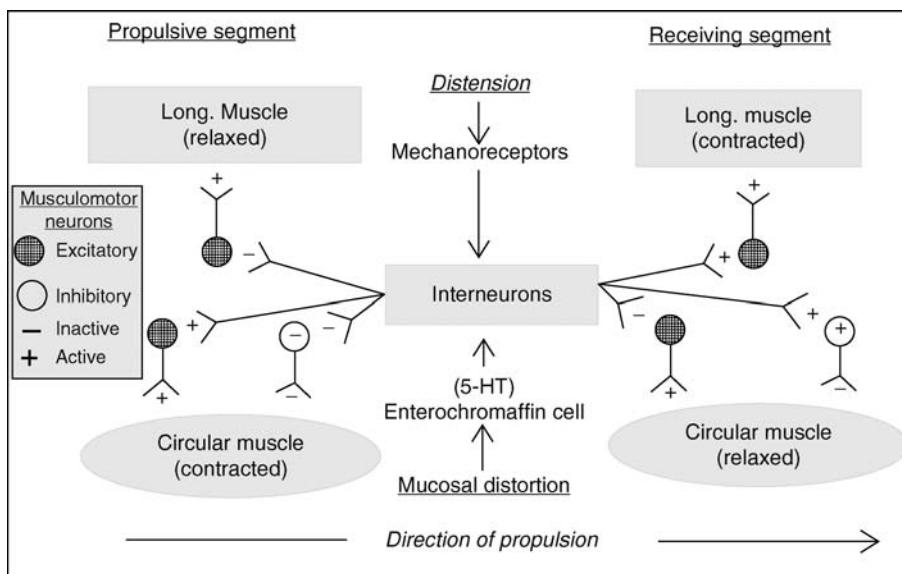
Integrated circuits of the ENS determine the distinctive patterns of motility that characterize the digestive and interdigestive states of the small and large intestine. The ENS microcircuits include a polysynaptic peristaltic reflex circuit (Fig. 3) that underlies all forms of propulsive intestinal motility.

The programs for physiological ileus (i.e. absence of motility), digestive and interdigestive motor and secretory behavior and small intestinal retropulsion during emesis are all stored in the integrated circuits of the ENS.

Microcircuits in the myenteric division of the intestinal ENS contain the musculomotor neurons to the musculature (Fig. 3). Like in the stomach, one subpopulation of musculomotor neurons excites the intestinal musculature to contract; another subpopulation inhibits muscle contraction. Acetylcholine and substance P are primary neurotransmitters released by the subpopulation of excitatory musculomotor neurons.



Autonomic/Enteric Reflexes. Figure 2 Morphology of the enteric nervous system.



Autonomic/Enteric Reflexes. Figure 3 A polysynaptic reflex circuit in the ENS evokes the peristaltic reflex. Two kinds of sensory input activate the reflex. One is distension of the intestinal wall and activation of stretch receptors that synapse with interneurons. Second is stimulation of release of 5-hydroxytryptamine from enterochromaffin cells by shearing forces on the mucosa. Output from the interneuronal reflex circuit activates excitatory musculomotor neurons to the longitudinal muscle and inhibitory musculomotor neurons to the circular muscle to form a receiving segment (see fig. 4) below the point of sensory stimulation. At the same time, the circuit inactivates excitatory musculomotor neurons to the longitudinal muscle, activates excitatory musculomotor neurons to the circular muscle, and inactivates inhibitory musculomotor neurons to the circular muscle in the propulsive segment above the point of stimulation (see fig. 4).

Nitric oxide, vasoactive intestinal peptide and ATP are implicated as inhibitory neurotransmitters.

Microcircuits in the submucosal division of the ENS contain ►secretomotor neurons that innervate the intestinal secretory glands (i.e. Brunner's glands and crypts of Lieberkühn). The secretomotor neurons are the efferent arm of secretory reflex arcs that release vasoactive intestinal peptide and/or acetylcholine at the neuroepithelial junctions to evoke secretion of H₂O, electrolytes and mucus. Collaterals of secretomotor neurons innervate submucosal blood vessels and stimulate vasodilation to increase blood flow in concert with elevated glandular secretion.

Chemical synapses connect ENS interneurons into integrated microcircuits that determine the timing and strength of neural outflow in the motor neuronal pathways to the musculature, secretory glands and vasculature. In addition to control of each of these individual effector systems, interneuronal synaptic circuits coordinate the activity of each of the systems to achieve homeostatic behavior at the level of the integrated organ system.

The ENS is envisioned as a “mini-brain” placed close to the effector systems it controls and this led to coining of the term “brain-in-the-gut” [6]. The brain-in-the-gut contains as many neurons as the spinal cord. Rather

than packing the 2×10^8 neurons required for control of gut functions into the skull as part of the brain, and relying on signal transmission over long-unreliable pathways to the gut, natural selection during biological evolution distributed the integrative neural networks in locations next to the effectors along the 7 m of human small intestine and 1.5 m of large intestine.

The Peristaltic Reflex

Peristalsis is a stereotyped propulsive motor reflex that underlies all propulsive motility patterns found in the small and large intestine. The peristaltic reflex is the ENS analog of spinal motor reflexes (e.g. monosynaptic patellar and Achilles tendon reflexes and polysynaptic withdrawal reflexes). Monosynaptic spinal reflexes are investigator-evoked artifacts arising from connections of stretch receptors in the muscle to alpha spinal motor neurons that innervate the same muscle. They reflect the effects of abrupt activation of stretch receptors (i.e. muscle spindles) in the muscle and have little relevance for fully understanding the complexity of fine neural control of movement. Polysynaptic spinal withdrawal reflexes occur in stereotyped fashion in response to noxious stimulation, such as touching the hand to a hot object. The peristaltic reflex is much the same as spinal reflexes in that it is a fixed response

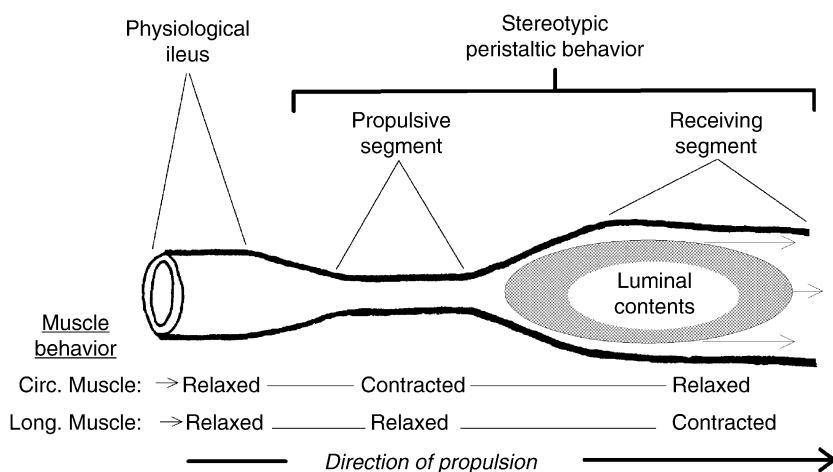
evoked by investigational stretching of the intestinal wall or stroking of the mucosa in isolated intestinal preparations. It is like a polysynaptic spinal reflex in that it is a motor response to sensory stimulation that is repeated the same way each time the “hardwired” reflex circuit is activated. The peristaltic reflex circuit is “wired” such that it evokes relaxation of the circumferentially oriented muscle layer, contraction of the longitudinal muscle below the point of stimulation and contraction of the circumferentially oriented muscle layer above the point of stimulation.

Like spinal reflexes, the peristaltic reflex is positioned at the lowest level of the hierarchical organization of neural control of intestinal motility, and undoubtedly underlies each of the various patterns of propulsive motility that impart functionality to the intestine during daily life. As with a spinal motor reflex, the sequencing of the pattern of behavior of the intestinal longitudinal and circular muscles is hardwired into the circuitry, while the strength of each motor component of the pattern, and the repetition rate of the pattern, are adjusted by sensory feedback or other commands to automatically compensate for local loads and higher functional demands on the intestine as a whole. Distance and direction in which propulsion occurs in the specific patterns of motility that characterize the various digestive states are additional factors requiring a higher order of neural control. Short distance propulsion in the postprandial digestive state, propulsion over intermediate distances during interdigestive

motility (i.e. the migrating motor complex) and long distance power propulsion, all in the orthograde direction, and retropulsion during emesis are neural control requirements that are met by the ENS. Better understanding of the neural basis for intestinal motility will require moving forward from the “over-worked” concept of the peristaltic reflex, on to investigation of microcircuits in positions at levels of organization beyond the reflex “hardwiring” that faithfully reproduces the muscle behavior each time the investigator stretches the intestinal wall or strokes the mucosa.

The muscle layers of the intestine contract and relax in a stereotyped pattern during peristaltic propulsion (Fig. 4).

This pattern is determined by the sequence in which the peristaltic polysynaptic reflex circuit activates excitatory and inhibitory musculomotor neurons to the longitudinal and circular muscle layers. During propulsion, the longitudinal muscle layer in the segment ahead of the advancing intraluminal contents contracts in response to activation of its excitatory motor innervation, while at the same time, the circular muscle layer relaxes in response to activation of its inhibitory motor innervation. The intestinal tube always behaves geometrically like a cylinder with constant surface area [10]. Shortening of the longitudinal axis of the cylinder during contraction of the longitudinal muscle is accompanied by a widening of the cross-sectional diameter. The simultaneous shortening of the longitudinal axis and relaxation of the circular muscle results



Autonomic/Enteric Reflexes. Figure 4 The circular and longitudinal muscle layers of the intestine behave in a stereotypical pattern during peristaltic propulsion. A polysynaptic reflex circuit in the ENS determines the pattern of behavior of the two muscle layers. During peristaltic propulsion, the longitudinal muscle layer in the segment ahead of the advancing intraluminal contents contracts while the circular muscle layer relaxes. Simultaneous shortening of the longitudinal intestinal axis and relaxation in the circumferential axis in the same segment results in expansion of the lumen, which becomes a receiving segment for the forward-moving contents. The second component of the reflex is contraction of the circular muscle in the segment behind the advancing intraluminal contents. The longitudinal muscle layer in the same segment relaxes simultaneously with contraction of the circular muscle, which results in conversion of this region to a propulsive segment that propels the luminal contents ahead into the receiving segment.

in expansion of the lumen, which prepares a receiving segment for the forward-moving intraluminal contents during peristaltic propulsion.

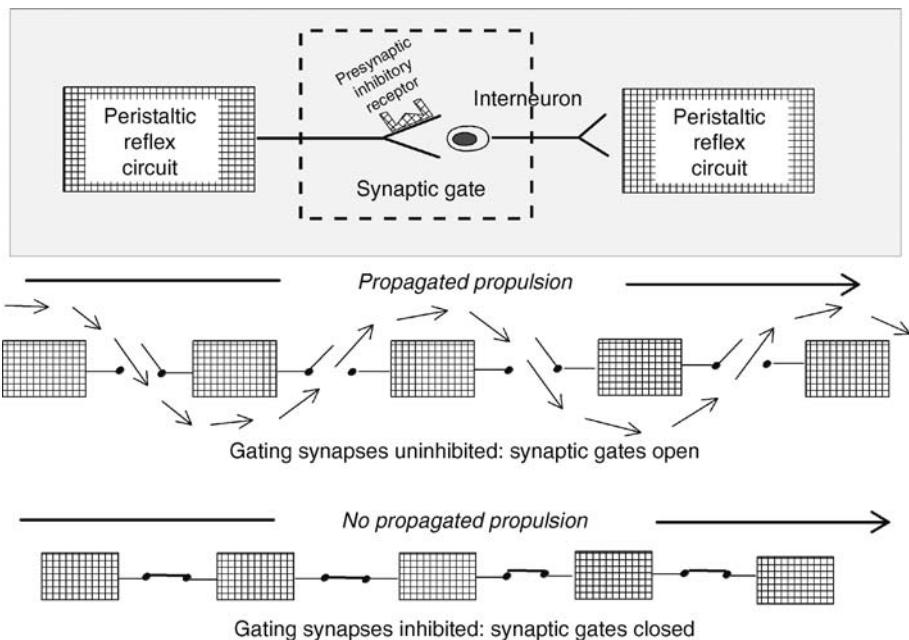
Organization of a receiving segment constitutes one-half of propulsive peristaltic reflex behavior. The second-half is contraction of the circular muscle in the segment behind the advancing intraluminal contents. The longitudinal muscle layer in this segment relaxes at the same time that the circular muscle contracts, resulting in the conversion of this region to a propulsive segment that propels the luminal contents ahead, into the receiving segment. The propulsive segment is formed when neural connections in the reflex circuit inactivate both the excitatory innervation to the longitudinal muscle and the inhibitory innervation to the circular muscle. Omnipresent myogenic pacemakers, which are also called intestinal electrical slow waves, evoke contraction of the circular muscle in the propulsive segment while the inhibitory innervation to the segment is silenced [2,8].

The heuristic model for peristaltic propulsion has blocks of the basic polysynaptic reflex circuit connected “in series” along the length of small intestine and large intestine (Fig. 5). A block of the basic polysynaptic circuit

is formed by synaptic connections between sensory neurons, interneurons, and motor neurons (Fig. 3). Propulsion occurs over extended lengths of intestine, as blocks of the basic circuit are recruited to activity in consecutive segments. In this respect, the intestine is like the spinal cord where connections for polysynaptic reflexes remain irrespective of the destruction of adjacent regions of the spinal cord. Resection of an intestinal segment does not alter the reflex circuitry in the two segments remaining on either side of the resection. Consequently, organized propulsion is not impaired after surgical resection of various lengths of bowel.

Synaptic “gates” connect the blocks of basic circuitry in the heuristic model and contribute to a mechanism for controlling the distance over which the complex of propulsive and receiving segments travels (Fig. 5). When the gates are opened, neural signals pass between successive blocks of the basic circuit resulting in propagation of the peristaltic event over extended distances. Long-distance propulsion is prevented when all gates are closed.

Well understood presynaptic facilitatory and inhibitory mechanisms in the microcircuitry of the ENS [7,9]



Autonomic/Enteric Reflexes. Figure 5 Synaptic gates determine distance of propagation of intestinal propulsive motility. Presynaptic mechanisms gate the transfer of signals between sequentially positioned blocks of peristaltic reflex circuitry. Synapses between the neurons that carry excitatory signals to the next block of circuitry function as gating points for control of the distance over which peristaltic propulsion travels. Messenger substances that act presynaptically to inhibit the release of transmitter at the excitatory synapses close the gates for transfer of information, and thereby determine the distance of propagation. Drugs that facilitate the release of neurotransmitters at the excitatory synapses (e.g. cisapride and 5-HT₄ partial agonists) have therapeutic application by increasing the probability of information transfer at the synaptic gates, thereby enhancing propulsive motility.

are presumed to be involved in gating the transfer of signals between sequentially positioned blocks of reflex circuitry in the heuristic model. Synapses formed by the interneurons that transmit excitatory signals to the next downstream block of circuitry are gating points for controlling the distance over which peristaltic propulsion travels (Fig. 5).

Messenger substances that act presynaptically to inhibit the release of transmitter at the excitatory synapses stop transmission and close the entrance gates to the next downstream block of circuitry, thereby determining the distance of propagation. So-called “prokinetic drugs” that facilitate the release of neurotransmitters at the excitatory synapses (e.g. cisapride and tegaserod) [3,9] have therapeutic application by increasing the probability of information transfer at the synaptic gates, and thereby enhancing propulsive motility.

Peristaltic Retropulsion

The enteric neural circuits can be programmed to control for peristaltic propulsion in either direction along the intestine. For example, if forward passage of the intraluminal contents is impeded in the large intestine of a mouse model for Hirschsprung’s disease, reverse peristalsis propels the bolus over a variable distance away from the obstructed segment. Retroperistalsis then stops, and forward peristalsis propel the bolus again in the direction of the obstruction [1]. During the act of vomiting, reverse peristalsis occurs in the small intestine and rapidly transports the luminal contents toward the open gastro-intestinal junction [5]. In this case, as well as in the obstructed intestine, the coordinated muscle behavior required for effective propulsion is the same except that it is organized by the ENS to travel in the oral direction.

References

1. Brann L, Wood JD (1976) Motility of the large intestine of piebald-lethal mice. *Am J Dig Dis* 21:633–640
2. Tamai T, Prosser CL (1966) Differentiation of slow potentials and spikes in longitudinal muscle of cat intestine. *Am J Physiol* 210:452–458
3. Tonini M, Galligan JJ, North RA (1989) Effects of cisapride on cholinergic neurotransmission and propulsive motility in the guinea pig ileum. *Gastroenterology* 96:1257–1264
4. Travagli RA, Hermann GE, Browning KN, Rogers RC (2003) Musings on the wanderer: what’s new in our understanding of vago-vagal reflexes? III. Activity-dependent plasticity in vago-vagal reflexes controlling the stomach. *Am J Physiol Gastrointest Liver Physiol* 284:G180–G187
5. Weisbrodt NW, Christensen J (1972) Electrical activity of the cat duodenum in fasting and vomiting. *Gastroenterology* 63:1004–1010
6. Wood JD (1981) Intrinsic neural control of intestinal motility. *Annu Rev Physiol* 43:33–51
7. Wood JD (2006) Cellular neurophysiology of enteric neurons. In: Johnson LR, Barrett KE, Ghishan FK, Merchant JL, Said HM, Wood JD (eds) *Physiology of the Gastrointestinal Tract* 4th edn. Elsevier, San Diego, CA pp 629–664
8. Wood JD (2009) Neurogastroenterology and digestive motility. In: Rhoades RA, Bell DR (eds) *Medical Physiology, Principles for Clinical Medicines* 3rd edn. Lippincott, Williams & Wilkins, Baltimore, MD pp 463–496
9. Grundy D, Al-Char ED, Aziz Q, Collins SM, Ke M, Taché E, Wood JD (2006) Fundamentals of neurogastroenterology: basic science. *Gastroenterology* 130:1391–1411
10. Wood JD, Perkins WE (1970) Mechanical interaction between longitudinal and circular axes of the small intestine. *Am J Physiol* 218:762–768

Autonomous System

Definition

In systems theory, the term indicates a dynamical system that does not have an external input, so that next state, or its rate of change, only depends on the actual state. In the context of robotics, the term refers to a robot that behaves without intervention of an external supervisor. These artefacts (also referred to as autonomous robots) are equipped with sensors and actuators. Their actions are determined by the available sensory information and by their internal logic.

► Computer-Neural Hybrids

Autopsychic Neurosis

► Personality Disorder

Auto-regressive Model

Definition

A model of a system as a differential equation where the output at a given time instant is a linear combination of

the outputs at previous time instances and the current input, usually taken to be a white noise input.

► Signals and Systems

Auto-regressive Moving Average Model [ARMA]

Definition

A model of a system as a differential equation, where the output at a given time instant is a linear combination of the outputs at previous time instances and the inputs at previous time instances.

► Signals and Systems

Auto-spectrum

Definition

The estimation of the frequency content of a stochastic signal. While cross-spectrum is the linear relationship between two different variables, expressed in the frequency domain, the auto-spectrum is computed as the cross-spectrum of a signal and itself.

► Signals and Systems

Aversion, Aversive Behavior

Definition

A repugnance for something with a desire of avoidance; Scientifically aversion or aversive behavior means the avoidance of certain stimuli, environments or situations.

Aversive Conditioning

► Aversive Learning

Aversive Learning

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Synonyms

Aversive conditioning

Definition

In aversive learning an aversion is created toward a targeted behavior by pairing it with an unpleasant stimulus, such as a painful electric shock.

Characteristics

Traditional analyses of learning posited two general classes of conditioning (i) classical or Pavlovian conditioning and (ii) operant or instrumental conditioning. In these analyses, the former involved stimulus–stimulus associations, whereas the latter reflected associations between responses and reinforcers. These paradigms were applied to both appetitive and aversive conditioning situations, and involved reinforcement or ►punishment, respectively.

In traditional models of aversive classical conditioning, the paradigm further emphasized that the unconditioned stimulus (US; usually some type of rapid onset pain such as footshock) elicits an unconditioned response, the UR. As associative conditioning develops, a conditioned response (CR) emerges in response to the conditioned stimulus (CS). The CR was regarded as basically the same response as the UR, with conditioning demonstrated by its elicitation by the formerly neutral CS.

Operant or instrumental learning involving aversive stimuli typically used the same types of US as in classical conditioning, but the learning component was evaluated by changes in responses that were either designed by the experimenter (e.g., bar pressing) or that enabled the animal to directly escape from a present US (►active avoidance learning) or to avoid the onset of a signaled US by inhibiting a previously punished response (►passive avoidance learning). In the ►learned helplessness model, animals undergo classic aversive conditioning to a shock US in an inescapable shock box, and are then tested in a two-way shuttle for ►active avoidance [1]. The effect depends on the degree of

controllability over the shock to which the animals are initially exposed.

These paradigms were less involved in analysis of responses to the US itself, except insofar as they might interfere with the operant response required to successfully escape from, avoid, or terminate the US. This interference could be substantial, particularly when elaborate operants such as bar pressing or wheel turning were required. In fact, higher levels of shock as a US often increased the time or trials required to learn an artificial, experimenter-imposed task, even though the higher shock should have produced an enhanced motivation to learn the response.

Although studies of classical and operant conditioning were about equally common several decades ago, with the rise of research on neural, neurochemical, and molecular mechanisms of learning, emphasis shifted from complex operant conditioning tasks (with the important exception of those analyzing behaviors related to addiction, most of which involve appetitive rather than aversive paradigms) to tasks providing simple, fast, and robust measures of conditioning. In terms of aversive learning, the shift has been dramatic, with the number of classical conditioning studies an order of magnitude higher than for operant conditioning, since the beginning of the millennium. This shift was associated with a number of developments in the analysis of aversive conditioning.

Two-factor theories of avoidance conditioning [1] long ago noted that the paradigm for classical conditioning is typically embedded in the operant paradigm: the CS that signals the opportunity to avoid necessarily has some temporal association with the US. In two-factor theory, the CS is regarded as eliciting an internal motivational state such as fear or anxiety that is reduced when the avoidance response was made. The operant behavior, avoidance, is reinforced by reduction of this aversive internal state, not by termination or omission of the US, per se. This formulation was useful in explaining difficulties in extinguishing avoidance learning with US omission.

Nonetheless, aversive conditioning studies were plagued by a number of poorly replicable or hard to explain results, many of which appeared to involve the intrusion of behaviors that did not reflect either the UR (in classical conditioning tasks) or to be related to the required CR in operant tasks. In analyzing these intrusive behaviors, R.C. Bolles coined the term “species-typical defensive responses” or “►SSDRs” [2], later commenting that “I have often regarded defensive behaviors as a great nuisance in the study of learning” [3]. Bolles argued that stimuli associated with danger elicit innate defensive reactions at the expense of any other behaviors, whether extensively reinforced or not. If a prominent SSDR is similar to a designated avoidance response rats quickly learn to perform well in that

situation. For example, animals rapidly learn to jump onto a ledge of the apparatus or run to an adjacent compartment [1]. However, animals perform poorly when there is a conflict between an elicited SSDR and the designated measure; for example when required to shuttle back and forth between two compartments of a shuttle box [1] or to learn an extraneous behavior such as lever pressing.

Freezing

Such SSDRs (more correctly called “species-typical defense reactions” or just “defensive behaviors” as they are highly conserved across mammalian species rather than specific to one group) have been extensively investigated in regards to both unconditioned threat and conditioning situations [3]. The first of these to be analyzed was an immobile “crouching” or “freezing” response following footshock. This behavior was strongly conditioned to the context in which shock occurred, sometimes after a single shock [4]. It was also elicited by exposure to nonpainful aversive stimuli such as noncontact encounters with predators or even partial predator stimulus such as odors [5]. Several features of this conditioning presented problems. Because the CR is quite different than the response to shock – generally limb twitching, running or jumping, depending on intensity – it is difficult to conceptualize freezing as a classical conditioned response, in terms of the classic model [6]. Similarly, a single aversive experience provides little scope for operant conditioning: The response to the shock is the only behavior that is consistently emitted just prior to shock termination, and thus positioned to be reinforced by termination of the aversive stimulus. As immobility, rather than the twitch/run/jump response, is the major behavior seen on replacement of animals into the shock situation, it is very difficult to view this as a conditioned operant response.

However, such immobility (for which the term “freezing” is most often employed) is so rapidly and robustly conditioned to contextual cues as to be virtually ubiquitous in a threat context, making it a particularly important modulator of other behaviors that might be used as measures in these tasks: The obvious solution has been to use freezing itself, rather than behaviors disrupted or facilitated by freezing, to evaluate classical aversive, or fear, conditioning. It has come to be one of the most common measures in aversive learning studies in a neuroscience context, with strong representation of both ►contextual fear conditioning ([7] for review) and cue conditioning, e.g., auditory fear conditioning ([8] for review).

The Startle Response

The other most common measure of classical aversive conditioning in a neurosciences context is the startle response. Startle is the response to a highly salient,

rapid-onset stimulus such as a loud noise or an air puff. In wild rats, which are generally more defensive than lab rats, rapid movement of a potential predator can elicit robust startle jumps. The intensity of the startle response can be enhanced by stimuli associated with shock or by a number of unconditioned factors that are aversive or associated with threat. Fear potentiated startle, in which a cue associated with shock potentiates startle to an auditory stimulus, has a long history in psychology [9]. Recent work with unconditioned potentiation of the startle response, for example by light or isolation has provided information on brain systems involved in such potentiation, enabling comparisons with those underlying fear potentiated startle and pointing out a number of differences between the two [9].

Analyses of the Biology of These Models

The neuroanatomical, chemical and molecular mechanisms involved in these classical conditioning models have been extensively investigated. There is a general consensus that aversive cue conditioning is mediated by information about the CS and US from sensory inputs that generally include the thalamus and sometimes sensory cortices as well [8] to the lateral and basolateral nuclei of the amygdala, with output projections from the central amygdala to behavioral, autonomic, and endocrine response control systems located in the midbrain and brainstem regions [8]. Many of these same sites are involved in ►context conditioning, but the hippocampus is conceptualized as playing a particularly important role when contextual memories are an important component of a learning paradigm [7]. The amygdala also appears to be involved in operant conditioning situations, but this involvement is seen as more variable and less essential than that of the amygdala in classical aversive conditioning.

Conditioning of Other Defensive Behaviors

Although freezing and startle are the most often utilized behaviors in classical aversive conditioning, a number of other defensive behaviors elicited by threat stimuli have been analyzed [3], and are coming to be used more extensively in classical conditioning situations. A single confrontation with a cat, or with the odor of a cat, is sufficient to produce conditioning to the exposure context or to specific cues associated with cat odor [10]. While freezing is often the focal measure in these studies, risk assessment, including orientation to the threat stimulus, and approach and investigation of it, is a particularly common defensive behavior to ambiguous or partial stimuli such as cat odor, and may be seen as a conditioned response to cues associated with threat.

A number of studies have mapped brain sites showing fos activation to cat-related stimuli [5]. Effects of lesions in many of these sites on unconditioned and

conditioned responses to cat or cat odor, and to foot-shock, suggest important differences in the brain systems serving shock-based versus predator-based unconditioned responses as well as conditioning to the two types of threat stimuli.

With regard to conditioning of defensive behaviors to partial predator stimuli, a current controversy may shed light on some possible evolutionary mechanisms involved in aversive conditioning. The odor of cat fur and skin supports one trial conditioning of responses such as freezing and risk assessment, whereas a number of additional predator-associated odors such as trimethylthiazoline (TMT), a component of fox feces, do not. However, given a number of trials, TMT does produce a conditioned aversive response in a two chamber “place preference” apparatus that enables avoidance of the situation where the odor was encountered. These data suggest two possibilities; First that TMT is effective in operant rather than classical conditioning tasks, or, second, that there is an important difference between conditioning based on aversive stimuli such as unpleasant odors, and those involving cues of potential danger, such as pain, confrontation with a predator, or the (rapidly dissipating and thus highly associated with cat presence) odor of cat fur/skin. According to the later view, rapid, i.e., 1-trial, learning of danger stimuli is particularly adaptive, whereas stimuli that are unpleasant or disgusting, but not dangerous can be conditioned in a more leisurely fashion. As responses to danger, rather than aversion of unpleasant stimuli, seem more likely to be involved in human emotional psychopathologies, this distinction may be an important one for understanding the role of aversive learning in emotional disorders.

Aversive Conditioning and Human Emotional Psychopathology

The potential relationship between aversive conditioning and human psychopathology has served as the spur for a number of particular approaches to aversive learning. One such approach studies neurochemical and molecular processes that control the inhibition of fear signaled by previously conditioned stimuli (otherwise known as “fear extinction”). The fear extinction procedure involves reexposure to a CS in the absence of the aversive US, thereby successive extinction trials cause a decline in fearful reactions. Fear extinction is cue specific in that it shows negligible generalization across different sensory modalities. Extinction is not permanent, as shown in studies of reinstatement, renewal, and spontaneous recovery. Similar to fear acquisition processes, extinction has been shown to be dependant on NMDA receptors within the basolateral amygdala [9]. Extinction of aversive memories is of obvious relevance to disorders such as post traumatic stress disorder, that involve intrusive and debilitating

memories of trauma [9]. Extinction is procedurally comparable to several types of exposure-based psychotherapeutic treatments. Similar to fear extinction training, exposure therapy includes exposure to the feared cue or context in the absence of danger, with simultaneous psychotherapy aimed to reduce anxiety levels.

However, another traditional use of aversive conditioning tasks, to evaluate anxiety-like behaviors for preclinical psychopharmacology research, has (comparatively) declined in recent years, giving way to measures based on unconditioned responses in tasks such as the elevated plus maze (EPM) and the Open Field (OF). The exceptions are those tasks described above: Fear conditioning (to context or cue) or potentiated startle, which have increased in use over time; albeit not so rapidly as have the EPM and OF. In contrast, tests of anxiety-like behaviors evaluating punishment effects in operant tasks have all but dropped out of the anxiety researchers' armamentarium. While the need for "high throughput" tasks undoubtedly constitutes one reason for this change in use of classical versus operant conditioning models, it also reflects a view that the learning components of human emotional psychopathology more robustly reflect the former than the latter. However, a variety of aversive conditioning techniques and situations are currently being used in an attempt to identify brain areas and events associated with emotion-linked processes in people, and it is predictable that these processes will prove to involve both classical and operant conditioning, as well as individual differences in unconditioned responsivity to evolutionarily significant danger stimuli and cues.

References

1. Mackintosh NJ (1983) Conditioning and associative learning. Clarendon, Oxford
2. Bolles RC (1989) Acquired behaviors; aversive learning. In: Blanchard RJ et al. (eds) Ethoexperimental approaches to the study of behavior. Kluver Academic, Boston, pp 167–179
3. Blanchard DC (1997) Stimulus, environmental and pharmacological control of defensive behaviors. In: Bouton M, Fanselow MS (eds) Learning, motivation and cognition. The functional behaviorism of Robert C. Bolles. American Psychological Association, Washington DC, pp 283–305
4. Blanchard RJ, Blanchard DC (1969) Crouching as an index of fear. *J Comp Physiol Psychol* 67(3):370–375
5. Dielenberg RA, Hunt GE, McGregor IS (2001) "When a rat smells a cat": the distribution of Fos immunoreactivity in rat brain following exposure to a predatory odor. *Neuroscience* 104(4):1085–1097
6. Fanselow MS (1997) Species-specific defense reactions: retrospect and prospect. In: Bouton M, Fanselow MS (eds) Learning, motivation and cognition. The functional behaviorism of Robert C. Bolles. American Psychological Association, Washington DC
7. Anagnostaras SG, Gale GD, Fanselow MS (2001) Hippocampus and contextual fear conditioning: recent controversies and advances. *Hippocampus* 11(1):8–17
8. LeDoux JE (2000) Emotion circuits in the brain. *Annu Rev Neurosci* 23:155–184
9. Davis M (2006) Neural systems involved in fear and anxiety measured with fear-potentiated startle. *Am Psychol* 61(8):741–756
10. Blanchard RJ et al. (2001) Cue and context conditioning of defensive behaviors to cat odor stimuli. *Neurosci Biobehav Rev* 25(7–8):587–595

Aversive Stimulus

Definition

An aversive stimulus is a signal or a cue that is repellent and leads the receiver away from the source of stimulation. The same stimulus can be attractive or aversive depending on physical features such as its intensity (for instance, concentration of an odor) or the behavioral context in which it is perceived.

- Attractive Stimulus
- Odor Coding

Aversive Taste Memory

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Synonyms

Aversive taste memory; Bait shyness; Garcia's effect; Learned taste aversion; Learned toxiphobia; Taste aversion learning

Definition

Conditioned taste aversion (CTA) is a robust type of learning relevant for predicting negative visceral consequences of oral intake. It relies on selective associations between taste and visceral cues. The association between a taste cue and a delayed visceral malaise can be readily formed in one trial. As a consequence the taste becomes disliked and it will be avoided in later presentations. This behavioral defensive mechanism, which favors survival by avoiding repeated poisoning, can be traced through the

phylogeny from invertebrates to humans and along the ontogenetic development from prenatal life to aging. Research on this type of learning has played a major role not only for modern learning theories but also for investigating the neurobiological basis of learning. It may also contribute to understand the learning mechanisms involved in human food selection, drug addiction, and cancer anorexia [1].

Characteristics

CTA is widely considered as a form of classical conditioning since an associative link is formed between taste (conditioned stimulus) and visceral (unconditioned stimulus) cues. The learned response consists in a shift of the ►taste hedonic value, thus becoming unpalatable and being avoided in later encounters. Shifts of the taste hedonic value can be assessed in rats using the ►taste reactivity test. However, the acquisition of CTAs exhibits several peculiar features that can not be found together in other classical conditioning preparations [2]. First, CTA can readily be acquired in a single conditioning trial. Second, robust taste aversions are induced in spite of long delays, lasting conventionally 15–30 min, between the taste presentation and the outcome of visceral malaise. Moreover, the delay may be extended to several hours if visceral distress takes place under an unconscious state. Learning in unconscious states is also a fact not found in other types of classical conditioning. Third, the peculiar features of CTA rely on selective association between chemical sensory modalities. Robust one-trial and long-delay learning takes place only if gustatory cues, but not somatosensory, auditory, or visual cues, are followed by visceral malaise. However, similar aversions to olfactory cues may be formed provided that a flavor (odor and taste) was previously conditioned, a phenomenon termed ►taste-potentiated odor aversion [2]. The potential relationship between other food attributes such as color, texture, or temperature and CTA is not fully understood.

The adaptive role of CTA resides on its value for survival, since it is an efficient behavioral defensive mechanism to avoid repeated poisoning. Accordingly, it is extensively found from invertebrates to humans. Although it shows specializations throughout the phylogeny, such as resting on visual cues instead of taste cues in birds, it always enables to establish predictive associations among the sensory modality that identifies edibles and the aversive consequences of ingestion. Furthermore, CTA is one of the earliest types of learning demonstrated along the ontogenetic development. Even if it may not show all the characteristics of adult learning, prenatal chemosensory learning has been demonstrated from insects to mammals, including amphibians, fish, and birds. Prenatal CTA in mammals depends on the composition of the amniotic fluid that the foetus swallows. While the potential protective role in utero of prenatal learned aversions requires further

research, these aversions can be retained after birth and they can be expressed during the postnatal life. Thereafter, the early development of the chemical senses allows mammals to learn in advance about the chemical environment to be encountered after birth, thus favoring survival. Moreover, CTA seems to be very resistant to aging. Far from being impaired, the acquisition of learned taste aversions is even enhanced in old rats as longer delays can be introduced between the taste cue and visceral malaise. This CTA facilitation by aging, which can not be attributed to an enhanced gustatory or visceral sensitivity, may represent an advantage for survival since to recover from poisoning may represent a stronger challenge during aging because physical deterioration [1].

Related Phenomena

The acquisition of learned taste aversions is influenced by several phenomena, which depend on the way that taste cues are presented and on the previous experience with the conditioned taste [3]. Taste novelty is a potent modulator of CTA. A novel taste induces an unconditioned neophobic response, leading to a reduced intake. Subsequent taste presentations lead to habituation of the neophobic response as the taste becomes familiar. Thus, ►taste neophobia may be evident either by a reduced intake compared with the baseline intake or by a reduced intake during the first presentation compared with a later presentation. In fact, the habituation of neophobia (►Habituation of taste neophobia) may take place in the absence of a reduced intake during the first presentation as it is the case of highly palatable tastes. Taste neophobia facilitates CTA. Robust learned aversions are developed to novel tastes. On the contrary, the repeated exposure to the taste without consequences before the conditioning session retards CTA acquisition, a phenomenon called latent inhibition. However, under other training circumstances taste preexposure may facilitate learning. When using complex compound tastes or discrimination tasks, the preexposure to the taste may reduce generalization and facilitate learning, as perceptual learning takes place.

The novelty of the visceral malaise experience is also an important modulator of CTA acquisition. CTA acquisition is retarded if the visceral malaise has been experienced before conditioning, a phenomenon called the effect of the US preexposure. Moreover, random preexposures of both taste and visceral malaise induce a greater impairment of later conditioning than preexposing either taste or visceral malaise separately. This phenomenon is called learned irrelevance. In addition to the preexposure effects mentioned, CTA shows a variety of complex learning phenomena, similar to those appearing in other learning tasks [3]. A schematic account of the behavioral procedures used to study complex learning phenomena is presented in Table 1.

Aversive Taste Memory. Table 1 Schematic account of the conditioned taste aversion procedures showing complex learning effects

	Phase I	Phase II	Test	Outcome
First-order CTA		A+	A	Aversion
Preexposure effects				
Attenuation of neophobia		A	A	Increased intake
Latent inhibition	A	A+	A	Reduced aversion
Effect of the US exposure	+	A+	A	Reduced aversion
Learned irrelevance	A/+	A+	A	Reduced aversion
Perceptual learning	A, B	A+, B	A, B	Increased discrimination
Cue-competition tasks				
Blocking	A+	AB+	B	Reduced aversion
Overshadowing		Ax+	X	Reduced aversion
Simultaneous compound tasks				
Negative patterning	A+, B+	AB	A, B, AB	A,B aversion AB no aversion
Positive patterning	A, B	AB+	A, B, AB	A,B no aversion AB aversion
Serial compound tasks				
Occasion setting	A...B+	B	B	Aversion only if A present
Sensory preconditioning	A...B	B+	A	Aversion
Second-order conditioning	B+	A...B	A	Aversion
Effects of context				
Context dependency of LI	A(Y)	A(X)+	A(X)	Increased aversion
Context dependency of CTA		A(X)+	A(Y)	Reduced aversion

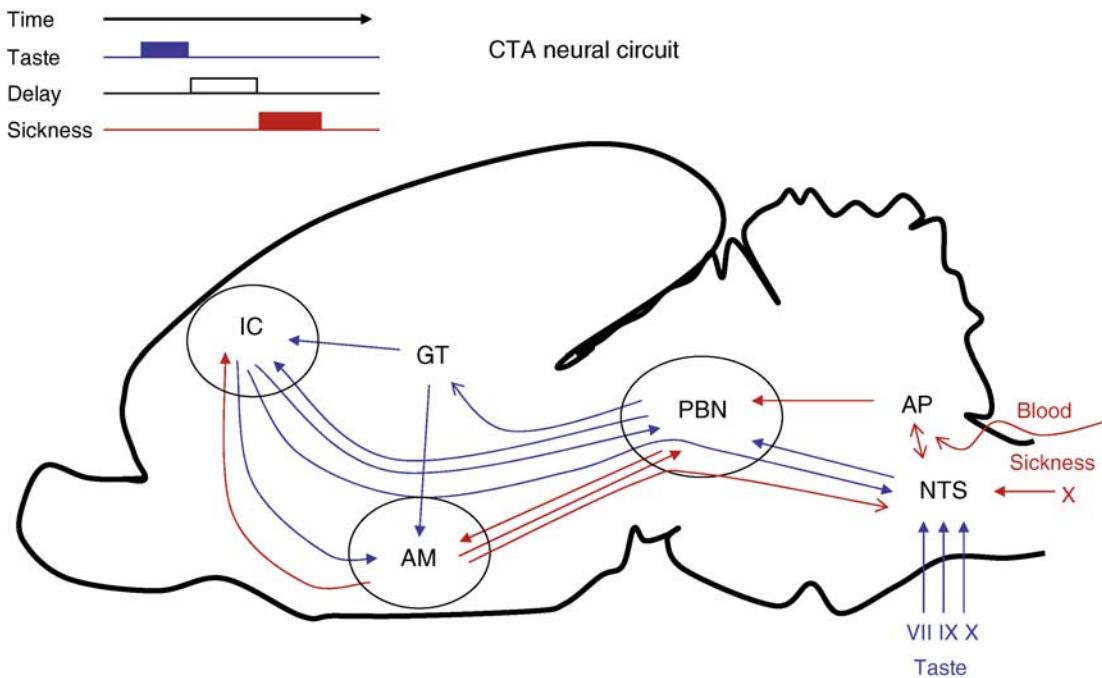
Most of them require two behavioral phases before testing. Note that control groups are not included. A and B represent tastes, (X) and (Y) indicate contexts and + means the aversive agent, such as LiCl. A/B refers to unrelated stimuli; AB refers to compound; “,” separates different trials and “...” indicates that the first taste precedes the second in the same conditioning trial.

Neural Circuit

In spite of being considered a primitive form of learning, the acquisition of CTA depends on a widely distributed neural circuit that engages multiple taste–visceral integration brain regions located at different levels from the brainstem to the forebrain [2,4–6]. Fig. 1 shows the rodent basic neural circuit involved in CTA acquisition.

On the one hand, facial, glossopharyngeal and vagus nerves convey taste afferents to the ►nucleus of the tractus solitarius (NTS), which in turn projects to the ►parabrachial area (PBN) in rodents and to the gustatory nucleus of thalamus directly in monkeys. Taste information reaches the gustatory area in the insular cortex (IC) either through thalamic or direct PBN projections. On the other hand, visceral information conveyed by the vagus nerve and the ►area postrema (AP) project to these brain regions in parallel with the gustatory projections and also reaches the amygdala (AM). Thus, the gustatory and visceral afferent pathways converge in the same brainstem areas from the first relay nucleus in the brainstem. Electrophysiological and immunohistochemical studies have

shown that CTA modifies the neural response to the conditioned taste in brainstem areas, such as the nucleus of the solitary tract and the parabrachial area. CTA induces a shift in the response of gustatory neurons processing the hedonic value but not the quality of the taste. Additional data provided by permanent and reversible lesion studies in rodents have pointed out to the PBN, second relay station both for taste and visceral sensory pathways, as a crucial site for the taste–visceral integration involved in CTA acquisition [7]. The proposal of a brainstem integration site relevant for CTA acquisition is consistent with the primitive nature of this type of learning. However, the acquisition of CTA requires also the taste and visceral information to reach forebrain areas, because chronic decerebrate rats do not show CTA. The location of the forebrain integration site or sites remains elusive, although both IC and AM seem to play relevant roles related with higher taste and visceral processing and integration [2,4,5,8]. It has been proposed that interactions among multiple brain regions may be required for CTA acquisition. A critical role of the gustatory insular cortex in long-term maintenance of CTA memories in



Aversive Taste Memory. Figure 1 Schematic drawing of the known rodent brain regions involved in conditioned taste aversion acquisition. AM, amygdala (central and basolateral nuclei); AP, area postrema; GT, gustatory thalamus (parvocellular part of the ventralis posteromedial thalamic nucleus); IC, insular cortex; NTS, nucleus of the tractus solitarius; PBN, parabrachial nuclei; VII, facial nerve; IX, glossopharyngeal nerve; X, vagus nerve.

rodents has been proposed [11]. The contribution of other brain regions associated with memory and central feeding control systems, such as the bed nucleus of stria terminalis, hypothalamus, the accumbens nucleus, the ventral tegmental area and prefrontal cortex to the acquisition, retention, and expression of CTA is not fully understood. As in other types of learning tasks, the hippocampal system may modulate CTA acquisition when complex learning phenomena are involved.

Predictivity

The high reliability, robustness, and easiness to obtain CTA in the laboratory using a variety of strain and species, in addition to the fact that it allows to study a wide range of learning phenomena, have made CTA a sensitive tool for the behavioral and neurobiological study of learning. In addition, CTA has proven to be a useful tool for the determination of taste psychophysics and characterization of drug toxicity. However, the results strongly depend on the behavioral procedure applied.

CTA was first studied in the laboratory by John Garcia and coworkers. Since their pioneering study published in 1955 [9], the rat has become the choice animal model in CTA research. Taste solutions are typically used to induce CTA in the laboratory, because they are easily handled and they allow a precise assessment of the amount

ingested. The procedure requires subjecting the animals to a water deprivation procedure. The standard behavioral procedure usually applies palatable taste solutions that will be avoided as a consequence of learning. After stabilizing the water consumption during the daily drinking sessions along several days, during the conditioning trial a novel taste solution is presented either for spontaneous drinking or intra oral administration. Several agents, such as radiation, body rotation, and a variety of drugs, being lithium chloride (LiCl) the most widely used, may induce CTA. All of them have in common the induction of behavioral and autonomic indexes of gastrointestinal illness, including emetic responses and also vomiting in those species with emetic ability. Testing consists either in a one-bottle session, with only the conditioned taste solution available or in a choice test in which the animals can choose between the conditioned taste solution and other (two-bottle test) or others (multiple-bottle test) nonconditioned taste solutions. One-bottle tests allow within-subjects comparison between the amount of taste solution drunk during the conditioning and testing sessions, and also between-groups comparisons with nonconditioned groups receiving a sham saline injection. The results of the choice tests are usually shown as a preference rate, which can be compared with that of the control nonconditioned groups. Choice tests are very sensitive for detecting weak

aversions, but they may not differentiate between groups showing different strength aversions. On the contrary, when using one-bottle tests weak aversions may be unnoticed, since the thirsty animal has no other choice to drink, but they are very sensitive for distinguishing among different strength aversions.

In addition, taste reactivity tests for recording orofacial and somatic responses may be required to assess the change of the hedonic response induced by CTA. CTA acquisition induces a change of the taste reactivity behavioral pattern from appetitive to aversive. Besides fluid rejection, the aversive pattern of responses to the conditioned taste include gaping, chin rubbing, forelimb flailing, increased locomotion, and aversive posturing.

Thereafter, when using basic CTA procedures, critical issues should be considered, such as unlearned palatability and novelty of the taste solution applied, form of taste solution presentation (spontaneous drinking versus intra oral administration) and testing protocol. If complex CTA learning procedures are applied, careful behavioral control groups for identifying potential alternative phenomena explaining the outcome should be designed.

Relevance to Humans

Learned aversions play an important role in the human everyday life food selection. It reduces not only the repeated intake of potentially noxious substances but it also may lead to the avoidance of nutritious foods [4]. Understanding the mechanisms of CTA is crucial for studying and treating daily likes and dislikes, which contribute to diet-induced diseases. However, this issue remains relatively unexplored due to the difficulty of assessing food aversions by conscious verbal reports, a commonly used procedure [4,10]. Studies applying taste reactivity tests in humans may help to understand and modify naturally occurring learned food aversions, such as those involved in the rejection of certain foods by children and the elderly.

CTAs have also important clinical applications related with cancer anorexia and drug abuse. Besides food aversions induced by certain kinds of cancer associated with abdominal discomfort, nausea, and vomiting, controlled clinical studies have indicated that learned food aversions develop in patients receiving chemotherapy and radiation, being gastrointestinal toxicity and nausea the inducing agents. Of interest for the later situation, a behavioral intervention method to reduce the likelihood of forming aversions to the familiar foods consists in providing a novel tasting food before the treatment. The novel taste has proven to act as a scapegoat and to prevent the decrease in familiar food consumption and preference, both in children and adults. A similar treatment using a novel flavor may be also applied to prevent or reduce the anticipatory nausea

described in cancer patients associated to the chemotherapy context [4].

Since the 1930s, chemical aversion induction by paired ethanol ingestion with emetically induced nausea was applied as a component of multimodal treatments for certain alcoholic populations [10]. At present, CTA have clinical applications to the aetiology and control of alcohol use and abuse, the receptor characterization of the motivational effects of drugs, the occurrence of drug interactions, and the characterization of drug withdrawal [1].

References

1. Riley AL, Freeman K (2007) Conditioned taste aversion: an annotated bibliography. Available at <http://www.ctalearning.com>
2. Bures J, Bermudez-Rattoni F, Yamamoto T (1998) Conditioned taste aversion: memory of a special kind. Oxford University Press
3. Gallo M, Ballesteros MA, Molero A, Moron I (1999) Taste aversion learning as a tool for the study of hippocampal and non-hippocampal brain memory circuits regulating diet selection. *Nutr Neurosci* 2:277–302
4. Bernstein IL (1999) Taste aversion learning: a contemporary perspective. *Nutrition* 15:229–234
5. Bermudez-Rattoni F (2004) Molecular mechanisms of taste-recognition memory. *Nat Rev Neurosci* 5:209–217
6. Yamamoto T, Shimura T, Sako N, Yashoshima Y, Sakai N (1994) Neural substrates for conditioned taste aversion in the rat. *Brain Res* 65:123–137
7. Reilly S (1999) The parabrachial nucleus and conditioned taste aversion. *Brain Res Bull* 48:239–254
8. Reilly S, Bornovalova MA (2005) Conditioned taste aversion and amygdala lesions in the rat: a critical review. *Neurosci Biobehav Rev* 29(7):1067–1088
9. Garcia J, Kimeldorf DJ, Koelling RA (1955) Conditioned aversion to saccharin resulting from exposure to gamma radiation. *Science* 122:157–158
10. Scalera G (2002) Effects of conditioned food aversions on nutritional behavior in humans. *Nutr Neurosci* 5:159–88
11. Shema R, Sacktor TC, Dubai Y (2007) Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKMzeta. *Science* 317(5840):951–953

Avian Auditory System

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Synonyms

Auditory System of Birds; Hearing in Birds

Definition

The avian auditory system is composed of multiple brain regions whose principal function is to process acoustical signals and to mediate sound source detection, localization and recognition.

Characteristics

Quantitative Description

The avian auditory system begins at the bird's ears and ends in what is referred to as higher or secondary auditory areas in the forebrain. These two end points are connected by a series of auditory processing stages that follow a gross anatomical plan very similar to the mammalian auditory system (see higher level structures). Birds rely heavily on the auditory sense (see function) and therefore have a well developed auditory system. Among the large number of avian species (~9,000), some auditory specialists have emerged. Barn owls hunt in total darkness and excel at localizing the sounds made by their prey. Songbirds use complex acoustic signals, including song and other calls, for social communication and use auditory feedback of their own vocalizations to guide vocal learning. In contrast with the mammalian system, the auditory hair cells, the sensory epithelium of the hearing system, in the bird's inner ear can regenerate after damage. For all the above reasons, the avian auditory system has become a powerful model system to study the neural basis of sound localization, as well as to investigate how the brain memorizes and processes vocalizations in order to mediate behavioral discrimination and recognition. The avian model has also been used to study neural plasticity in the auditory system and its potential in treating deafness.

Higher-Level Structures

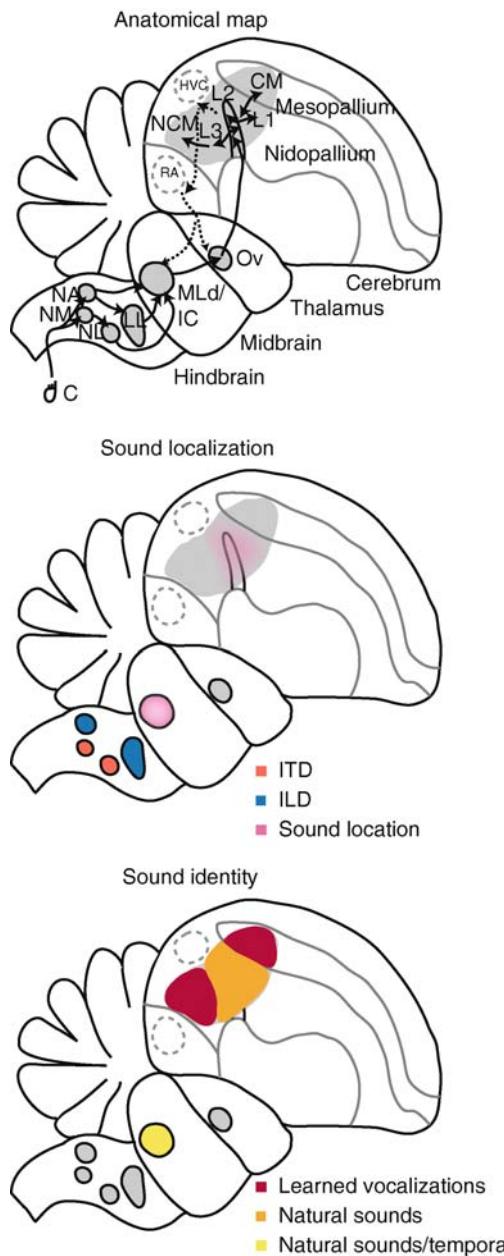
The auditory system of vertebrates is an evolutionarily conserved structure. Therefore the avian system shares gross features across all avian groups and resembles other vertebrates, including mammals ([► The Evolution of the Avian Auditory System](#)). The most noticeable similarity rests in the number of auditory nuclei (or neural processing stages) and the pattern of feed-forward connections from the cochlear nucleus to the auditory forebrain. As shown in [Fig. 1](#), afferents from the hair cells in the ear project to two cochlear nuclei in the medulla, called nucleus magnocellularis (NM) and nucleus angularis (NA), which are analogous to the anterior ventral and dorsal subdivisions, respectively, of the mammalian cochlear nucleus. As in mammals, the connections between the cochlear nuclei and the auditory midbrain have both a direct and an indirect route. In birds, the indirect route is via the nucleus laminaris (NL) and the nuclei in the lateral lemniscus. These pathways converge in the midbrain, in the dorsal

lateral nucleus of the mesencephalon (MLd), which is analogous to the inferior colliculus (IC) in mammals [[1](#)]. Both MLd and IC are used in the avian literature. The auditory midbrain projects to a relay nucleus in the thalamus, Ovoidalis (Ov), just as the IC projects to the medial geniculate body (MGB) in mammals. Ov, in turn, sends projections to the primary auditory area in the pallium, field L. Field L has been further divided into subregions (L1, L2a, L2b/L, and L3) based on differences in cyto-architecture and connectivity [[2,3](#)]. Input from the auditory thalamus goes to subregions L2a and L2b, which in turn project to L1 and L3. Subregions L1 and L3 make bi-directional connections with two secondary auditory areas in the pallium: the nidopallium caudal medial (NCM) and the caudal mesopallium (CM).

Noticeable differences between the mammalian and the avian auditory system are observed in the feedback and inter-hemispheric connectivity patterns. In mammals, the primary auditory cortex shows strong feedback projections to the thalamus and more limited ones to the midbrain ([► Mammalian Auditory Cortex](#)). In birds this feedback circuitry exists, but it involves two additional processing stages in the forebrain, in the shell regions of song system structures HVC and the robust nucleus of the arcopallium (RA). Feedback circuitry in songbirds, is illustrated in the figure, and it lies in similar anatomical locations in non-songbirds. The direct inter-hemispheric connectivity between primary auditory cortex present in mammals is absent in birds.

Lower-Level Components

The micro-circuitry of the lower auditory nuclei is relatively well known, particularly those involved in sound localization ([► sound localization](#)). In the medulla, excitatory neurons from NM converge bilaterally in NL providing temporal information for detecting interaural time differences ([► ITD](#)), whereas GABAergic neurons originating in the superior Olive provide a mechanism for gain control. Further morphological adaptations are observed on this pathway to enhance or to preserve temporal information. In the pathway involved in the computation of interaural level differences ([► ILD](#)), neurons in the lateral lemniscus receive excitatory input from the contralateral NA, and inhibitory input from the contralateral lateral lemniscus. At the next level of auditory processing, in MLd/IC, ILD and ITD information is combined by multiplication. This multiplication is performed by the local network and cellular mechanisms. The local network combines focused excitatory input from the concurrence of desired ILD and ITD responses with more diffuse inhibitory input from non-desired ILD and ITDs. The cellular properties provide a non-linear thresholding operation. This structure leads to neurons that are tuned for particular ILD and ITDs and correspondingly to a single location of a sound source [[1](#)].



Avian Auditory System. Figure 1 Anatomical and functional cartoons of the avian auditory system shown in saggital section. *Top row: Anatomical map.* The figure shows the auditory nuclei and regions in gray as well as two of the song system nuclei that would be found in songbirds (HVC and RA). The feed-forward pathways are shown in solid and the feedback pathway is shown with a dotted line. Note that not all the pathways are shown: for example, the reciprocal pathway between NCM and CM has been omitted for clarity. The diagram is also only approximately anatomically correct: NCM would be found in a more medial region than the one drawn here. See text for the name of the areas. *Middle row: functional map for sound localization.* The figure shows the auditory areas specialized for extracting

The micro-circuitry of the higher auditory areas, the morphology of neuron types and their cellular properties have not been examined in detail. Golgi stains suggest the presence of at least four types of neurons in the auditory forebrain [4]. The auditory telencephalon is also densely packed with inhibitory ►GABAergic neurons, most of which are very small and presumed to be ►interneurons.

Structural Regulation

The development of the auditory system occurs either in the egg or soon after hatching. As in other sensory systems, both maturational and experience-dependant factors affect the neural structure. This interaction has been studied best in the sound localization system of the barn owl [5].

Higher Level Process

As described above, a significant fraction of neural computations underlying sound localization are performed in the auditory medulla and midbrain, leading in the MLd/IC to an anatomically mapped representation of space based on sound source location. The relative contribution of these two areas for auditory scene analysis is currently being investigated [1].

The avian auditory system has also been used extensively to examine how complex acoustical communication signals – bird song and social calls – are processed by the nervous system for detection, recognition and memorization. Neurophysiologists have recorded responses to vocalizations and other complex sounds throughout most of the auditory system and have found a hierarchical processing that leads to specialized

interaural time differences (ITD), interaural level differences (ILD) and the brain regions where neurons coding sound source location are found. The sound source location neurons in MLd/IC are found in the shell of the nucleus and make a topographical map of space. The sound source location neurons in the forebrain are found diffusively and are not organized in a mapped fashion. *Bottom row: functional map for sound identity.* The figure illustrates the hierarchical processing of complex sounds. MLd/IC is tuned for low-level statistics of natural sounds and its population response efficiently represents the temporal changes in the amplitude envelope of the sound. The primary auditory forebrain also efficiently represents sounds with natural statistics and, in addition, its neurons code complex temporal and temporal acoustical features. The secondary areas are sensitive to higher order acoustic features found in vocalizations. The neural response in these areas is also affected by the sounds that the animal learned and remembered. In both functional maps, the areas in gray indicate that the function of these nuclei has not been well characterized.

selectivity for complex natural sounds, and ►conspecific vocalizations in particular [6].

Auditory neurons in MLD respond robustly to pure tones, complex tones, and songs, but show higher information rates for stimuli that contain the spectrotemporal features of natural sounds. The population neural response is able to track the temporal changes found in birdsong very accurately.

Neurons in the primary auditory forebrain area, field L, show an additional degree of selectivity in the sense that many of them respond poorly to simple synthetic sounds. Selectivity for conspecific sounds is present in field L but restricted to selection for the relatively low-level statistics of the spectrotemporal acoustical structure found in vocalizations and in other natural sounds. Neurons in MLD and field L can also be classified according to their joint spectrotemporal tuning. This classification shows specialization for detecting distinct acoustical features. Different groups of neurons specialize for detecting fast temporal changes in the sound envelope, the entire sound envelope, slow precise harmonic features or a coarse spectral shape. The efficient representation of these distinct acoustical features might underlie basic acoustical percepts such as rhythm, pitch, and timbre and constitute the building blocks for more selective representations in the secondary auditory regions [7].

Neurophysiological recordings with complex stimuli showed a higher number of selective units in CM than field L. Neurons in CM were also more sensitive than field L neurons to the natural phase of the temporal and spectral modulations found in song. Lesion experiments further support the role in CM for song discrimination.

Experiments using the degree of expression of the immediate early gene (►IEG), *zenk*, in NCM show selectivity for conspecific song as opposed to ►heterospecific song, and show a lack of response to tone bursts. Neurophysiological studies in NCM also suggest selectivity for complex sounds, which might be absent in subarea L2a of field L. The degree of selectivity for vocalizations in the two secondary auditory areas NCM and CM, and their respective roles in processing and memorizing song in songbirds, is an active area of research.

Songbirds have evolved another specialized set of interconnected brain areas known as the song system, whose function is to produce, and to learn motor control of, ►song. The song system receives input from the auditory system from potentially multiple pathways, the most established one being via auditory area CM. The song system must receive information about what to sing (the tutor's song), about what the bird is actually singing (the bird's own song), and from acoustical signals that trigger singing (e.g., songs of other conspecific males and female calls). The pathway between the avian auditory system and the song system, and

the nature of the acoustical information entering the song system, are other active areas of research.

Lower Level Process

The cellular physiology of the auditory system has been investigated most in the lower-level auditory areas, as described above. There is a lack of neurophysiological research at the cellular level in the higher levels of the auditory system. On the other hand, studies using histochemical techniques in the auditory telencephalon of songbirds have assessed the expression of receptors for particular neurotransmitters and neuromodulators, as well as ►sexual hormones. More recently, gene-array technology in combination with *in situ* hybridization has been used to make maps of gene expression in the auditory system [8].

Process Regulation

Short-term and long-term plasticity have been well studied in the responses of neurons tuned to the spatial location of sound, in the external nucleus of the IC/MLD. These neurons change their tuning if there is a mismatch between the location specified by the auditory information and that obtained from visual feedback information. The plasticity is observed both in young barn owls and to a lesser extent in adult owls. In adults, greater neural plasticity is observed for owls that have had experience with mismatched feedback as juveniles [5].

Short-term plasticity has also been measured in adult birds during the processing of complex sounds, in the tuning of neurons in the secondary auditory forebrain areas NCM and CM.

NCM exhibits stimulus specific adaptation (SSA). SSA manifests itself as a reduced neural response to repeated stimulation. However, unlike the ubiquitous neural adaptation which is a function of the output of the neuron, SSA is specific to the input of the neuron in the sense that the presentation of a novel (or unfamiliar) stimulus during SSA yields a normal response. SSA can last days and can therefore be considered a form of memory. SSA has been measured in NCM using both IEG studies and neurophysiological recordings. Recent neurophysiological experiments showed that the tutor song memorized by a young bird will later elicit an adapted response in the adult bird, even if that tutor song was not heard for an extended period of time. IEG and behavioral studies involving lesions similarly point to NCM as a potential auditory region where a memory trace for the tutor song resides [9].

Shorter-term plasticity has been measured in neurophysiological recordings in CM. After training birds to recognize individual conspecific songs either in a two-alternative forced choice (AFC) or a go/no-go paradigm, neurons in CM became selective as a population

for the songs. Interestingly, in the AFC experiment the two songs elicited similarly enhanced responses, whereas in the go/no-go experiment, the response to the go song was enhanced relative to the response to the no-go song. Therefore the learned selectivity cannot simply be explained by familiarity but must also involve top-down processing [10].

The avian auditory system also has great potential as a model to study the effect of sensory experience (beyond tutor song) on neural development. This line of research has just recently been initiated. The first study on this subject observed significant changes in the response of field L neurons of birds that were deprived of normal acoustical experience during early development; both the selectivity and the organization of frequency tuning properties were altered [6].

Function

The acoustical sense is important in birds for detecting predators (of all species), for finding prey (e.g., in the barn owl), for echolocation (e.g., in the cave swiftlet) and, perhaps more remarkably, for complex communication. Listening to others allows birds to classify them as conspecific or heterospecific, neighbor or stranger, male or female, mate or non-mate, parent or non-parent, kin or non-kin. Birds are known to be particularly adept at recognizing individual conspecifics based solely on their vocalizations, often in unfavorable acoustical environments. How the auditory system performs such a difficult auditory scene analysis remains unknown. Furthermore, the communication signals are not just a signature of the sender but carry specific messages. Birds produce calls to maintain contact (contact call), to restore contact (separation call), to obtain food (begging call) or to advertise danger (alarm call). The complex song produced by birds of the suborder oscine (the songbirds) is used by males for territorial defense and mate attraction, and by male-female pairs for pair-bonding and cooperation. In songbirds, audition serves another important function: juvenile songbirds need to listen to adult conspecific song as well as their own vocalizations in order to learn to sing.

Pathology and Therapy

The avian auditory system is also an experimental model system to study the effects of deafness, sensory deprivation or noise exposure, and hair cell regeneration on the central auditory circuitry.

References

1. Konishi M (2003) Coding of auditory space. *Annu Rev Neurosci* 26:31–55
2. Fortune ES, Margoliash D (1992) Cytoarchitectonic organization and morphology of cells of the field L complex in male zebra finches (*Taenopygia guttata*). *J Comp Neurol* 325(3):388–404
3. Vates GE et al. (1996) Auditory pathways of caudal telencephalon and their relation to the song system of adult male zebra finches (*Taenopygia guttata*). *J Comp Neurol* 366:613–642
4. Saini KD, Leppelsack HJ (1981) Cell types of the auditory caudomedial neostriatum of the starling. *J Comp Neurol* 198:209–230
5. Knudsen EI (2002) Instructed learning in the auditory localization pathway of the barn owl. *Nature* 417 (6886):322–328
6. Theunissen FE, Shaevitz SS (2006) Auditory processing of vocal sounds in birds. *Curr Opin Neurobiol* 16 (4):400–407. Epub 2006 Jul 13
7. Theunissen FE et al. (2004) Song selectivity in the song system and in the auditory forebrain. *Ann NY Acad Sci* 1016:222–245
8. Clayton DF (2004) Songbird genomics: methods, mechanisms, opportunities, and pitfalls. *Ann NY Acad Sci* 1016:45–60
9. Bolhuis JJ, Gahr M (2006) Neural mechanisms of birdsong memory. *Nat Rev Neurosci* 7(5):347–357
10. Gentner TQ, Margoliash D (2003) Neuronal populations and single cells representing learned auditory objects. *Nature* 424(6949):669–674

Avian Pineal Gland as “Third Eye”

Definition

The pineal gland of birds is capable of photoreception and, therefore, light can directly regulate melatonin synthesis and release. The light perceived by the pineal gland can be used by the birds to entrain the entire circadian system. At least two functional photopigments.

Pinopsin and Melanopsin, are present in the pineal gland. One of these photopigments may mediate the acute suppression of melatonin synthesis while the other may mediate the entrainment of the circadian pacemaker that drives melatonin synthesis.

Avoidance Behavior

Definition

A response to elude negatively valenced events such as painful stimulation. One of the primary organizers of avoidance behaviors is the mid-cingulate cortex where predictions are generated about the outcomes of particular events and motor system responses are determined to minimize or avoid physical harm.

► Cingulate Gyrus

Avoidance Learning

Definition

Form of learning that leads to the recognition of dangerous or harmful situations and results in avoidance of such stimuli.

AVOR (Angular VOR)

- Vestibulo-Ocular Reflex

Awakening Agents

- Stimulants

Axo-axonal Synapse

Definition

Synapse formed between two axons.

- Synaptic Transmission: Model Systems

Axogenesis

- Axon Outgrowth

Axon

Definition

A tubular process extending from a nerve cell body towards target cells and carrying action potentials from the cell body to the nerve terminal. Axons may have

varying diameters depending on their function. They may be myelinated or non-myelinated.

- Action Potential
- Action Potential Propagation

Axon Degeneration and Regeneration of Peripheral Neurons

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Definition

Axon degeneration and regeneration of ►peripheral neurons refers to a series of sequential events that occur following a peripheral nerve injury. Axon degeneration involves the breakdown of axons and myelin distal to an injury site, a requisite for subsequent regeneration, or regrowth of axons.

Characteristics

Introduction

Long term disability from neurological disease depends as much on loss of axons, or connections, as it does on loss of parent neurons. Sundered axons cannot simply reattach to restore function. Instead, axons must regrow, navigating their way to target tissues once again, as they did during development. Unfortunately this task is incomparably more difficult during adulthood. Cues once present and growth factors once plentiful may no longer exist.

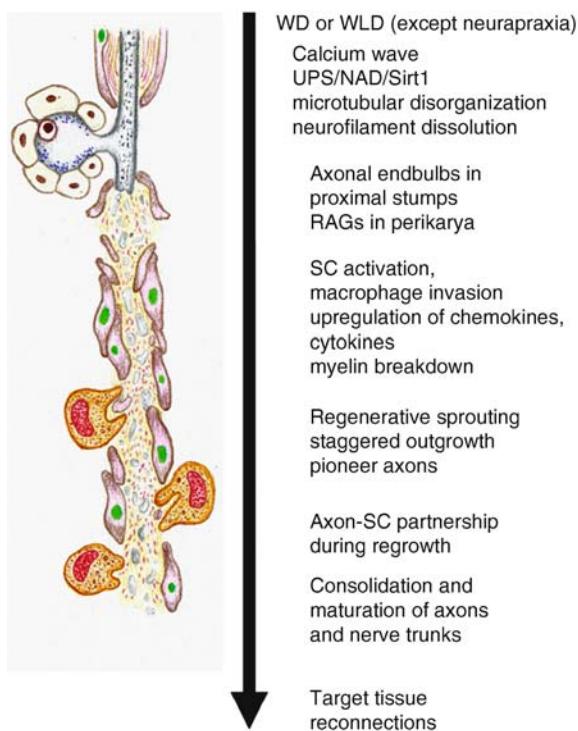
This brief review will address some newer and older concepts concerning ►axonal regeneration of peripheral neurons. Contrary to assumptions otherwise, while peripheral axons regrow, they do so slowly and incompletely. They are also much more frequently injured by trauma or disease than axons of the spinal cord. In a patient with a brachial plexus lesion that disrupts axons supplying the upper limb, it is unlikely that regeneration of motor and sensory axons as far as the hand will occur. Hand movement and sensation are unlikely to be restored. The further axons must grow the less likely they are to find the correct target. Moreover, the pathway they follow becomes far less hospitable. Nerve trunks distal to an injury that have not been reinnervated for several months become much less supportive of regrowth [1]. The Schwann cell (SC), the essential partner of regrowing axons, changes its

phenotype, becomes atrophic and is unlikely to elaborate growth factors to support new axons.

The challenges of peripheral axon regeneration however, start immediately after the injury. These barriers require unique consideration of how axons interact with their microenvironment during the events of regeneration. Before axons re-enter a distal nerve following injury, it is essential that previous material from degenerating axons and myelin are cleared and that basement membrane pathways, or Bands of Bungner, are prepared for them. Injured axons must reseal, sprout, navigate the injury site they encounter, then move en masse towards their targets. Each step of this process can have a major bearing on the success of regeneration and I will briefly cover some aspects of each here (Fig. 1).

Sequential nerve regeneration

INJURY: Neurapraxia, axonotmesis, neurotmesis



Axon Degeneration and Regeneration of Peripheral Neurons. Figure 1 A simplified schema listing major sequential events involved in regrowth of peripheral nerves after injury. Wallerian degeneration and axon regrowth are involved in injuries that damage axons (axonotmesis and neurotmesis). Neurapraxic lesions are milder injuries involving segmental demyelination without axon interruption or **►axonal degeneration**. The image on the left illustrates SC proliferation and macrophage entry into a zone of Wallerian degeneration distal to an injury site (illustration by Scott Rogers).

Wallerian and Wallerian-Like Degeneration

In 1850 Augustus Waller described a series of morphological changes that developed in peripheral nerve axons following a transection injury. This series of events has subsequently been described as “►Wallerian degeneration” [2]. Strictly speaking, Wallerian degeneration (WD) refers to events that follow a nerve transection, also known as a neurotmesis or a Sunderland Type V injury of a nerve trunk. In this injury, the proximal and distal stumps of the nerve trunk are completely separated. “Wallerian-like degeneration” describes similar events and shared mechanisms that occur after many types of traumatic nerve injury where the injury may not be as catastrophic e.g. crush or blunt injuries. It also occurs in diseases of nerves known as neuropathies. In the central nervous system, Wallerian-like degeneration (WLD) is also an essential prelude to axon regrowth but it operates at a much slower and less complete pace, a factor linked to very poor regrowth. Finally, axonal “pruning” in development or regeneration, a process that scales back supernumerary axons, shares in the machinery and mechanisms of WD.

WD involves the breakdown of axons and myelin distal to the injury site. Until recently, WD was thought to be a passive distal degeneration because of loss of protein axoplasmic transport from the cell body of the neuron. It is now recognized that WD is an active process with a unique set of signals triggered by an initial calcium transient [3]. The subsequent signals involve the ubiquitin-proteasome system (UPS) and inhibitors of the UPS can delay WD. Additional machinery involved in WD was identified through investigations of a spontaneous mouse mutant known as *Wld^S*. This mouse has axons that survive and persist for long periods after they have been transected: they appear to resist degeneration. The *Wld^S* mutation is a triplication that forms a fusion protein involving UFD2/E4 (a protein involved in protein ubiquination), and nicotinamide mononucleotide adenyllyltransferase (Nmnat, an enzyme involved in nicotinamide metabolism). As a result of this mutation and overexpression of the fusion protein, rises in Nmnat activity increase levels of nicotinamide adenine dinucleotide (NAD), an axonal protectant. NAD, in turn, operates through a protein deacetylase known as SIRT1 (a member of the Sir family of protein deacetylases). Discovery of these new mechanisms of WD offer opportunities to interrupt axon damage in some circumstances, such as axonal damage from peripheral neuropathies.

The next steps of WD involve axon microtubule dissolution, breakdown of the neurofilament axon lattice and, in the case of myelinated axons, a change in the phenotype of SCs associated with these fibers. “Activated” SCs upregulate a series of protein markers including GFAP(glial fibrillary acidic protein), N-CAM,

A5E3, Ran-2 and p75 [4], dissolve their own myelin and behave as phagocytes. To effectively break down axons and clear myelin debris, an inflammatory cascade is next required. This results from invasion of blood borne macrophages within the first 3–5 days after injury. In concert with inflammatory cell invasion, nerves undergoing WD express a series of cytokines and chemokines including IL-1 β , IL-6, IFN- γ , TNF- α , MCP-1 (monocyte chemoattractant protein-1) and MIP-1 α (macrophage inflammatory protein 1 α). These molecules help coordinate inflammatory cell trafficking, axon and myelin digestion, or may operate as trophic factors for new axons. Interruption of their expression delays WD and subsequent regeneration.

Nitric oxide (NO) is an important participant in WD and it is generated by iNOS (inducible nitric oxide synthase) expressed in SCs and macrophages. Local NO dilates local blood vessels to promote clearance and to deliver trophic factors to the injured peripheral nerve trunk. Through lipid peroxidation, NO also promotes myelin breakdown, a task that removes inhibitory myelin products from areas of new axon ingrowth. Mice lacking iNOS have slowed WD and subsequent regeneration. Overexpression of iNOS and excess generation of NO however, may be detrimental to regeneration. NO released during intense inflammation or local infection can paradoxically shut down regeneration and collapse growth cones [5].

Thus, overall evolving concepts concerning WD emphasize its role as an active molecular cascade that later involves a directed inflammatory response. WD is an essential prelude to successful later regrowth.

Early Regenerative Events

Once severed, axons quickly reseal then change the configuration of their microtubules, an alteration that may alter axoplasmic transport turnaround. Turnaround refers to the change in axoplasmic transport from anterograde to retrograde movement. Axonal endbulbs or boutons, originally described by Cajal as “sterile clubs” or necrotic profiles, next form at the proximal ends of transected axons. These structures, distinguished from growth cones, accumulate axoplasmic material that can include depolymerised neurofilaments, peptides, ion channels, enzymes and other molecules. As bulbs degenerate, some of their constituents can egress into the injury microenvironment and influence local glial cells, other axons or local microvessels. The neuropeptide CGRP (calcitonin gene-related peptide) released from endbulbs can dilate local microvessels and helps to render hyperemia, or rises in nerve blood flow, at injury sites. Endbulbs can also accumulate functional opioid receptors, sodium channels and nitric oxide synthases that generate NO within the injury milieu. These

contents of axonal endbulbs may thereby influence the development of ectopic axon electrical discharges associated with neuropathic pain.

Axon sprouting develops at the ends of injured axons, or at nodes of Ranvier proximal to the injury zone in myelinated fibers. Sprouting is a local phenomenon that does not require a connection to the cell body and may normally be suppressed by nodal molecules. For an early sprout to form thereafter into a mature and growing new axon however, does require a connection to the perikaryon. In fact, an injury to an axon is associated with a cascade of changes in the parent cell body that shift its phenotype from a “stable” transmitting neuron to a robust regenerating one [6]. The genes that change in association with injury and regeneration are known as ►RAGs (regeneration associated genes). While the list of these changes is now extensive, key alterations include downregulation of neurofilament subunits, upregulation of tubulin that forms microtubules, upregulation of GAP43/B50 (growth associated protein 43) an actin assembly molecule, upregulation of nNOS (neuronal nitric oxide synthase) and upregulation of HSP27 (heat shock protein 27), a chaperone protein that helps refolding. Some RAGs develop from impaired retrograde transport of trophic factors and can be reversed with their replacement. Alternatively, in the CNS an attenuated RAG response may contribute to poor regeneration.

The overall progress of axon outgrowth and the behavior of growth cones therefore depends on coordinated activity between the cell body and local axons. For example, Perlson and colleagues have described a complex retrograde kinase signaling mechanism involving interactions between importins, dynein, depolymerized vimentin and pErk. Vimentin, an intermediate filament protein, and β importin, upregulated in sciatic axons after injury, complex with dynein and recruit phosphorylated activated Erk. Delivery of pErk to the cell body then allows it to influence nuclear gene transcription [7]. It is likely that more anterograde and retrograde signalling cascades like this will be identified. The interaction does illustrate how a nominal structural intermediate filament, vimentin, is upregulated in axons but subsumes a completely new role when depolymerised. Multiple tasking and interactions of neuronal molecules underlie regenerative events.

Ras Superfamily GTPases

The list of molecular players influencing growth cones is also rapidly expanding. Their roles *in vivo* however, are less well defined during peripheral neuron regeneration. The Ras family GTPases (►Ras GTPases), specifically RHO GTPases, are molecular switches important in defining cell polarity and directed growth. In neurons, they appear critical to growth cone advance

or collapse. One member, RHOA, has emerged as a critical brake on regenerative activity within the injured spinal cord. Additional RHO GTPase members are CDC42 and RAC1 that promote filopodia and lamellipodial extension and facilitate growth cone advance. RAC1 influences actin filament behavior, stabilizes adherent contacts, and activates the kinase PAK (p21-activated kinase) to then activate NF κ B and MAPK.

RHOA localizes to the leading edges of migrating cells, or growth cones in neurons where it can promote its actions [8]. It interacts with p75, formerly known as the “low affinity” nerve growth factor receptor, and other molecules that include LINGO-1, TAJ/TROY, and the epidermal growth factor receptor (EGFR). RHOA, operating through a kinase known as ROK (RHO kinase) and other pathways, collapses growth cones through increases in actin “arc” formation and central actin bundle contractility and stability. To accomplish this task, ROK enhances myosin II phosphorylation and subsequent actin mediated growth cone retraction. It may also accomplish retraction by inhibiting of myosin phosphatase and by activating LIM kinase. This latter pathway in turn phosphorylates and deactivates *cofilin* (also known as actin depolymerizing factor [ADF]) interrupting growth cone advance. There is a long list of additional players that influence actin dynamics and the fate of peripheral nerve regeneration. They include the Arp 2/3 complex, N-WASP, cortactin, Scar/WAVE, Ena/Mena/VASP proteins, Cap Z, actin monomer binding proteins, and profilin to name a few. Further protein cascades and interactions, not discussed here, but including RHO GTPases, are involved in microtubular plasticity, a second major determinant of growth cone behavior.

RHOA has garnered particular attention because its inhibition facilitates axon outgrowth. This has been demonstrated in several ways using central neurons or peripheral neurons growing on inhibitory central substrates such as myelin or myelin-associated glycoprotein (MAG). RHOA is activated by a number of molecules that include Nogo-66, MAG, semaphorins, ephrins, oligodendrocyte myelin glycoprotein and chondroitin sulphate proteoglycans. Wu and colleagues [9] have demonstrated that RHOA GTPase is actually synthesized in growth cones where it facilitates collapse in response to inhibitory cues. In peripheral neurons, an important role for RhoA in inhibiting *in vivo* regeneration across transection injuries also exists. Blocking ROK improves regeneration.

The role of RHOA in suppressing axon outgrowth is contrasted with that of PI3K-Akt (phosphatidylinositol 3-kinase-Akt; Akt is also called protein kinase B [PKB]), a growth factor activated pathway that promotes growth and differentiation. One of its actions is to phosphorylate and inactivate glycogen synthase kinase 3 β (GSK3 β), a multifunctional serine/threonine

kinase at the leading edges of growth cones that suppresses growth cone extension and axon formation. When it is phosphorylated through the PI3K-Akt signaling pathway, GSK3 β activity is shut down, allowing growth to occur.

Overall, while the impact of many of these proteins has been examined *in vitro* or in the CNS, their role specifically on peripheral nerve regeneration is less well known. Some are synthesized by the perikaryon and transported to growth cones to effect their actions. Some however, are also locally synthesized by axons, a novel mechanism for responding to regeneration cues including those from SCs [10]. The other important caveat is that optimal early growth cone behavior in complex injured nerve trunks does not necessarily translate into optimal functional reconnections. Each step of the regenerative process can enhance or inhibit the final outcome.

Schwann Cell Plasticity

► Schwann cells (SCs) are essential partners for axon maintenance and outgrowth in the peripheral nervous system. Activated SCs lead axons, in part with long laminin trails, through three dimensional trajectories during regeneration. Long and delicate SC processes closely accompany outgrowing axons and participate in a bidirectional exchange of molecules. SCs lay down adhesive substrates of the extracellular matrix such as laminin and fibronectin, but they also provide gradients of growth factors. Axons, in turn, offer substantial signals of their own to SCs that lead, for example, to a change in the “stable” phenotype associated with an intact myelinated axon to a “reactive” SC. Reactive SCs recapitulate development in that they re-express markers such as GFAP and others listed above. Interestingly, many of these markers have ongoing expression in SCs of Remak bundles, the structures that ensheathe unmyelinated axons in peripheral nerve trunks. Neuregulins (NRGs), a critical signal to SCs, are products of alternative-splicing of the NRG1 gene and belong to a family of growth and differentiation factors. NRGs are released from axons to act on SC receptors erbB2 and erbB3 in order to activate an intracellular second messenger cascade. NRGs thus support new axon outgrowth but may also operate also during WD and myelination. SCs can coax NRG release from axons by offering a menu of growth factors to them first.

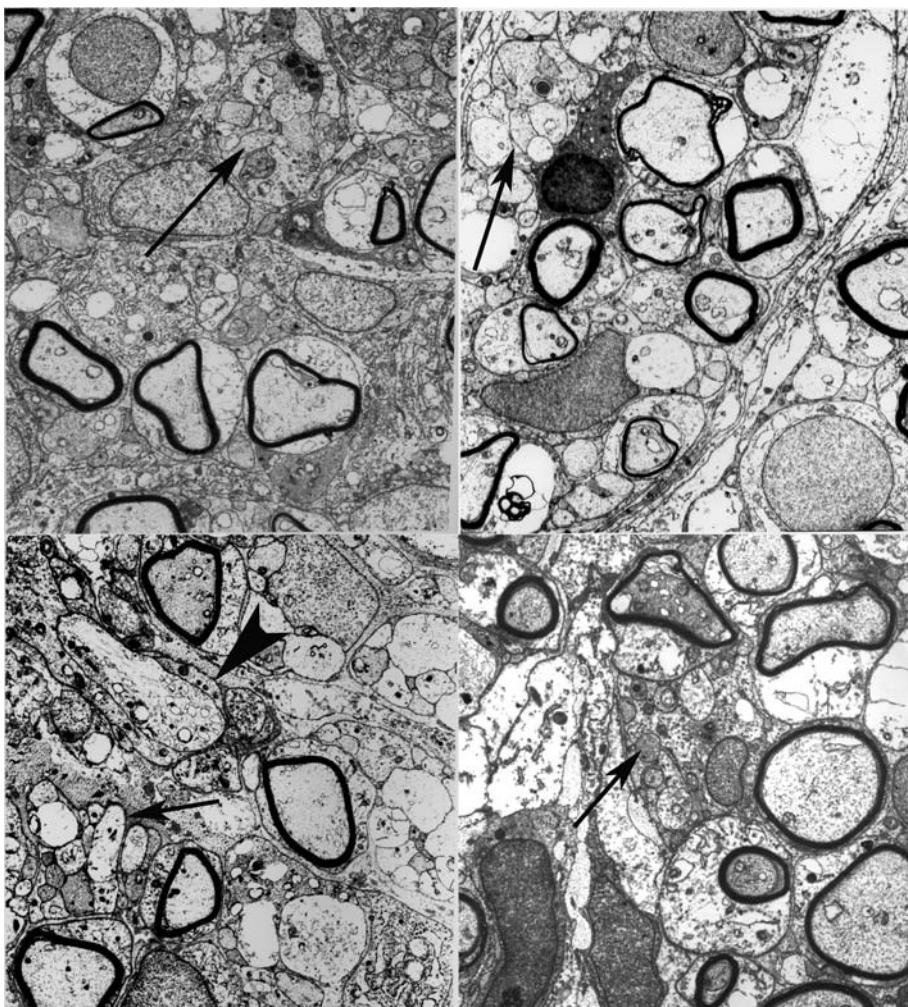
Overall, we have labelled these essential bidirectional exchanges the “axon-Schwann cell dance.” The importance of this relationship is illustrated by experiments in which SC proliferation is deliberately inhibited by radiation or a mitosis inhibitor. Regeneration is severely limited. Alternatively, deliberately seeding gaps between proximal and distal nerve stumps after transection with SC precursors, substantially facilitates regeneration. Only rare axons advance “naked” for any

significant distances during regrowth. To support regeneration therefore, SCs must dedifferentiate, proliferate and migrate. In some injuries, such as nerve trunk crush, activated proliferating SCs form Bands of Bungner, guidance pathways for regrowth of axons into the distal denervated stump.

Staggered and Preferential Regeneration

One of the interesting conundrums facing peripheral neurobiology revolves around why outgrowth of axons, for example from proximal nerve stumps, is not synchronized. Classical depictions of axon outgrowth envision simultaneous advance of growth cones and axons from all of their parents in the proximal nerve

stump. This view, however, is incorrect and we now recognize that outgrowth is “staggered” such that some axons grow out early, and others lag far behind. After transection nerve injuries, for example, only a small proportion of axons from the proximal nerve stump may cross into the regenerative zone even within the first week. In regenerative bridges, instead of a uniform pattern of new axons of similar maturity, new axons exhibit a wide variation in their level of maturity (Fig. 2). “Staggered” axon regeneration has only recently been highlighted by Gordon and colleagues during regrowth of motor axons [1]. This interesting phenomenon was also linked to another, known as preferential motor reinnervation (PMR) described by Brushart [1]. PMR



Axon Degeneration and Regeneration of Peripheral Neurons. Figure 2 An electron composite micrograph from a regenerative bridge connecting a transected peripheral nerve trunk forming a few days after injury. The bridge consists of regenerative clusters and axons of varying levels of maturity and myelination. The arrows point to small clusters of regenerating axons. The arrowhead shows a longitudinally directed axon process, probably a growth cone, accompanied by fine SC processes on either side of it. Although the nerve trunk underwent a single injury, the bridge illustrates “staggered” regeneration in which more mature elongated axons are closely associated with later appearing smaller and less mature axons (image taken by David McDonald, Zochodne lab).

refers to the tendency of motor axons to prefer to regrow along “motor” pathways when offered a choice.

Both “staggered” and preferential regeneration illustrate the less explored concept that local cues for guidance and outgrowth have major impacts on the success of peripheral nerve regeneration. PMR may be accounted for by specific basement membrane molecules expressed by “motor” SCs, but not others that prefer to interact with sensory axons. Axons may have staggered growth because they need these kinds of cues to begin their advance. “Pioneer” axons, following leading migrating SCs, may start the process, and they facilitate axons to follow by offering cues.

Other Features of the Regenerative Cascade

We provide here only a brief overview of some selected topics and players in the early regenerative cascade of a peripheral neuron. There are many other parts to this story. These include the role of nerve microvessels, or vasa nervorum, during the support of nerve trunk regrowth. A major topic for consideration is the problem of target tissue innervation. Targets include the neuromuscular junction with its specialized complement of terminal SCs and the skin where both dermal and epidermal fiber innervation are required. Regrowing axons must reform the proper architecture of a nerve trunk, re-establish disrupted blood-nerve barriers and in many cases, acquire a stable mature myelin sheath. I have also not discussed the burgeoning topic of neuron growth factors and their downstream intracellular signals. The list has extended well beyond the classical neurotrophin family of nerve growth factor, first discovered by Levi-Montalcini almost 50 years ago. New neuron growth factors, sometimes originally described in other tissues, have emerged such as erythropoietin, GDNF family members and bone morphogenic proteins (BMPs), and vascular endothelial growth factors (VEGFs). Finally, the roles of adhesive molecules interacting with axon and SC integrin receptors are critical to the regenerative process. Not only do these interactions provide outgrowth and guidance cues, but they can generate intracellular signals of their own, interacting for example with growth factors.

Summary

Peripheral nerve regeneration is a complex, coordinated cascade of events that involves multiple cellular players and an intensive series of molecular interactions. Central among these are the axon-SC partnership and their bidirectional exchange. There is a beauty to the sequential unfolding of all of these relationships, yet they remain largely unexploited for therapeutic purposes. While nerves regenerate, they have major barriers to do so and frequently fail to accomplish their tasks. The upsurge of interest and work on these barriers does promise to overcome them.

Acknowledgements

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References

- Fu SY, Gordon T (1997) The cellular and molecular basis of peripheral nerve regeneration. *Mol Neurobiol* 14:67–116
- Stoll G, Jander S, Myers RR (2002) Degeneration and regeneration of the peripheral nervous system: from Augustus Waller's observations to neuroinflammation. *J Peripher Nerv Syst* 7:13–27
- Luo L, O'Leary DD (2005) Axon retraction and degeneration in development and disease. *Annu Rev Neurosci* 28:127–156
- Jessen KR, Morgan L, Stewart HJ, Mirsky R (1990) Three markers of adult non-myelin-forming Schwann cells, 217c(Ran-1), A5E3 and GFAP: development and regulation by neuron–Schwann cell interactions. *Development* 109:91–103
- Hess DT, Patterson SI, Smith DS, Skene JH (1993) Neuronal growth cone collapse and inhibition of protein fatty acylation by nitric oxide. *Nature* 366:562–565
- Verge VM, Gratto KA, Karchewski LA, Richardson PM (1996) Neurotrophins and nerve injury in the adult. *Philos Trans R Soc Lond B Biol Sci* 351:423–430
- Perlson E, Hanz S, Ben-Yakov, K et al. (2005) Vimentin-dependent spatial translocation of an activated MAP kinase in injured nerve. *Neuron* 45:715–726
- Luo L, Jan LY, Jan YN (1997) Rho family GTP-binding proteins in growth cone signalling. *Curr Opin Neurobiol* 7:81–86
- Wu KY, Hengst U, Cox LJ et al. (2005) Local translation of RhoA regulates growth cone collapse. *Nature* 436:1020–1024
- Willis DE, Twiss JL (2006) The evolving roles of axonally synthesized proteins in regeneration. *Curr Opin Neurobiol* 16:111–118

Axon Elongation

► Axon Outgrowth

Axon Guidance

► Axon Pathfinding

Axon Outgrowth

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Synonyms

Axon elongation; Axogenesis; Neurite extension

Definition

The **►axon** is the crucial output machinery of neurons. Along this cable, electrical signals, called **►action potentials**, are propagated and transmitted to other cells via a **►synapse**. Axon outgrowth is an important developmental process, in which the axon is projected from the cell body (**►soma**) toward specific target cells. Both intrinsic and extrinsic factors precisely control this process to make sure that the nervous system builds up the correct wiring pattern of axons, because the neural network is fundamental to the complex functioning of the nervous system. The **►growth cone** at the distal tip of axons plays a primary role in axon outgrowth, sensing extrinsic factors and determining the direction of the growth. Neurite is a special term referring to a fiber that has outgrown in culture, where the distinction between axons and **►dendrites** is not necessarily clear.

Characteristics

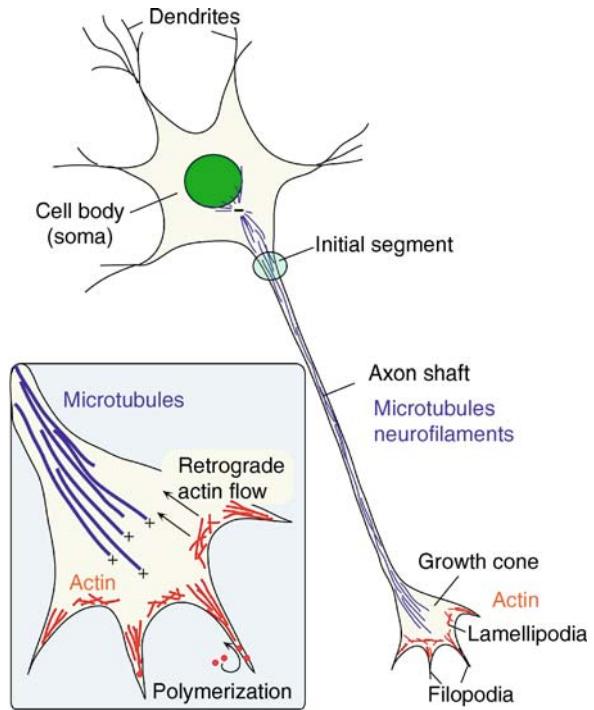
Quantitative Description

The lengths of axons vary enormously according to the type of neuron. For example, motor neurons in human have axons that sometimes reach one meter in length, while **►interneurons** tend to have much shorter axons, such as tens of microns. The speed of axon outgrowth also depends on neuronal type. The typical speed of axonal outgrowth in culture is in the range of tens to hundreds of micrometers per hour [1]. It is difficult to measure the speed of axon outgrowth *in vivo*, but the speed has been estimated to be in this range in living animals such as *Xenopus* and *C. elegans* in which axon outgrowth is accessible [2]. The speed of **►axon regeneration** in peripheral nerves is usually assumed to be 2–3 mm per day.

Lower-Level Structures

The distal tip of the axon is called the growth cone and comprises finger-like protrusions, the **►filopodia** and ruffling membrane called the **►lamellipodia** (Fig. 1).

The **►actin** cytoskeleton is the major structural component of the growth cone and the driving force for its movement. Bundled **►actin filaments** control the extension and retraction of the filopodia and branched



Axon Outgrowth. Figure 1 Structure of a neuron developing neurons can be divided into several parts such as the dendrite, cell body, axon shaft, initial segment and growth cone, each of which has a specific cytoskeletal composition. The *inset* is a close-up of the growth cone showing active cytoskeletal dynamics.

actin meshwork controls the ruffling movement of the lamellipodia. **►Microtubules**, another major cytoskeletal component, are the backbone of the axon shaft and also partially populate the central part of the growth cone. **►Neurofilaments**, which belong to a class of intermediate filaments, are also abundant in the axon shaft and seem to add stability to the axon cytoskeleton. The axon initial segment or the **►axon hillock**, which is positioned at the boundary between the axon and the cell body (soma), usually develops a specialized structure in which various membrane scaffold proteins and ion channels are concentrated and serves as the ignition site for action potentials.

Higher-Level Structure

The ultimate goal of axon outgrowth is making synapses onto specific targets. During the process, axon terminals turn into **►pre-synaptic** structures, in which synaptic vesicles and the releasing machinery are properly installed. The pre-synaptic structure is usually perfectly matched with the **►post-synaptic** structure on the target cell. This structural matching is achieved by accurate distribution of a variety of molecules such as cell-adhesion, cytoskeletal and scaffold proteins and ion

channels, through bi-directional signaling between the pre- and post-synaptic elements.

The ►myelin sheath is another important feature of the high level structure of axons. This intricate membrane is synthesized by ►oligodendrocytes and ►Schwann cells in the central and peripheral nervous systems respectively, wraps around many long axons in vertebrates and insulates electrical activity along the axons from leaking, so that the axons can propagate action potentials rapidly.

Structural Regulation

The actin cytoskeleton and microtubules are dynamically controlled in axons [3]. Actin filaments are continuously transported in the proximal direction within the growth cone (retrograde actin flow in Fig. 1). To cope with this flow, actin filaments are polymerized by incorporating actin monomers at the distal end facing the leading edge of the growth cone. For axons to outgrow, the speed of actin polymerization has at least to keep up with that of the retrograde flow. If not, actin filaments will be withdrawn from the growth cone, stripping off the filopodia and lamellipodia altogether, leading to the reaction called growth cone collapse. Most repulsive ►guidance molecules induce growth cone collapse by affecting actin dynamics and inhibiting axon outgrowth. Microtubules also have a polarized structure and position the fast-polymerized plus-end to the distal direction of axons. When axons grow, microtubules selectively invade the distal part of the growth cone along actin filaments, converting the growth cone into the shaft and actually lengthening the axons. These cytoskeletal dynamics are regulated by a number of tubulin- and ►actin-binding proteins.

Upstream Process

Generally, neuronal differentiation and migration precede axon outgrowth, although some types of neurons begin to grow axons while their cell bodies are still migrating. In culture, many neurons initially extend multiple immature processes that have the characteristics of neither axons nor dendrites. Subsequently, one of the processes, usually the longest one, is chosen and differentiates into the axon, whereas the others are committed to be dendrites [4]. Although we cannot see the exactly same phenomenon *in vivo*, a similar competitive interaction among initial processes is believed to take place in the establishment of the highly polarized structure of neurons that have a single axon and multiple dendrites.

Downstream Process

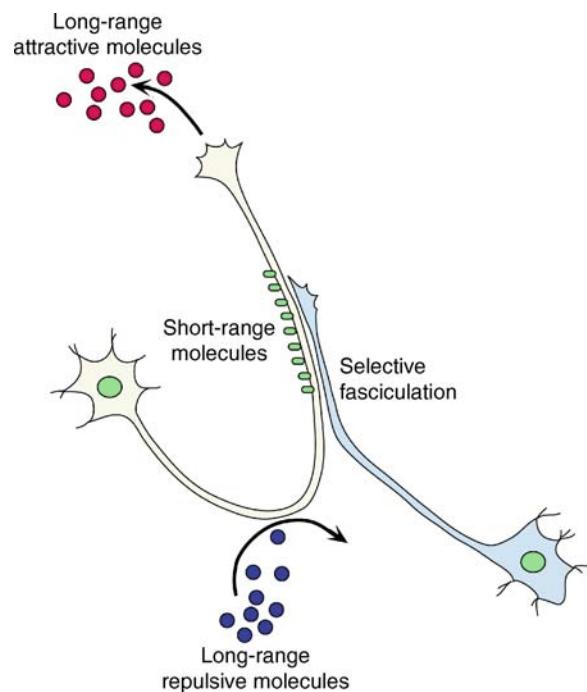
The axon is not always a simple single line structure but sometimes bifurcates and makes branches, which enable it to connect to multiple target cells and broaden

the terminal field. There is also a naturally occurring degenerative process for axons, in which axons that have once projected are later eliminated. This ►axon pruning is widely used for the refinement of early rough neural networks and the establishment of more functional circuits during a later stage of development.

Process Regulation

The route of axon outgrowth is stereotyped and barely differs among individuals, suggesting that it is mainly determined genetically. Indeed, the direction of axon outgrowth is controlled by a variety of extrinsic signals called guidance molecules, which are synthesized at a fixed time and place according to the developmental genetic program. The guidance molecules, which are basically proteins, can be categorized into several groups (Fig. 2).

One group is that of attractive molecules that pull the growth cone by changing the cytoskeletal status locally within the growth cone. ►Netrin is a famous example of this category. Another group is that of ►repulsive molecules, which repel the growth cone and create a domain inaccessible to axons. The repulsive molecules



Axon Outgrowth. Figure 2 Guidance of axon outgrowth. Axon outgrowth is guided by attractive or repulsive guidance molecules. Either attractive or repulsive guidance molecules can act in the short- or long-range. In a later developmental stage, selective fasciculation can be a strong guidance force for the following axons.

destroy the actin cytoskeleton in the growth cone and induce collapse, thereby inhibiting axon outgrowth. Recent studies have identified many molecules that belong to this category including ►semaphorin, ►ephrin and ►slit. Another type of classification from a different standpoint is that of long-range versus short-range guidance molecules. The long-range molecules diffuse from their source and form a concentration gradient, which determines the pattern of axon outgrowth. The short-range molecules are somewhat immobilized in the place where they were synthesized and act only locally on axons. ►Extracellular matrix proteins and ►cell-adhesion molecules are often categorized in this group. Theoretically, either attractive or repulsive guidance molecules can have short- or long-range actions.

During outgrowth, axons are not always individual navigators but often travel together, bundling with each other in the same route. This is especially marked in later projecting axons, some of which simply follow earlier axons by adhering to them (Fig. 2). This selective ►fasciculation apparently eases the pathfinding task of followers; only the first ►pioneer neurons are assigned to the challenging job of pioneering the pathway.

Function

Axon outgrowth is an important process that enables neurons to connect with distant targets. Therefore, this process underlies all the functions of the nervous system such as sense, movement, perception, memory, emotion and behavior.

Pathology

Genetic engineering technology has generated many animals that have mutations in various types of genes involved in axon outgrowth and guidance. These animals show specific phenotypes and pathologies in the nervous system according to properties of the genes and could serve as animal models for various human diseases.

Therapy

In mammals, axon outgrowth is only marked during development and the axons lose the capacity to grow with maturation of the central nervous system. Clinically, it remains extremely difficult to induce re-growth of central axons, although this field has been investigated extensively. Differences in the growing capabilities of developmental and adult axons can be partly attributed to the growth-inhibitory environment of the adult central nervous system. Especially, myelin in the adult central nervous system is assumed to be a component of the materials that prohibit axon regeneration.

References

- Yamamoto N, Higashi S, Toyama K (1997) Stop and branch behaviors of geniculocortical axons: a time-lapse study in organotypic cocultures. *J Neurosci* 17:3653–3663
- Chien CB, Rosenthal DE, Harris WA, Holt CE (1993) Navigational errors made by growth cones without filopodia in the embryonic *Xenopus* brain. *Neuron* 11:237–251
- Dent EW, Gertler FB (2003) Cytoskeletal dynamics and transport in growth cone motility and axon guidance. *Neuron* 40:209–227
- Dotti CG, Bunker GA (1987) Experimentally induced alteration in the polarity of developing neurons. *Nature* 330:254–256

Axon Pathfinding

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Synonyms

Axon guidance; Axonal targeting

Definition

During development, axons grow to appropriate directions and reach their target cells to form synaptic connections. In this developmental event, axons are guided by various molecular cues. Fundamentally, there are two types of axon guidance molecules, attractive and repulsive molecules. These molecules are further categorized into diffusible and contact-mediated cues, based on their chemical properties and/or actions.

Characteristics

Quantitative Description

The volume of adult human brain is 1300–1500 cm³ and composed of approximately 100 billion neurons. During development, neurons are produced by proliferation from neuronal stem cells, at a speed of 250,000 per min. After mitosis, a neuron extends an axon, a fine process with a small diameter (less than one micron in most cases). Axons grow at a speed of several ten microns per hour (~1mm/day). An axonal tip is called a growth cone, which is a swelling structure with various detectors to sense surrounding molecules. The size of a growth cone is varied among nervous systems and species, ranging from several to several ►tens of microns. One axon extends from a neuronal cell body, but forms branches and synaptic connections with numerous target cells.

Higher Level Structures

The fundamental patterns of neural connections are surprisingly stereotyped. For instance, in the visual system (Fig. 1a), a million of the retinal axons originating from one eye run towards the midline of the brain.

Half of them further project to the opposite (contralateral) side of the brain to form connections with ►contralateral visual thalamus (lateral geniculate nucleus, LGN). The remaining half alters the direction at the midline (optic chiasm) and project to the LGN in the same (ipsilateral) side. Axons from the LGN, in turn, send axons to the ipsilateral visual cortex. In a microscopic view, LGN axons project to a particular layer of the visual cortex, which is composed of six cell layers. These connection patterns are completely the same among individuals and even common in higher mammals. Such stereotyped connections are found ►in many other systems. Thus, axons run in specific pathways and form connections with their target cells.

Lower Level Components

Axons grow towards the location where diffusible attractive factors are concentrated, whereas axons turn away from the source of diffusible repulsive factors. The former and latter phenomena are called chemoattraction and chemorepulsion, respectively. Netrins and ►semaphorins (secreted type) are well-known protein families that have chemoattractive and chemorepulsive activities.

Cell surface and ►extracellular matrix (►ECM) molecules can also act as guidance molecules. Immunoglobulin domain-containing proteins and cadherins (calcium-dependent cell adhesion proteins) are typical

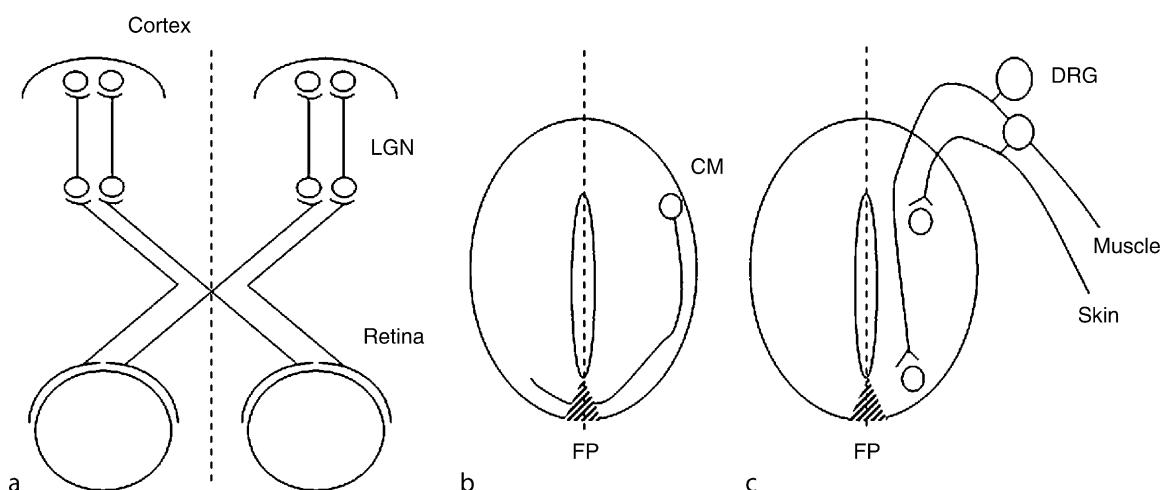
cell surface molecules which influence axon growth. Ephrins, ligands for a receptor tyrosine kinase family (Eph family), are also cell surface molecules, and are known to act as ►repulsive guidance molecules for axonal growth. Laminin and fibronectin are large glycoproteins in ECM, and promote axon growth of peripheral and central neurons. Proteoglycans, proteins with abundant sugar residues, are also ECM molecules and known to affect axon growth. The proteoglycans are categorized into several types such as heparan-sulfate proteoglycans and chondroitine sulfate proteoglycans based on kinds of sugar residues.

On the other hand, growth cones have various receptors that sense the above guidance molecules. Unc5 families and DCC (deleted in colorectal carcinoma) are receptor proteins for netrin family members; neuropilin and plexin are receptors for semaphorin family; Ephs are ephrin receptors; Integrin families are receptors for laminin and fibronectin. These receptors are membrane proteins with specific cytoplasmic domains, which influence cytoskeleton components *via* second messenger systems and/or gene expression.

Higher Level Processes

Chemotactic Behavior and Contact-Mediated Behavior

The growth cone exhibits ►chemotaxis in *in vitro* experiments. When attractive factors are applied to a growth cone through a glass micropipette, it begins to extend towards the pipette [1]. When a repellent factor is applied, growth cones turn away from the source. Such turning behavior is thought to reflect a guidance property of chemoattractive and chemorepulsive factors *in vivo*: If target or intermediate target cells release attractive factors, growth cones could be directed



Axon Pathfinding. Figure 1 Stereotyped neural connection patterns in the central and peripheral nervous systems. (a) Neural connections from the retina to the visual cortex. (b) Trajectory of commissural axons in the spinal cord. (c) Projection patterns of distinct sensory neurons. Dashed lines represent the midline. *LGN* lateral geniculate nucleus; *CM* commissural neurons; *FP* floor plate; *DRG* dorsal root ganglion.

toward them. Conversely, axons could avoid entering the brain region where chemorepulsive factors are released.

Growth cones exhibit not only chemotactic but also contact-mediated responses. When growth cones of retinal axons encounter (make a contact) axons from peripheral neurons *in vitro*, retinal growth cones are repelled by the peripheral axons [2]. By contrast, retinal growth cones do not exhibit retraction when meeting other retinal axons. Such contact-mediated cues also contribute to axon guidance.

Pathway Choice and Target Selection by Attraction and Repulsion

Pathway choice and ►target selection are required for the formation of appropriate neural connections in the brain. In the spinal cord, commissural neurons, which interconnect both sides, are located in the dorsal part. During development, axons from these neurons extend ventrally, pass through the ventral midline and reach the contralateral side (Fig. 1b). *In vitro* experiments have shown that commissural axons from the dorsal spinal cord explant grow towards the cocultured floor plate (midline structure of the spinal cord), but do not grow towards explants dissected from the other parts of the spinal cord [3]. Commissural axons from the hindbrain also exhibit similar behavior [4]. These findings indicate that some factor released from floor plate cells, the intermediate target, acts as an attractive factor for commissural axons.

The dorsal root ganglion (DRG) neurons that are involved in pain or heat sensation (nociceptive DRG neurons) send axons to the interneurons that are located in the dorsal part of spinal cord, but do not project to motor neurons in the ventral part of spinal cord

(Fig. 1c). In a culture experiment, the developing ventral spinal cord has been shown to secrete the factor that inhibits the growth of these sensory axons [5]. The DRG neurons that sense muscular extension (proprioceptive DRG neurons) are not affected by the factor. Correspondingly, these sensory axons enter the ventral spinal cord to form synaptic connections with motor neurons. Thus, each type of DRG neurons can select their target cells (►target selection).

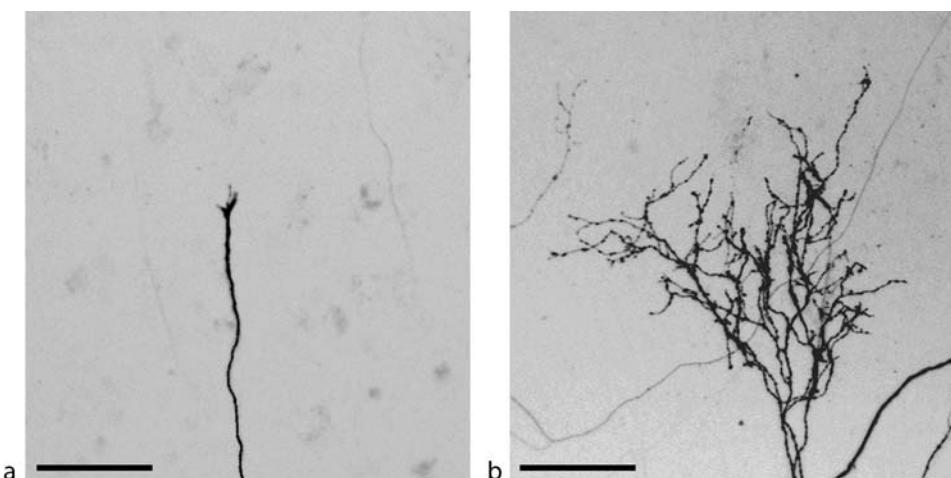
Fasciculation and Axonal Branching

Axons often make a bundle in their pathways. The axon that first extends towards the target cells during development is called a pioneer fiber. The axons originating from the same origin follow the pioneer fiber, and form a bundle (fasciculation). Once these axons reach the target zone, they separate each other (defasciculation). Individual axons further grow to more specific locations and form branching to connect with a certain number of target neurons. In the retinogeniculate system, retinal axons form a bundle (optic tract), but defasciculate in the LGN and form arbors to make synaptic contacts with several LGN neurons. Moreover, LGN axons grow towards the visual cortex with fasciculation (optic radiation). Once arriving at the visual cortex, LGN axons defasciculate to innervate a lot of cortical neurons. Individual axons further form branching in their target layer (target selection) to form synaptic connections (Fig. 2) [6].

Lower Level Processes

Molecular Mechanisms of Attraction and Repulsion

Ligand-receptor interactions are critical for axon guidance. In the commissural axon guidance, netrin family members are released from the floor plate and



Axon Pathfinding. Figure 2 Axon growth and branching. (a) Growth cone of a thalamocortical axon extends in the cortex *in vitro*. (b) Thalamocortical axon forms arbors in later developmental stages (*in vitro*). Scale bars in a and b represent 0.05 and 0.1 mm, respectively.

act as attractive factors for the commissural axons that express netrin receptors (Fig. 1b) [7].

Interactions between a member of the semaphorin family and its receptor, neuropilin are necessary for repulsive axon guidance of nociceptive DRG neurons. In this system, the semaphorin is expressed in the ventral half of the spinal cord and act as a repulsive guidance molecule for nociceptive DRG axons [5]. As a result, these axons do not enter the ventral spinal cord. By contrast, proprioceptive DRG axons can enter the ventral spinal cord as they do not express the receptor. However, these ligands do not necessarily produce the same effects in terms of attraction and repulsion. Netrins act as attractive factors in the commissural axon growth, but produce a repulsive action for axon guidance of a particular type of motor neurons. This is true for action of semaphorins.

Another molecular species also contribute to attractive and repulsive guidance mechanisms. Ephrin-Eph interaction produces growth-inhibitory action. Axons expressing Eph receptors are repelled by the brain region where ephrin ligands are expressed [8]. Moreover, chondroitine sulfate proteoglycans, an ECM molecule, also act as repulsive guidance molecules. On the other hand, laminin and fibronectin, ECM molecules, can promote axonal extension in a contact-mediated manner from most central and peripheral neurons that express integrin receptors.

Molecular Mechanisms for Fasciculation and Branching

Adhesion molecules are involved in axonal fasciculation primarily through their homophilic binding properties. If two axons express the same adhesion molecule, these two axons could run side by side, as high affinity is present between their extracellular domains. Immunoglobulin-superfamily proteins such as the neural cell adhesion molecule (NCAM) is crucial to form axon bundle. Axonal defasciculation is also ►regulated by adhesion molecules. In motor nerve projections, axons from motor neurons form a bundle on the way, but defasciculate around target muscle cells. A certain amount of sugar residues binding to NCAM promote the defasciculation by weakening homophilic binding of L1, the other adhesion molecule [9].

Axonal branching is also regulated by adhesion molecules, ECM and cell-surface molecules. In the cortex, thalamocortical axon branching is inhibited by the sugar residues, whereas it is promoted by ECM or cell surface molecules in the target layer [6]. Axonal branching is further regulated by neurotrophic factors secreted from target cells.

Process Regulation

Expressions of guidance molecules and their receptors are regulated primarily by transcriptional factors. For instance, ephrin (ligand of receptor tyrosine kinase)

expression is graded rostrocaudally in the visual center of amphibians as well as mammals. This expression pattern matches that for En (►Engrailed), which is a homeodomain-containing transcriptional factor. Similarly, the receptor expression in the retina is also regulated transcriptionally.

Function

Brain functions are mostly attributable to its neural networks, that is, axon pathfinding mechanisms produce elaborate neural circuitries that enable us to sense everything and behave appropriately.

References

1. Gundersen RW, Barrett JN (1979) Neuronal chemotaxis: chick dorsal-root axons turn toward high concentrations of nerve growth factor. *Science* 206:1079–1080
2. Kapfhammer JP, Grunewald BE, Raper JA (1986) The selective inhibition of growth cone extension by specific neurites in culture. *J Neurosci* 6:2527–2534
3. Tessier-Lavigne M, Placzek M, Lumsden AG, Dodd J, Jessell TM (1988) Chemotropic guidance of developing axons in the mammalian central nervous system. *Nature* 336:775–778
4. Shirasaki R, Tamada A, Katsumata R, Murakami F (1995) Guidance of cerebellofugal axons in the rat embryo: directed growth toward the floor plate and subsequent elongation along the longitudinal axis. *Neuron* 14:961–972
5. Messersmith EK, Leonardo ED, Shatz CJ, Tessier-Lavigne M, Goodman CS, Kolodkin AL (1995) Semaphorin III can function as a selective chemorepellent to pattern sensory projections in the spinal cord. *Neuron* 14:949–959
6. Yamamoto N, Inui K, Matsuyama Y, Harada A, Hanamura K, Murakami F, Ruthazer ES, Rutishauser U, Seki T (2000) Inhibitory mechanism by polysialic acid for lamina-specific branch formation of thalamocortical axons. *J Neurosci* 20:9145–9151
7. Kennedy TE, Serafini V, de la Torre JR, Tessier-Lavigne M (1994) Netrins are diffusible chemotropic factors for commissural axons in the embryonic spinal cord. *Cell* 78:425–435
8. Nakamoto M, Cheng HJ, Friedman GC, McLaughlin T, Hansen MJ, Yoon CH, O’Leary DD, Flanagan JG (1996) Topographically specific effects of ELF-1 on retinal axon guidance *in vitro* and retinal axon mapping *in vivo*. *Cell* 86:755–766
9. Rutishauser U, Landmesser L (1996) Polysialic acid in the vertebrate nervous system: a promoter of plasticity in cell-cell interactions. *Trends Neurosci* 19:422–427

Axon Reaction

- Chromatolysis
- Neuronal Changes in Axonal Degeneration and Regeneration

Axon Reflex

Definition

Generally, the term *axon reflex* denotes a neurally mediated effector response that is brought about by the passage of nerve impulses along axons without traversing a synapse, except that between the nerve ending and the effector tissue. Specifically, an axon reflex is elicited by a stimulus that excites afferent neurons which without transmission to efferent neurons modify the activity of effector tissues. The best known example is the cutaneous *flare* response of Thomas Lewis' triple response to irritation or injury. The reddening (flare due to vasodilatation) that spreads beyond a pin-point injury of the skin is explained as the result of axon reflexes between the arborizing collaterals of sensory nerve fibers. When some axon branches are activated by an irritant stimulus, nerve impulses travel centrally to the branching points where they pass antidromically to the other branches and thus back to the skin. Here, periarteriolar branches of sensory neurons can release vasoactive transmitters (e.g., calcitonin gene-related peptide and substance P) and thereby cause arteriolar dilatation.

- Calcitonin Gene Related Peptide CGRP)
- Nociceptors and characteristics
- Substance P

- Neuronal Cell Death and Axonal Degeneration: Neurofilaments as Biomarkers
- Neurons
- Wallerian-Like Degeneration

Axonal Neuropathies

Definition

Subgroup of ►peripheral neuropathies in which the ►myelin sheaths remain intact.

Axonal Pathfinding and Network Assembly

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Synonyms

Growth cone guidance

Definition

For correct functioning of the mature nervous system, precise synapse formation and network assembly during development is required. The neurons, which are the signaling units of the nervous system, possess specialized neurite processes known as dendrites and axons, which are responsible for receiving and sending signals. These neuritic processes, which grow out from the cell body of the neuron during development, must make accurate connections with appropriate targets. The axon in particular, may need to traverse great distances before reaching such targets and the process by which the axon navigates to its eventual destination is known as axonal pathfinding. The structure responsible for this pathfinding task is known as the neuronal ►growth cone [1].

Characteristics

Early Development of the Nervous System – A Prelude to Axon Pathfinding and Network Assembly

The construction of an organ as complex as the human nervous system requires an integrated series of precise developmental steps that precede the formation of connections between maturing nerve cells. These

Axonal Conduction

Definition

- Action Potential Propagation

Axonal Degeneration

Definition

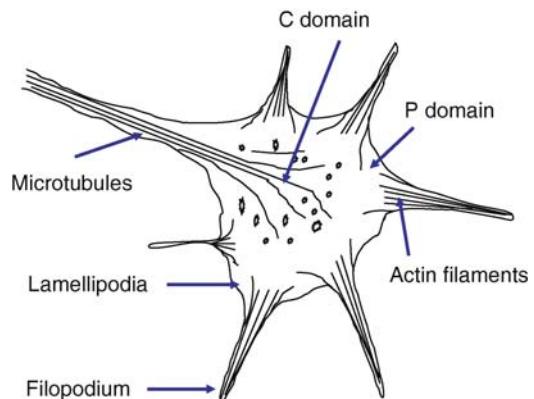
There are two types: (i) Wallerian degeneration occurs distal to a lesion and effectively removes the damaged axon; (ii) dying back neuropathy occurs proximal to the lesion and ultimately causes apoptosis of the neuron.

- Axon Degeneration and Regeneration of Peripheral

connections ultimately lead to the ability of these networks to process information and mediate complex behaviors. Uncommitted ectodermal cells in the future dorsal side of the embryo require factors provided by neighboring mesodermal and endodermal cells to become a columnar neuroepithelium, the neural plate, in a process called neural induction. Cellular shape changes and mitotic activity in this layer of cells leads to the folding up of this plate and formation of a dorsal **►neural tube**. The neural tube contains an inner layer of cells called the germinative or ependymal layer consisting of the mitotically active progenitor cells for both neurons and glia of the brain and spinal cord. As these progenitor cells cease dividing, their fates as specific neuronal cell types or glial cells (**►Radial glia**) are determined by both intrinsic and extrinsic factors in the local environment of the early neural tube. Extrinsic factors include many diffusible molecules, cell surface glycoproteins and extracellular matrix factors (**►Collagens**). These factors influence the array of gene products produced in these now committed progenitors which influence neuronal shape, axonal pathway selection, connectivity and chemistry. Once determined, cells migrate away from the ependymal layer through the ever thickening neural tube, toward their final destinations. At the same time, within the dorsal outermost layer of the tube, a population of cells unique to vertebrates, the **►neural crest cells**, are beginning to migrate along specific paths toward their ultimate destination in the periphery of the developing embryo. Once there, depending upon a mix of intrinsic factors and target-derived signals, they will differentiate into a wide variety of cell types, including autonomic and sensory ganglia as well as peripheral glia (Schwann cells).

Structure of the Growth Cone

The growth cone is a small motile expansion of the cytoplasm at the ends of growing axons and dendrites and was first characterized in the late 1800s by the famous neuroanatomist Santiago Ramon y Cajal. The basic morphology of the growth cone is often described as resembling a hand, though growth cone appearance may vary depending upon its surrounding environment. *In vivo*, growth cones tend to acquire a compact shape, whereas *in vitro*, there is a tendency for the growth cone to splay out and enlarge, sometimes reaching diameters as great as 50 μm for large invertebrate neurons. Structurally, the growth cone is divided into two major domains, the central or C-domain and the peripheral, P-domain. Two characteristic features of the growth cone, the filopodia and lamellipodia, emanate from the P-domain. Filopodia are long, slender protrusions that extend from the growth cone and are important for sensing the external environment, whereas the lamellipodia are flattened veils between the adjacent filopodia. The thicker central (C)



Axonal Pathfinding and Network Assembly.
Figure 1 Schematic of a neuronal growth cone.

domain of the growth cone, unlike the filopodia and lamellipodia, contains organelles, vesicles and **►microtubules** extending into the C-domain from the axonal shaft (**Fig. 1**).

The Cytoskeleton

The growth cone is a highly motile structure, a feature which is dependent on the fact that the cytoskeleton of the growth cone is dynamic in nature [2]. Within the P-domain, extending filopodia contain bundled microfilaments made up of F-actin, the continuing polymerization of which pushes the **►filopodium** outwards. The sheet-like lamellipodia contain a meshwork of short actin filaments, as well as longer, bundled filaments. Microtubules, which are long polymers of α - and β -**►tubulin**, extend down the axon shaft and enter the growth cone, radiating out distally in the C-domain, sometimes forming kinks and loop structures. Microtubules have also been seen entering the P-domain in such a way that they are aligned with a filopodium, even entering the most proximal portion of it. **►Microtubule** growth has a polarity such that polymerization occurs at the “plus-end,” which is directed into the growth cone. Microtubules are the key players in neurite extension, while the actin filaments are more important for filopodia and lamellipodia extension.

The ability of the growth cone to collapse the cytoskeleton in some regions, while constructing new cytoskeletal domains, underlies the motility of the growth cone. Due to the dynamic nature of the cytoskeleton, a host of specialized proteins are needed both to help stabilize, but also remodel the cytoskeleton. Microtubule-associated proteins (MAPs) known to be present in the growth cone include Tau and MAP1B (microtubule stabilizers), MAP2 (a microtubule bundling protein), SCG10 (a microtubule destabilizer) and Ezrin (a linking protein used to join microtubules and actin filaments). A different set of proteins contribute

to actin filament dynamics. These include ADF/cofilin (actin filament depolymerization), α -actinin and fascin (actin filament bundling), and GAP-43 (actin filament length control), among many others [1]. Ultimately, an environmental signal that affects elongation of the axon or growth cone behavior, will somehow regulate the actin and microtubule assemblies described above.

Responses to Environmental Cues

A large number of guidance cues that direct the motile growth cone have now been identified [3,4]. These include cell surface molecules which generally act as short-range signals, or secreted and diffusible molecules that may act as long-range signals. These signals act in either a repulsive or attractive manner. Repulsive signals may cause a growth cone to turn away from the source, whereas attractive signals induce growth cone turning toward the source. An alternative behavior is growth cone collapse, which often results in the growth cone “shriveling up” (and sometimes retracting) in response to a contact-mediated or diffusible inhibitory signal.

The most well-known cell surface molecules that mediate attraction are the ►cell adhesion molecules (CAMs); for example, the cadherins and neural cell adhesion molecule (NCAM). EphrinAs are examples of repulsive cell surface signals that play an important role in retinotectal mapping [5]. Another repulsive surface signal is myelin associated glycoprotein, MAG, which is a component of myelin and can induce growth cone collapse *in vitro*. MAG may be one molecule that prevents neuroregeneration in some animals, (though it is necessary for both forming and maintaining the myelin sheath). Secreted or diffusible guidance signals are numerous and include the well studied netrins, slits, and semaphorins (class 3), but also include ►growth factors such as nerve growth factor (NGF) and brain-derived growth factor (BDNF), classical morphogens such as Wnts and bone morphogenetic proteins (BMPs), neurotransmitters, and extracellular matrix proteins such as the ►substrate adhesion molecules (SAMs), ►laminin and ►fibronectin.

Transduction of Signals

A neuronal growth cone possesses a remarkable sensitivity to chemical gradients of guidance cues and has the capacity to detect a concentration difference of as little as one molecule across its surface [6]. The binding of a guidance cue (or ligand) to a surface receptor on the growth cone generates a signal that is ultimately transduced to the cytoskeleton, but exactly how this occurs is not clear. A number of second messengers have been identified as playing important roles in this process including calcium [7] and the cyclic nucleotides cAMP and cGMP [8]. The role of calcium has been known for many decades and it is generally proposed that global increases in growth cone calcium

regulate the growth of the neurite (►Neurite outgrowth), whereas local asymmetric increases in the growth cone determine the turning response. Studies on the role of cyclic nucleotides have shown that the ratio of these messengers may be one determining factor for the growth cone’s response. For example, studies in *Xenopus* spinal neurons have shown that the direction of growth cone turning in response to the cue netrin-1 is determined by the ratio of cAMP to cGMP, such that a high ratio supports chemo-attraction and a lower ratio, chemo-repulsion. Signaling involving cAMP generally involves the cAMP-dependent protein kinase (PKA) while cGMP involves cGMP-dependent protein kinase (PKG). Both of these kinases are able to affect changes in the cytoskeleton, which is important for the motility of growth cones.

Though most well known guidance factors act by binding to receptors on the surface of the growth cone there are others that may act at the cytoplasmic level and these include nitric oxide, retinoic acid and even a transcription factor, Engrailed-2 (which is internalized by the growth cone). Furthermore, the ability of electric fields to influence growth cone behavior, though not a recent observation, is gaining new attention [9]. Recent research suggests that electric fields may bring about changes in growth cone behavior *via* small GTPases which alter the cytoskeleton. In addition, electric fields may interact with trophic factors such as BDNF and the neurotrophins NT-3 and NT-4, thereby modulating growth cone responses. Table 1 provides some representative examples of guidance factors and their actions on specific cell types.

Switching Responses

Growth cone responses to a particular guidance cue are not rigid or absolute, but can vary, depending on a number of conditions. The response to a guidance cue may be cell-type specific and even then, a single neuron may produce a differing response depending on the types of receptors present, the ratio of second messengers activated, the source of calcium, as well as the age of the cell. It is also very likely that most guidance signals do not act in isolation, but rather that the growth cone integrates many signals at any given moment in time. A growth cone’s response will thus depend greatly on the context in which a specific guidance cue is encountered. A well-known example involves the retinal ganglion cell axons exiting the retina at the optic nerve head, to which netrin-1 serves as an attractive cue. If laminin is ectopically added at the optic nerve head however, netrin-1 is converted to a repulsive cue and the retinal ganglion cell axons fail to exit the eye. When the retinal ganglion cell axons travel from the retina to their targets in the brain, the repulsive guidance cue slit helps to define their pathway by constraining where these axons can grow. However, the

Axonal Pathfinding and Network Assembly. Table 1 Representative examples of chemotropic molecules and their effects on growth cone behavior

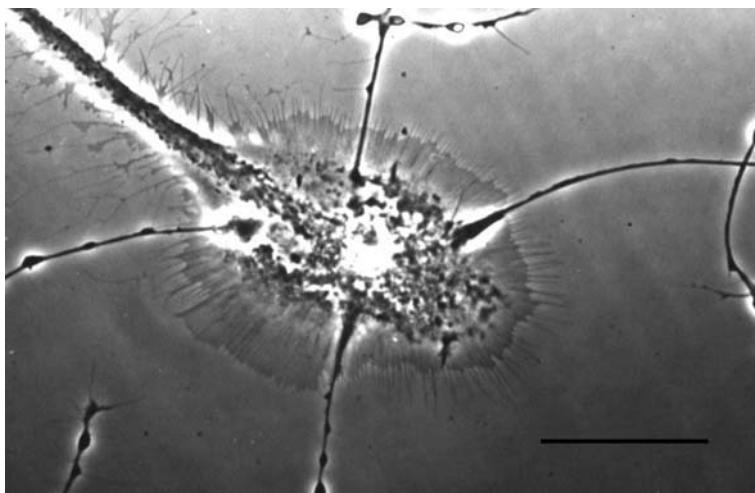
Chemotropic molecule	Response	Cell type
<i>Neurotransmitters</i>		
GABA	Attractive	Rat spinal cord neurons
Acetylcholine	Attractive	<i>Xenopus</i> spinal neurons
Dopamine	Repulsion	<i>Lymnaea</i> PeA neurons
Nitric oxide (high concentration)	Repulsion	<i>Helisoma</i> B5 neurons
<i>Classical guidance molecules</i>		
Netrin-1	Attractive	Chick commissural neurons
Netrin-1	Repulsive	Rat trochlear motor neurons
Semaphorin3A	Repulsive	Rat DRG neurons
Semaphorin3F	Attractive	Rat cerebellar neurons
Slit-2	Repulsive	<i>Xenopus</i> retinal neurons
<i>Neurotrophins</i>		
Nerve growth factor (NGF)	Attractive	Chick DRG neurons
Brain-derived neurotrophic factor (BDNF)	Attractive	<i>Xenopus</i> spinal neurons
<i>Transcription factors</i>		
Engrailed-2	Attractive	<i>Xenopus</i> nasal retinal neurons
Engrailed-2	Repulsive	<i>Xenopus</i> temporal retinal neurons
<i>Morphogens</i>		
BMP-7	Attractive	<i>Xenopus</i> spinal neurons
BMP-7	Repulsive	<i>Xenopus</i> spinal neurons
Retinoic acid	Attractive	<i>Lymnaea</i> visceral F neurons
Wnt-1	Repulsive	Mouse motor cortical neurons
Wnt-4	Attractive	Rat commissural neurons
FGF-2	Repulsive	<i>Xenopus</i> retinal ganglion neurons
FGF-8	Attractive	Rat trochlear neurons
Sonic hedgehog	Attractive	Rat spinal cord neurons
Sonic hedgehog	Repulsive	Chick commissural neurons
<i>Other</i>		
SDF-1 (a chemokine)	Repulsive	Rat cerebellar neurons
Endocannabinoids	Repulsive	Rat cortical interneurons

chemokine CXCL12 (SDF-1) is able to attenuate the repulsive effect of slit, thereby modulating the response of the growth cone. There may also be changes within a growth cone which lead to altered responses to a particular guidance cue. In *Xenopus* spinal neurons, BMP7 is initially attractive but later becomes repulsive. This change is mediated by the insertion of a calcium channel leading to the influx of calcium.

Growth Cone Autonomy

It has become increasingly clear that growth cones are capable of local protein synthesis and that this is likely to contribute to rapid growth cone responses to environmental guidance cues [10]. One example is the requirement for local synthesis of the small GTPase Rho A in the collapsing response of *Xenopus* growth

cones to the inhibitory factor Sema 3A. mRNAs that have been identified in developing axons include β-actin, β-tubulin, RhoA and cofilin, which likely play an important role in local regulation of the cytoskeleton. However, there is also evidence that membrane receptors may be synthesized locally at key developmental stages, such as the insertion of the ephrin receptor EphA2 following mid-line crossing in chick embryos. With local protein synthesis, comes the need for local control over mRNA expression. Localization signals may include “zip-code” sequences present on the mRNA, and control over local translation may involve microRNAs, short polynucleotide sequences that are incorporated into the RNA-induced silencing complex (RISC) and mediate repression of mRNA translation. In addition to local protein synthesis, local



Axonal Pathfinding and Network Assembly. Figure 2 A *Lymnaea* growth cone in cell culture. Photomicrograph of regenerated neuritic processes from individually identifiable cultured neurons taken from the central nervous system of the pond snail, *Lymnaea stagnalis*. The large central growth cone is being contacted by 4 different target cell growth cones. Scale bar = 25 μ m (Spencer and Syed, unpublished).

protein degradation plays an important role in producing some growth cone behaviors.

Experimental Systems Used for Studying Axonal Pathfinding

Axonal pathfinding and growth cone behavior have been studied in many systems including vertebrate models such as chicks and frogs (*Xenopus laevis*) as well as invertebrate models such as worms (*C. elegans*), flies (*Drosophila*) and molluscs (*Aplysia californica* and *Lymnaea stagnalis*) (Fig. 2)).

Perhaps some of the most well-studied systems to date include the role of netrins and their receptors (DCC/UNC5) at the midline in the vertebrate spinal cord, the role of slit and the roundabout (robo) receptor in crossing the midline, and the role of ephrinAs and ephrinBs and their receptors (EphAs and EphBs) in the establishment of topographic projections from the retina to the brain [3].

Target Recognition Precedes Synapse Formation and Network Assembly

At the end of its journey, the neuronal growth cone is required to identify its appropriate target cells or synaptic partners, which include other neurons, glands or muscle cells. In order for correct formation of synapses and network assembly, this target cell selection must be an accurate process. It involves a number of processes that might include branching of the axon, growth cone stalling, increased morphological

complexity of the growth cone, and eventual molecular recognition of the appropriate synaptic target, at which point, the axonal growth cone will eventually form the presynaptic terminal.

Acknowledgements

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References

1. Gordon-Weeks P (2000) Neuronal growth cones. Cambridge University Press, Cambridge, UK
2. Kalil K, Dent E (2005) Touch and go: guidance cues to the growth cone cytoskeleton. Curr Opin Neurobiol 15:521–526
3. Chilton J (2006) Molecular mechanisms of axon guidance. Dev Biol 292:13–24
4. Huber A, Kolodkin A, Ginty D, Cloutier J (2003) Signaling at the growth cone: ligand-receptor complexes and the control of axon growth and guidance. Annu Rev Neurosci 26:509–563
5. Erskine L, Herrera E (2007) The retinal ganglion cell axon's journey: insights into molecular mechanisms of axon guidance. Dev Biol 308:1–14
6. Rosoff W, Urbach J, Esrick M, McAllister R, Richards L, Goodhill G (2004) A new chemotaxis assay shows the extreme sensitivity of axons to molecular gradients. Nat Neurosci 7:678–682
7. Henley J, Poo MM (2004) Guiding neuronal growth cones using Ca²⁺ signals. Trends Cell Biol 14:320–330
8. Piper M, van Horck F, Holt C (2007) The role of cyclic nucleotides in axon guidance. Adv Exp Med Biol 621:134–143

9. McCaig C, Rajnicek A, Song B, Zhao M (2005) Controlling cell behavior electrically: current views and future potential. *Physiol Rev* 85:943–978
10. Hengst U, Jaffrey S (2007) Function and translational regulation of mRNA in developing axons. *Semin Cell Dev Biol* 18:209–215

Axonal Regeneration

Definition

The unique series of steps involved in the reconnection of damaged axons to their targets.

- Axon Regrowth
- Axon Degeneration and Regeneration of Peripheral Neurons
- Peripheral Nerve Regeneration and Nerve Repair

Axonal RNA Translation

- mRNA Targeting: Growth Cone Guidance

Axonal-soma Synapse

Definition

Synapse formed between an axon (presynaptic) and a cell body (postsynaptic).

- Synaptic Transmission: Model Systems

Axonal Sprouting

Definition

The process where fine nerve processes – sprouts - grow out from the intact axons or nerves to make contacts with target cells that have lost their nerve fibers.

- Axonal Sprouting in Health and Disease

Axonal Sprouting in Health and Disease

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Definition

► Axonal sprouting is a process where fine nerve processes – sprouts – grow out from the intact axons to reinnervate denervated muscle fibers. Thereby the sprouting sustains the nerve supply to muscles and, in turn, the ability to move.

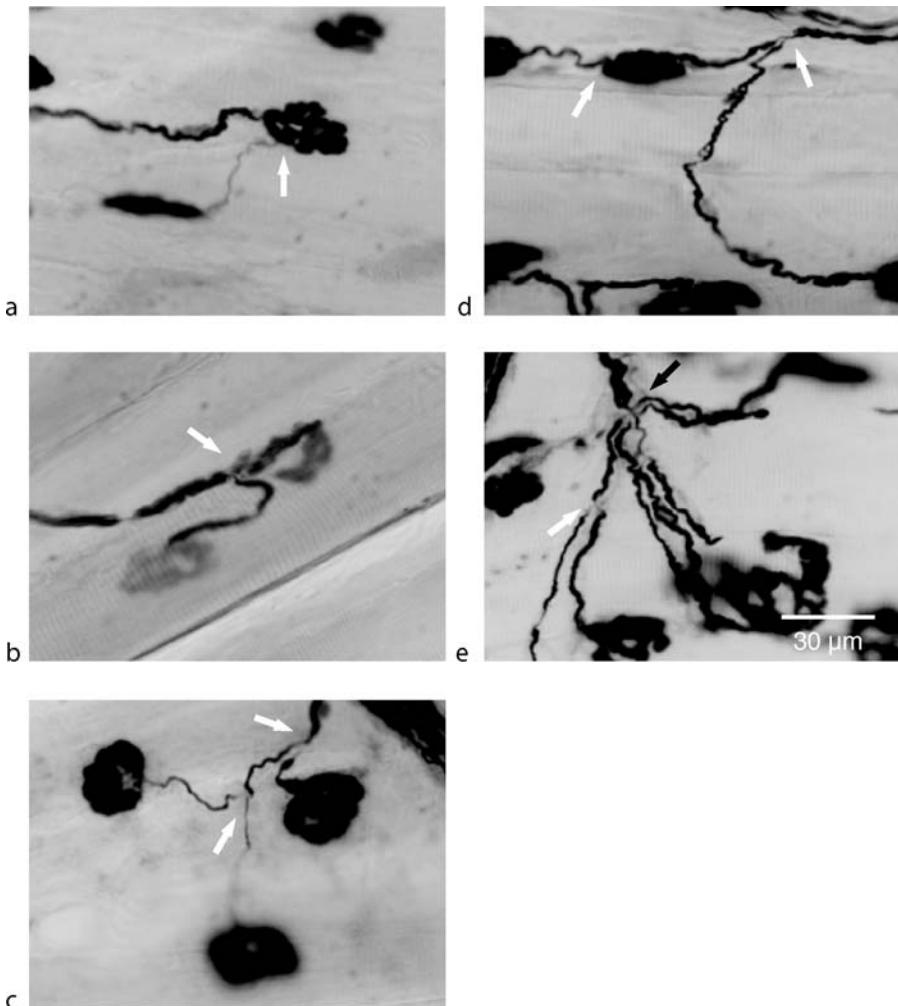
Characteristics

Axon sprouting from intact ►motor units (a ►motoneuron and the muscle fibers that it supplies) commonly compensates for motoneuron loss in aging and/or in diseases such as poliomyelitis and amyotrophic lateral sclerosis, and/or partial nerve injuries due to the loss of axonal contact and/or death of many of the motoneurons [1]. The Schwann cells at the neuromuscular junction, the ►perisynaptic Schwann cells, play an essential role in leading the axon sprouts from intact axons to the denervated muscle fibers to reinnervate them at the neuromuscular junction. Excessive neuromuscular activity interferes with the normal role of the perisynaptic Schwann cells and thereby the enlargement of motor units (the inclusion of more muscle fibers) by sprouting. In ageing and in post-polio syndrome the number of functional motor units declines progressively. High levels of neuromuscular activity may be counter-indicated due to the inhibitory effects of the neuromuscular activity on the perisynaptic Schwann cells and in turn, on the enlargement of the surviving motor units.

Axonal Sprouting and Motor Unit Enlargement

Axonal sprouting is a process where fine nerve processes – sprouts – grow out from the intact axons including ultraterminal (Fig. 1a), preterminal (Fig. 1b), and nodal sprouts to reinnervate denervated muscle fibers (Fig. 1c). More complicated sprouting can occur (Fig. 1d, e).

Each motoneuron normally innervates as few as 10 muscle fibers and as many as thousands, the motoneuron and its muscle fibers being referred to as a motor unit (MU) [1] (Fig. 2). The muscle fibers that lose some of their nerve supply after nerve injuries and/or pathology, or motoneuron diseases, may be reinnervated by axonal sprouts such that the number of muscle



Axonal Sprouting in Health and Disease. **Figure 1** Types of axonal sprouts visualized with silver staining. Ultraterminal (a), preterminal (b) and nodal (c) sprouts. When more extensive sprouting is demanded a single axon can give rise to more than 1 sprout type (Fig. 1d: an ultraterminal and a nodal sprouts) or numerous sprouts of the same type (Fig. 1e: nodal sprouts). (Reproduced from Tam et al. 2001 with permission).

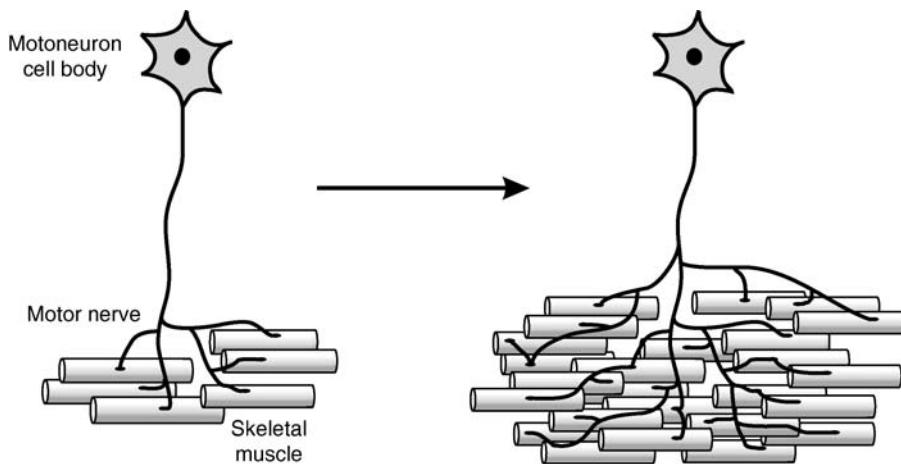
fibers innervated by each motoneuron increases up to a maximum of 8-fold [2]. Hence sprouting is able to compensate for loss of as many as 85% of the normal number of MUs. When less than 20% of functional MUs remain, the maximal capacity of axonal sprouting is exceeded, reinnervation of all denervated muscle fibers fails, and muscle weakness becomes evident [2].

Axonal sprouting is commonly seen to compensate for motoneuron loss at least in part, in aging and/or in diseases such as poliomyelitis and amyotrophic lateral sclerosis (ALS), and/or partial nerve injuries due to the loss of axonal contact and/or death of many of the motoneurons [1]. Although the etiology of these neurodegenerative diseases is not well understood, it has been suggested that the severe debilitation suffered

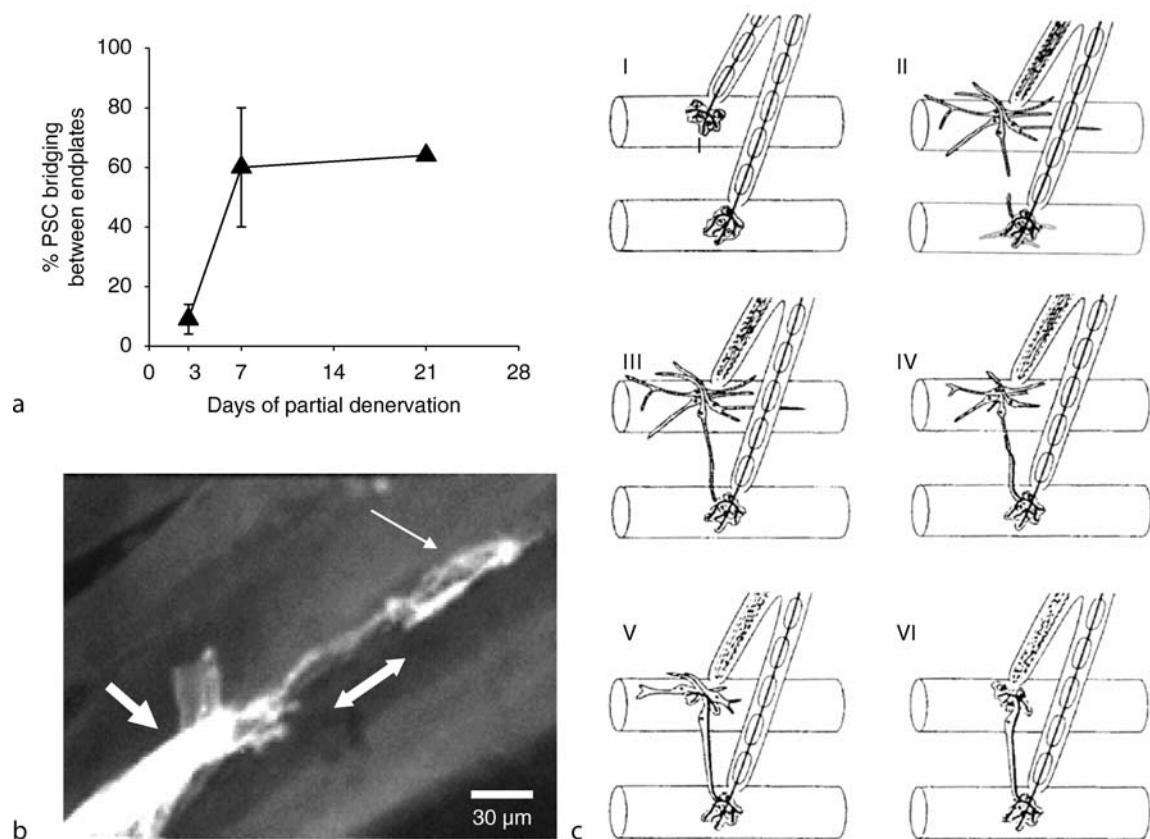
by the patients with these diseases, is a direct consequence of over-exhaustion and subsequent loss of the chronically enlarged MUs.

The Role(s) of Perisynaptic Schwann Cells in Axonal Sprouting

► **Perisynaptic Schwann cells (PSCs)**, which cover the intramuscular nerve terminals, play a critical role in supporting axonal sprouting in partially denervated muscles [3] (Fig. 3). PSCs at both innervated and denervated endplates form cellular processes which bridge between both types of endplates to the maximum level within about 1 week (Fig. 3a). These bridges behave like “tunnels” to guide the growing axonal sprouts to the denervated endplates (Figs. 3a, b). Muscarinic ► **acetylcholine** receptors on the PSCs at the endplate



Axonal Sprouting in Health and Disease. Figure 2 The motor unit and its enlargement by sprouting. Each motoneuron innervates many muscle fibers. When some muscle fibers are denervated by nerve injury or motoneuron disease, axonal sprouts from intact motor units can expand the size of the motor unit (the number of muscle fibers per motoneuron) to a maximum of 3–8 times.



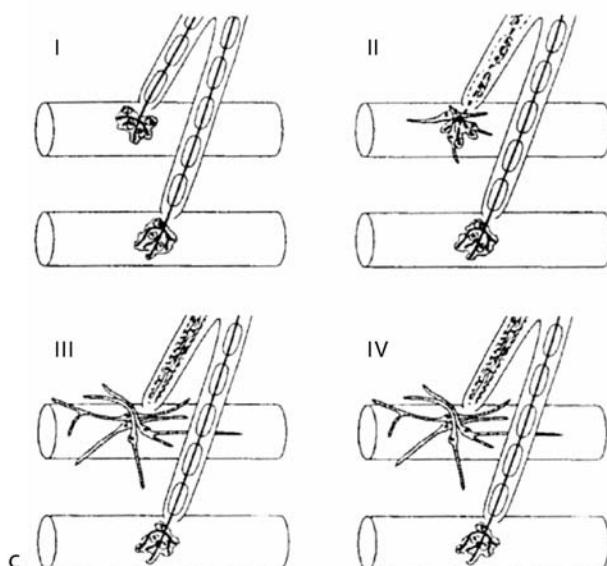
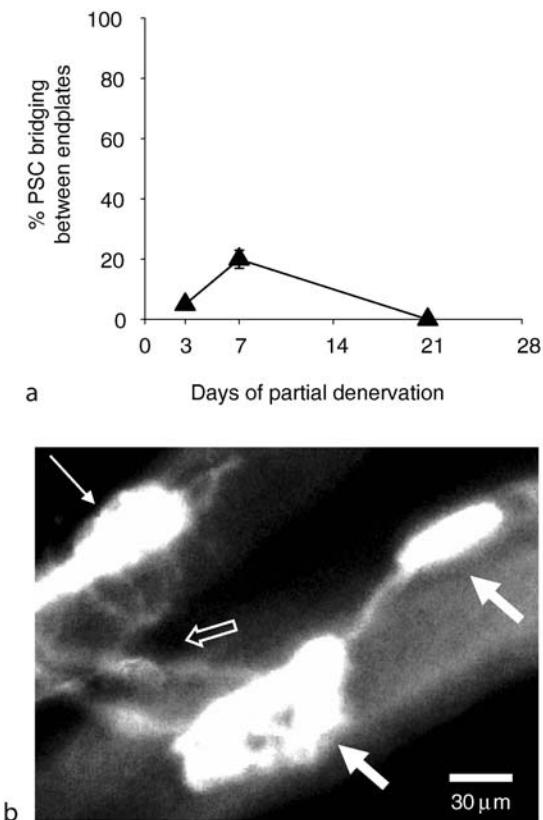
Axonal Sprouting in Health and Disease. Figure 3 Guidance of axonal sprouting by the bridging of perisynaptic Schwann cells (PSCs) between **►muscle endplates**. This bridging reaches a maximum within 1 week of partial muscle denervation (a). PSC processes formed at both innervated and denervated endplates form bridges to direct sprouts to reinnervate denervated endplates (b). Once a sprout reaches its target, the PSC processes withdraw (c). (Reproduced from Tam et al. 2001 with permission).

region of the neuromuscular junction normally respond to acetylcholine released from nerve terminals. The acetylcholine causes an influx of calcium which maintains low levels of glial fibrillar acidic protein (GFAP), in association with the absence of PSC processes (Fig. 3cI) [4]. Upon partial muscle ▶denervation, the PSCs at the denervated endplates, which are no longer exposed to acetylcholine, upregulate GFAP and extend processes (Fig. 3cII). It has been postulated that the short-range diffusible, sprout-inducing stimuli generated from the denervated or inactive muscle fibers, have sufficient influence on the PSCs at the innervated endplates in the partially denervated muscles to trigger these PSCs to produce processes (Fig. 3cII) [1]. The PSC processes that form at both the innervated and the denervated endplates navigate out and bridge to support axonal sprouting (Fig. 3cIII). Once the sprouts make functional neuromuscular contact, the PSCs

withdraw their processes in response to release of nerve acetylcholine (Fig. 3cIV–VI).

Effects of Neuromuscular Activity on Axonal Sprouting

The effect of increased neuromuscular activity on axonal sprouting and MU enlargement was unclear and controversial for many years [3]. In attempt to clarify the controversy, we undertook a thorough evaluation to re-examine this issue. We analyzed MU enlargement in several functionally different rat hindlimb muscles whose extent of ▶partial denervation was determined. This study clearly demonstrated that high daily neuromuscular activity imposed either by functional electrical stimulation (FES) or daily exercise constrained axonal sprouting and MU enlargement [5], by inhibiting PSC bridging (Fig. 4) [3]. The effect of neuromuscular inactivity on axonal sprouting was not inconsequential:



Axonal Sprouting in Health and Disease. Figure 4 Increased neuromuscular activity inhibits bridging of perisynaptic Schwann cells. Daily exercise abolishes the PSC bridging right from the early stage (a). Immunofluorescent labeling with S-100 shows that high neuromuscular activity inhibits formation of PSC processes at innervated endplates (thick arrows) (b). Despite the formation of cellular processes of the PSCs at denervated endplates (thin arrow), the cellular processes entangle around the endplate regions and do not navigate out and in turn, do not bridge (open arrow) with the innervated endplates. A schematic representation details that daily exercise does not impair the formation of perisynaptic Schwann cell processes (C I, II) but effectively prevents the bridging of the processes from innervated to denervated endplates and thereby, prevents sprouting of axons from innervated to denervated muscle endplates (C III–IV) (Adapted from Tam et al., 2003).

blockade of neuromuscular activity using either or ▶ **tetrodotoxin** or ▶ **α -bungarotoxin**, significantly reduced axonal sprouting and MU enlargement in partially denervated muscles [6,7].

Normal Aging: Progressive Loss of Functional MUs in the Context of Progressive Increase in Oxidative Stress and Neuromuscular Activity

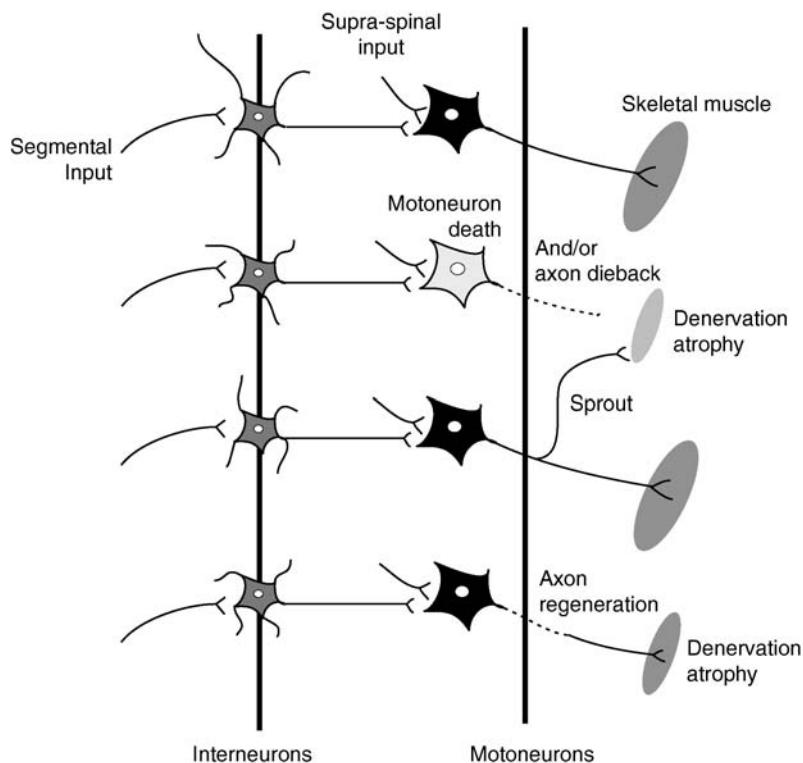
With aging, there is a slow progressive decline in numbers of motoneurons and loss of ventral root axons that becomes more obvious from the sixth decade of life [8]. Oxidative stress progressively rises in the aging motoneurons, oxidative stress being generally defined as a condition where production of reactive oxygen species produced during normal aerobic metabolism overwhelms the endogenous antioxidant defence systems [1]. Ultimately the anti-oxidative enzymes, including copper/zinc superoxide dismutase (SOD1) in the cytoplasm and manganese superoxide dismutase (MnSOD) in the mitochondria, can no longer eliminate reactive oxygen species (superoxide and hydroxyl radicals) effectively. The oxidative stress progressively reduces neuromuscular efficacy. This is followed by loss of functional MUs,

decline in axon transport rates, and transmitter storage and release that eventually reduces the capacity of MUs to sustain stable nerve-muscle connections, the endplate region undergoing progressive expansion and finally axonal die-back [1] (Fig. 5).

As the number of functional MUs declines with age, neuromuscular activity may be counter-indicated due to inhibitory effects of very high neuromuscular activity of progressively fewer intact MUs on the bridging of PSCs between denervated and innervated endplates [5]. Hence the sprouting and enlargement of the intact MUs becomes progressively compromised with age [9].

ALS: Progressive Loss of MUs in Relation to Progressive Increase in Levels of Neuromuscular Activity and/or Oxidative Stress

ALS, unlike acute poliomyelitis, is strictly an adult onset disease, which usually presents in the fifth or sixth decade of life with a survival time of 3–5 years. Approximately 10% of all ALS cases are familial in origin, and of these 20% are linked to mutations in the SOD1 gene. The identified mutations to SOD1



Axonal Sprouting in Health and Disease. Figure 5 Loss of motor units as a result of aging and motoneuron diseases. At the initial stage of ageing and motoneuron disease, motor axons die back and the infected or susceptible motoneurons in the case of poliomyelitis or early stage of ALS, respectively, succumb to cell death. The remaining intact motoneurons enlarge their sizes by axonal sprouting to reinnervate the denervated muscle fibers which have lost their nerve terminals from axonal die-back and undergone denervation atrophy. The axons, which have died back and lost connections with affected muscles may regenerate their axons to reinnervate the denervated muscle.

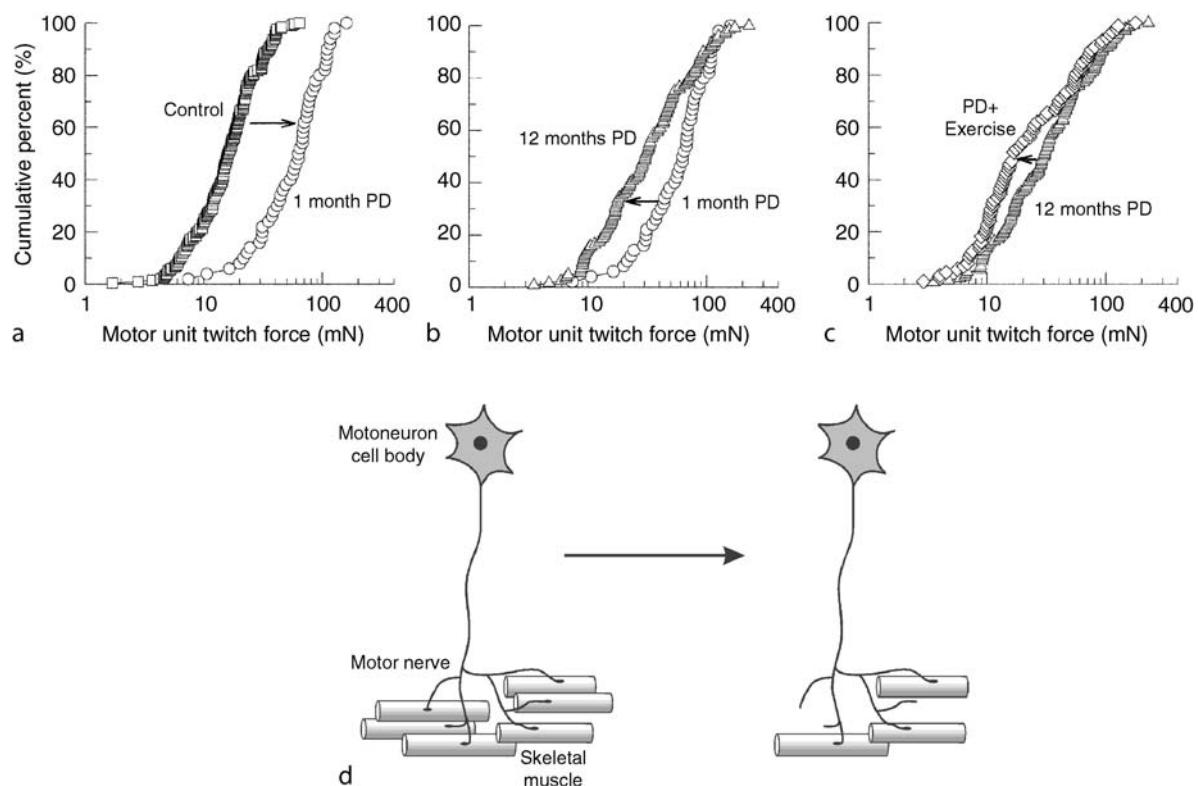
confer a gain of cytotoxic function that increases the susceptibility of motoneurons to cell death, most likely linked to a direct involvement of misfolded SOD1 in the disease process, and through elevations in oxidative stress that can cause cellular damage, ►glutamate excitotoxicity, disruption of calcium homeostasis, motoneuron die-back and their subsequent neuronal death (Fig. 5).

Higher than normal levels of oxidative stress in association with genetic and/or environmental factors in familial and sporadic ALS, may be compounded by age-related accumulations of oxidative stress-induced cellular damage possibly contributing to a rapid decline in the safety factor of neuromuscular transmission and, in turn, the axonal die-back that initiates denervation of motor endplates [1]. The largest motoneurons with the lowest ►oxidative potential [8,10] are likely to be the most vulnerable to oxidative stress. Indeed, these motoneurons are the first ones whose axons die back and whose intact axons progressively fail to sprout effectively. It is only the motoneurons with higher

oxidative capacity that supply the more oxidative muscle fibers that sustain their sprouting capacity [10]. In most muscles that contain relatively few oxidative muscle fibers, there is a rapid attrition of the motoneurons with progressive muscle weakness and paralysis [1].

PPS: Progressive Loss of Enlarged MUs in Relation to Progressive Increase in Levels of Neuromuscular Activity and/or Oxidative Stress

Infection by the polio enterovirus results in extensive axonal die-back and death of many of the affected motoneurons [8] (Figs. 2, 3). While the surviving axotomized motoneurons may regenerate their axons, the remaining intact MUs undergo adaptive sprouting. Both the surviving intact and regenerating MUs enlarge their normal size to a maximum of 5–8-fold to reinnervate those muscle fibers that were denervated by death of their parent motoneurons [1]. The enlarged MUs are able to sustain muscle function for periods of time as long as 25 years or more until the chronically enlarged MUs progressively deteriorate in association



Axonal Sprouting in Health and Disease. Figure 6 Regression in the size of motor units (MUs) in post-polio syndrome (PPS). In a rat PPS model, the maximum enlargement of MU force that is observed a month after partial (a) has receded after 12 months of partial denervation (b). There is a preferential decline of the size of the enlarged MUs at the lower end of the force spectrum, indicating that the least active motoneurons sustain more stable neuromuscular connections. High daily exercise imposed on chronically denervated nerve-muscle connections reduces the size of the enlarged MUs (c) by further destabilizing functional MUs. The destabilization and withdrawal of synaptic contacts by motoneurons in PPS is illustrated figuratively (D).

with the age-related loss of functional MUs. Because the reduced number of functional MUs are unable to enlarge beyond the normal limit of 5–8 fold, muscles become progressively denervated with the onset of muscle fatigue and weakness—post-polio syndrome (PPS) [8] (Fig. 2).

In PPS, the reduced numbers of enlarged MUs that survive the acute phase of the disease become progressively vulnerable to destabilization of nerve terminals and axon die-back, possibly concomitant with an increasing state of oxidative stress in the remaining motoneurons that had sprouted and sustained long-term innervation of large numbers of muscle fibers [1]. As the number of MUs declines, the high levels of neuromuscular activity will compromise the capacity of the surviving motoneurons to undergo sprouting to reinnervate denervated muscle fibers and, in turn, to compensate for the axonal die-back. This was shown in a study using an animal model of PPS in which rat muscles were partially denervated during adulthood and the remaining intact MUs enlarged maximally to compensate for the loss of motoneurons (Fig. 2). The MUs, showed a time-dependent regression of nerve terminals and a reduction in their size 1 year after partial denervation (Fig. 6a, b) [8]. The preferential decline of in the size of the enlarged MUs at the lower end of the force spectrum indicated that the most active MUs progressively failed to reform stable connections and hence the process of axonal sprouting became maladaptive. When these fewer MUs were subjected to high daily neuromuscular activity, significant reductions in MU size were detected (Fig. 6c).

In summary, motor axons can sprout to reinnervate denervated muscle fibers to enlarge MUs up to 8-fold. This compensatory mechanism is compromised by high levels of neuromuscular activity. The effects of this compromise are evident physiologically during the process of aging and, pathologically, in motoneuron diseases where sprouting may become maladaptive with instability and withdrawal of the axon sprouts.

References

1. Gordon T, Hegedus J, Tam SL (2004) Adaptive and maladaptive motor axonal sprouting in aging and motoneuron disease. *Neurol Res* 26:174–185
2. Rafuse VF, Gordon T (1996) Self-reinnervated cat medial gastrocnemius muscles. I. Comparisons of the capacity of regenerating nerves to form enlarged motor units after extensive peripheral nerve injuries. *J Neurophysiol* 75:268–281
3. Tam SL, Gordon T (2003) Neuromuscular activity impairs axonal sprouting in partially denervated muscles by inhibiting bridge formation of perisynaptic Schwann cells. *J Neurobiol* 57:221–234
4. Georgiou J, Robitaille R, Charlton MP (1999) Muscarinic control of cytoskeleton in perisynaptic glia. *J Neurosci* 19:3836–3846

5. Tam SL, Archibald V, Jassar B, Tyreman N, Gordon T (2001) Increased neuromuscular activity reduces sprouting in partially denervated muscles. *J Neurosci* 21:654–667
6. Tam SL, Archibald V, Tyreman N, Gordon T (2002) Tetrodotoxin prevents motor unit enlargement after partial denervation. *J Physiol* 543:655–663
7. Connold AL, Vrbova G (1991) Temporary loss of activity prevents the increase of motor unit size in partially denervated rat soleus muscles. *J Physiol* 434:107–119
8. McComas AJ (2001) Skeletal muscle. Human Kinetics, Champaign, IL
9. Tam SL, Archibald V, Tyreman N, Gordon T (2002) Effect of exercise on stability of chronically enlarged motor units. *Muscle Nerve* 25: 359–369
10. Frey D, Schneider C, Xu L, Borg J, Spooren W, Caroni P (2000) Early and selective loss of neuromuscular synapse subtypes with low sprouting competence in motoneuron diseases. *J Neurosci* 20:2534–2542

Axonal Targeting

► Axon Pathfinding

Axonal Tip

► Growth Cones

Axonal Transport

Definition

Axonal transport is the transport of molecular cargo and organelles bidirectionally within the axon. Anterograde axonal transport carries cargo from the cell body to the periphery, whereas retrograde transport carries materials from the periphery towards the cell body. Neurons need to provide a constant supply of new material to the growth cone and mature synapse. The majority of proteins and all mRNA and membrane are synthesized in the cell body of a neuron, and need to be transported in an anterograde direction down the length of the axon.

Microtubules, oriented in axons with their plus ends distal to the cell body, are known to provide the support on which rapid axonal transport occurs. There are specific microtubule-based molecular motors called

dyneins and kinesins that move cargo towards the minus and plus ends of microtubules, respectively.

- Dynein
- Growth Cones
- Kinesin
- Microtubule

Axonal Wrapping

Definition

Wrapping of axons by glial cells to insulate them from the hemolymph, and to form the Blood-Brain Barrier.

- Blood-Brain Barrier

Axontemesis

Definition

A nerve injury in which axons are interrupted, but with little disruption of the internal connective tissue elements within the peripheral nerve. With this injury severity type, nerve regeneration tends to be excellent.

- Peripheral Nerve Regeneration and Nerve Repair

Axoplasma

Definition

Fluid within an axon.

- Membrane Potential: Basics

Axospinous Synapses

Definition

A synapse that is formed between an axon terminal and a dendritic spine.

- Synaptic Transmission: Model Systems

Axotomy

Definition

Transection or severing of an axon. This type of denervation is often used in experimental studies on neuronal physiology and neuronal death or survival, towards an understanding of nervous system disease.

Ayurveda

Definition

It is a traditional system of Indian Medicine dating back many centuries, and is still popular in India. The Charak Samhita and Sushruta Samhita form the basis of most of the Ayurvedic practices. Surgical procedures are believed to have their origin in Ayurveda, and Sushruta is said to be the Father of Surgery. Charaka has described many herbs for treating various ailments including disorders of the brain. Many modern and standardized herbal products manufactured in India are based on the Ayurvedic principles mentioned in the Charak Samhita.

- Central Nervous System Disease – Natural Neuro-protective Agents as Therapeutics