Cells, Synapses, and Neurotransmitters 4.2

Learning Objectives

- List the four different types of glial cells, recognize their structure, and briefly describe their function
- Contrast the myelin sheath in the CNS and PNS
- Identify soma, dendrites, axon, myelin sheath, node of Ranvier and axon hillock
- Define the synapse and distinguish between electrical and chemical synapses
- List in order the events that occur in chemical synaptic transmission, including the shut-off of the signal
- Describe the major mechanisms for removing neurotransmitters
- Describe the recycling of synaptic vesicles
- Distinguish between ionotropic and metabotropic transmitters
- Define pre-synaptic and post-synaptic membranes or cells
- Describe the conductance changes underlying EPSPs or IPSPs
- Describe fast and slow axonal transport

NERVOUS SYSTEM BEHAVIOR DERIVES FROM CELL BEHAVIOR

An axiom of physiology states that organ physiology derives from cell physiology: the summed behavior of its component cells determines the overall behavior of an organ. How this summation occurs is complex and in many cases our understanding of it is inadequate. The topology of the system, which is the connectedness of the cells and their spatial arrangement, plays an important role in determining how the cells interact to produce organ behavior. Cells in the central nervous system (CNS) are organized in clear spatial patterns. Although it appears that these spatial patterns are extremely important, how they produce their desired effects is not so easily discerned. Regardless of our present inability to show how neuronal function produces higher brain function, most neurophysiologists adhere to the axiom that *all* brain behavior has a cellular basis.

NERVOUS TISSUE IS COMPOSED OF NEURONS AND SUPPORTING CELLS

Neurons are the "functional units" of the nervous system. These cells receive inputs, make a "decision" based on these inputs, and transmit "information" on to other cells. They are characterized by their ability to produce action potentials in response to inputs. The action potentials are useful because they allow one part of the cell to communicate with its extreme edges within a few milliseconds, even though the extreme edges could be as much as a meter away. There is no faster way for a physiological signal to travel from one part of the body to another. There are about 10^{11} of these neurons, distributed among a variety of neuron types. The other category of cells in the nervous system is the supporting cells. These cells actually comprise the major part of the nervous system, outnumbering the neurons 10 to 1. There are four major types of glial cells in the CNS and another type in the peripheral nervous system (PNS). There are collectively called **neuroglia**, which literally means "nerve glue."

GLIAL CELLS PROTECT AND SERVE

In the CNS, there are four distinct types of neuroglial cells. These comprise the following: (A) **ependymal cells**; (B) **astrocytes**; (C) **oligodendroglia**; and (D) **microglial** cells.

Ependymal cells are cuboidal epithelial cells that line the internal cavities of the ventricles of the brain and the central canal of the spinal cord. They contribute to the formation of cerebrospinal fluid. Ependymal cells have cilia that project into the CSF and help circulate it. Neurons in the adult lose their mitotic capabilities so that destruction of neurons results in irreplaceable loss of neurons. However, the glial cells retain mitotic capabilities and so they can replace lost glial cells. Recent studies suggest that ependymal cells may serve as stem cells not only for lost glial cells but also to replace neurons (see Figure 4.2.1).

The word **oligodendroglia** comes from the roots for "few," ("oligo"), "branches" ("dendro"), and "glue" ("glia"). This describes the role of these cells, which is to form the myelin sheaths around a few axonal processes. These cells send out large flat branches of cytoplasm that wrap around axons in the CNS and in the spinal

DOI: http://dx.doi.org/10.1016/B978-0-12-800883-6.00034-3

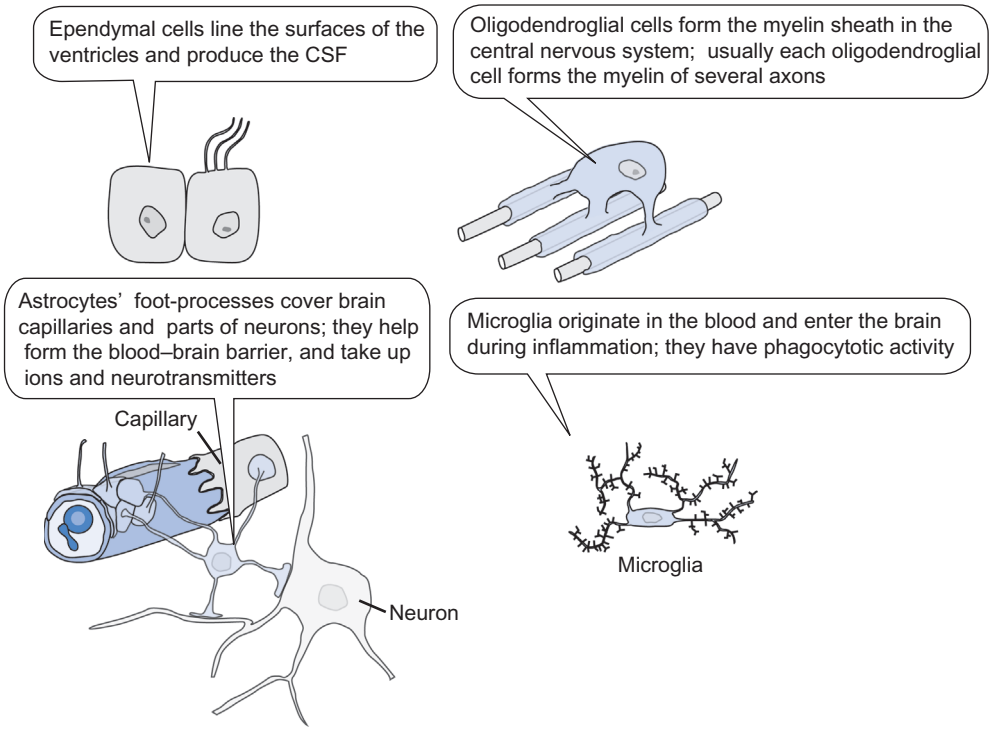

FIGURE 4.2.1 Types of neuroglial cells. Ependymal cells are ovoid or cuboidal cells that line the ventricles and produce the cerebrospinal fluid. Oligodendroglial cells extend their cytoplasm around axons to form an insulating myelin sheath in the brain and spinal cord. In the PNS, Schwann cells form myelin. Astrocytes are star-shaped cells that send out processes to envelope capillaries and neurons. Astrocytes in the white matter are typically fibrous astrocytes; those in gray matter are protoplasmic astrocytes. Microglia do not derive from the same embryonic tissue as neurons, but instead derive from the blood.

cord. The glial cells squeeze out the cytoplasm and form an insulating sheath of coiled cell membranes. In cross sections in electron micrographs, these coils appear to be stacks of membrane. The stacked membranes insulate the axon's plasma membrane from the external solution, markedly increasing the resistance between axoplasm and the extracellular fluid and decreasing the electrical capacitance. These effects increase the length constant and the speed of conduction of action potentials (see Chapter 3.3). Small gaps, the **nodes of Ranvier**, separate the cell process of one oligodendroglia from the next. Regenerative currents flow across the **axolemma**, the plasma membrane of the axon, only at the nodes. In the PNS, the cells that form myelin are called **Schwann cells**. Figure 4.2.2 illustrates how the myelin sheath is formed and the nodes of Ranvier in the CNS and PNS.

Astrocytes derive their name from their star shape. There are two basic forms: **fibrous astrocytes** have many filaments in their cytoplasm and they are found in bundles of axons of myelinated fibers in the white matter of the brain; **protoplasmic astrocytes** have fewer filaments and are found in the gray matter. Astrocytes perform a number of functions:

1. Astrocytes provide a kind of scaffold for the proper generation of spatial relationships of neurons during development and for the maintenance of this relationship during adulthood.
2. Astrocytes interact with the capillaries within the CNS to form tight junctions, which make up the blood–brain barrier. The astrocytes send out foot processes to cover the capillaries, reinforcing the tight junctions.
3. Astrocytes help shut off neurotransmission by taking up released neurotransmitters such as **GABA** (gamma amino butyric acid) and **glutamate**. They degrade the neurotransmitters into materials that can be used to resynthesize the neurotransmitters in the neurons.
4. Astrocytes take up K^+ released from the neuron during repolarization after the action potential. Most of the time the Na^+–K^+ ATPase returns the Na^+ that entered the neuron and the K^+ that left it during the action potential. During high activity the Na^+–K^+ ATPase can be outpaced, so K^+ builds up in the Extracellular fluid (ECF). Removal of the excess K^+ helps keep the resting membrane potentials at the proper level so that neuronal activity can continue.
5. After injury to areas of the brain, **reactive astrocytes** appear that **phagocytose** cellular debris. Phagocytosis refers to "cell eating" and describes the clean up of cellular debris. Together with fibroblasts, the astrocytes form glial scars.
6. Astrocytes contain the enzyme **carbonic anhydrase**, which speeds up the equilibrium between dissolved CO_2 and carbonic acid, H_2CO_3, which promptly dissociates into HCO_3^- and H^+. By speeding up the reaction, astrocytes help regulate the pH of the interstitial fluid.

Unlike the other glial cells, **microglia** originate from the blood and migrate into the brain when the brain is damaged. They remove cellular debris by phagocytosis.

NEURONS DIFFER IN SHAPES AND SIZE

The common features of all neurons include the following: (a) the cell body, or **soma**; (b) processes that gather information either from a sensory device or from other neurons; and (c) one or more processes that convey excitation either towards other neurons or towards

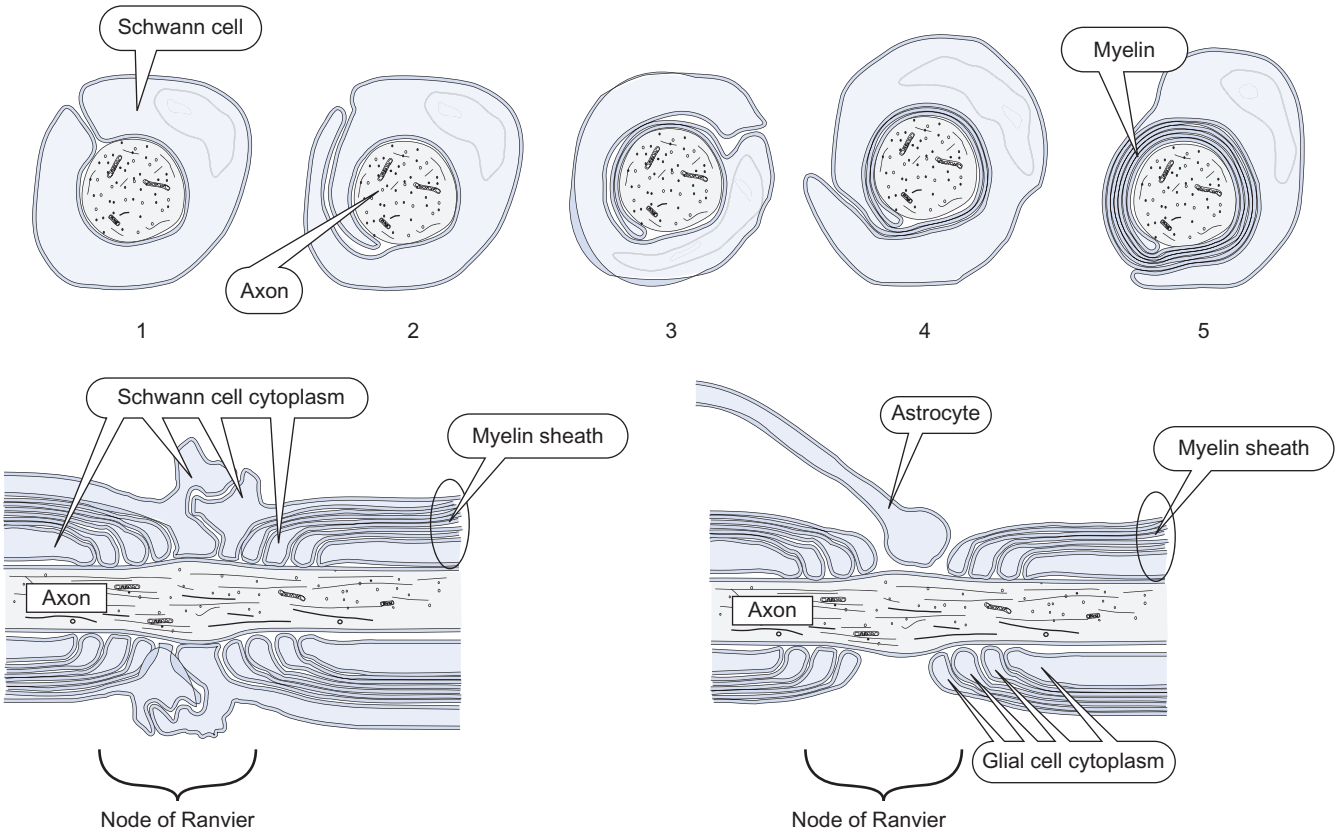

FIGURE 4.2.2 Stages in the formation of myelin by Schwann cells. Schwann cells wrap around axons in the PNS, forming myelin by the compact stacking of their cell membranes. Although the myelin is actually a spiral stack of Schwann cell membranes, cross sections appear as stacks. In the CNS oligodendroglial cells form myelin around several axons. The lower illustrations show longitudinal sections of myelinated nerves in the PNS and CNS. At the node of Ranvier, the axon has access to ions in the extracellular fluid.

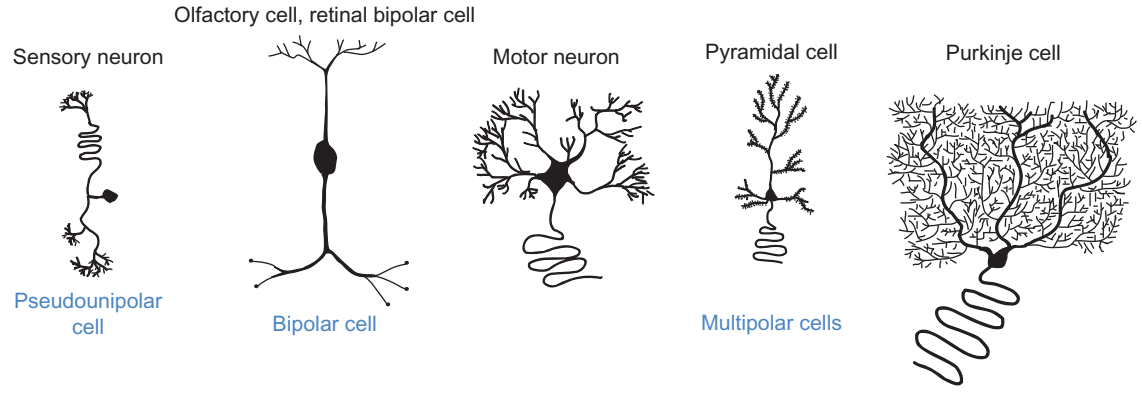

FIGURE 4.2.3 Drawing of various neurons. The sensory neuron is typical of somatosensory neurons in the skin. It is a pseudounipolar neuron because one process exits the cell body, but it divides into a sensory branch that reaches the periphery and a central branch that makes connections to neurons in the CNS. Cells in the olfactory epithelium, in the eye, and in the ear are bipolar neurons and make connection between sensory stimuli (odorants, light, and sound, respectively) and sensory areas of the brain along cranial nerves I, II, and VIII, respectively. Examples of multipolar neurons include the motor neuron, an efferent neuron found in the ventral horn of the spinal cord; the pyramidal cell, an interneuron in the cerebral cortex; and a Purkinje cell, an interneuron found in the cerebellum.

effector cells in muscles or glands. The soma surrounds the cell nucleus, or **karyon**, and so sometimes the soma is referred to as the **perikaryon**. Nerve cells come in a variety of shapes and sizes that can be categorized according to their processes (**unipolar**, **bipolar**, or **multipolar**) or according to their function (**sensory**, **interneurons**, and **efferent neurons**). A variety of names are given to the many varieties of specific cell types found in specific locations in the brain. Examples of these are the Purkinje cells of the cerebellum and pyramidal cells of the cerebral cortex, which are interneurons, and the lower motor neurons in the ventral horn of the spinal cord, which are efferent neurons. Figure 4.2.3 shows examples of some different neurons.

INPUT INFORMATION TYPICALLY CONVERGES ON THE CELL AND OUTPUT INFORMATION DIVERGES

A "typical" nerve cell (Figure 4.2.4) has multiple dendrites and a single axon that branches to form collaterals near the point of termination. This typical nerve cell forms junctions with other neurons by closely apposing its axonal end feet to the membrane of the other cell, forming junctions called **synapses**. Typically, information transfer across synapses is unidirectional. The cell sending the message is the **pre-synaptic cell**, and the cell receiving it is the **post-synaptic cell**. The dendrites receive inputs from a staggeringly large number of sources and its output diverges onto the set of cells with which it forms synapses. Integration of signals on the input side makes use of **temporal summation** and **spatial summation**, as discussed previously in Chapter 3.6. Spatial summation depends heavily on the location of synapses with respect to the site of initiation of the action potential. Figure 4.2.5 shows that synapses occur on almost any neuronal surface. Synapses are named for the anatomical parts that participate in their formation. **Axosomatic** synapses occur between a pre-synaptic axon and a post-synaptic soma; **axodendritic** synapses between an axon and a dendrite; **axoaxonic** synapses between an axon and another axon; **dendrodendritic** synapses occur between two dendrites; **axoextracellular** synapses have no post-synaptic membrane—the axon dumps its transmitter into the extracellular fluid; and in **axosecretory** connections the axon dumps its transmitter into the blood. Sometimes axoaxonal synapses occur close to the point at which an axon makes another axoaxonal connection. These are called **pre-synaptic connections**.

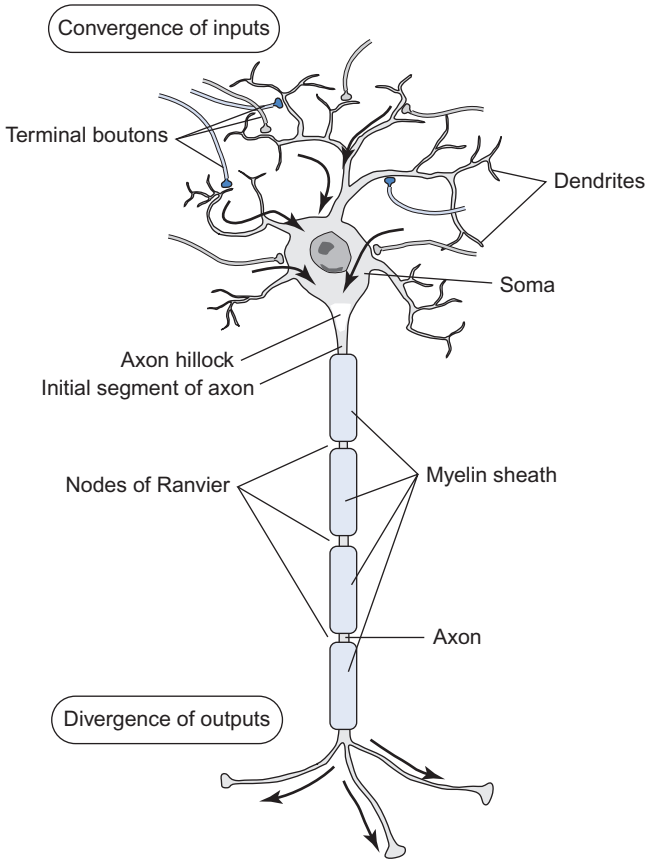

FIGURE 4.2.4 Structure of a "typical" nerve cell. The soma, or cell body, contains the organelles associated with protein synthesis including the nucleus, nucleolus, nuclear membrane, rough and smooth endoplasmic reticulum, and Golgi apparatus. The dendrites are long extensions of the soma that generally receive inputs, which are then integrated in the soma. Action potentials are initiated in the axon hillock, a clear, cone-shaped region of the cytoplasm where the initial segment of the axon leaves the soma. The axon may branch many times and produce hundreds of terminals that end either on other neurons or on effector cells. Thus, the neuron converges inputs into a single effect—the firing of action potentials along the axon, and it diverges its output onto a number of effector cells.

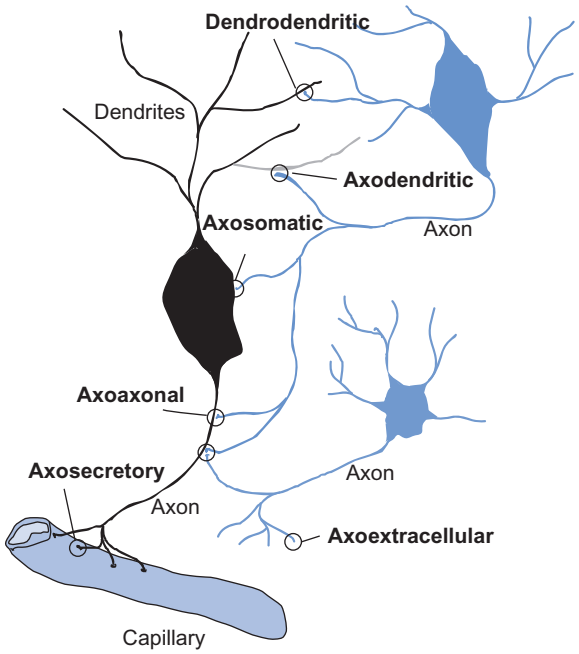

FIGURE 4.2.5 Locations of synapses. Synapses can occur between two dendrites on different cells (dendrodendritic); between an axon and a dendrite (axodendritic); between an axon and a soma (axosomatic); between an axon and another axon (axoaxonal); between an axon and another axon near a synapse onto a third axon (a pre-synaptic axoaxonal connection); between an axon and the extracellular fluid (axoextracellular); and at an axon terminus on a blood vessel (axosecretory).

CHEMICAL SYNAPSES ARE OVERWHELMINGLY MORE COMMON

The root word for "synapse" means "connection." There are two basic kinds of synapses: **chemical synapses** and **electrical synapses**. In electrical synapses, the membranes make very close approach and in electron micrographs appear to be fused, and there is a direct electrical connection between the two cells. Electrical synapses form when a **connexin** hexamer on one cell membrane joins up with a second connexin hexamer on the other cell membrane. The connexin hexamer forms a pore that allows low-molecular-weight materials such as ions (Na^+, K^+, and Ca^{2+}) and signaling molecules such as

cAMP and cGMP to pass from one cell to another. Electrical events such as depolarization, hyperpolarization, or an action potential are readily transferred from one cell to another through the channels formed by the aligned connexins. The close juxtaposition of these membranes is actually accomplished through multiple connexins, and the structure is called a **gap junction**. These synapses are bidirectional.

In chemical synapses, there remains some separation between the pre-synaptic and post-synaptic membrane, typically on the order of 50 nm, but it can be as large as 150 nm. The transmission of excitation across the gap in chemical synapses occurs by the fusion of vesicles containing neurotransmitter with the pre-synaptic membrane. The chemical released into the gap diffuses to the post-synaptic membrane where it binds to specific receptors in that membrane. The effect of the neurotransmitter on the post-synaptic cell depends on the neurotransmitter and on the receptor. Chemical synapses are by far more numerous than electrical synapses. Typically, **transmission across chemical synapses is unidirectional** because the vesicles containing neurotransmitter must be present on the pre-synaptic side. By this criterion, electron micrographs reveal that some synapses appear to be bidirectional. They in fact comprise two adjacent unidirectional synapses. Figure 4.2.6 illustrates the types of synapses.

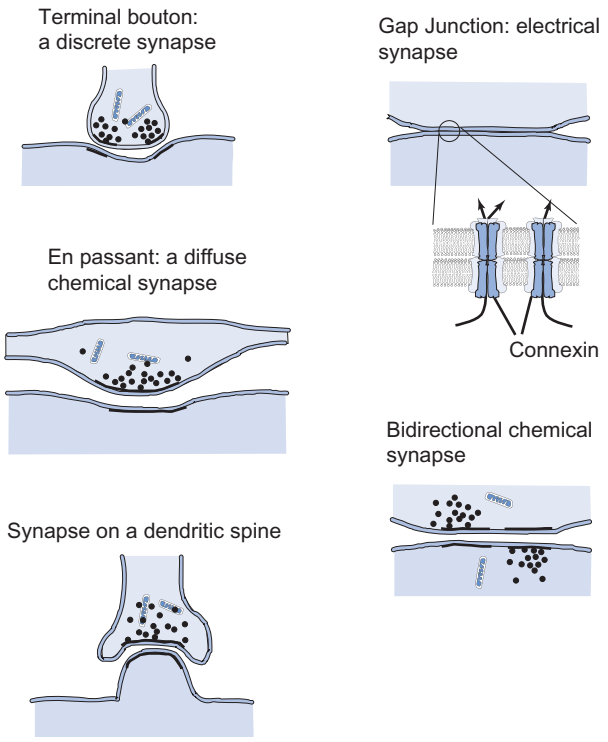

FIGURE 4.2.6 Different types of synapses. Synapses can be either chemical or electrical. Chemical synapses transmit excitation across the gap between cells by the fusion of vesicles with the pre-synaptic membrane and diffusion of transmitter to the post-synaptic cell membrane. Electrical synapses occur where the pre-synaptic cell membrane fuses with the post-synaptic cell membrane, so that diffusable ions and other small molecular weight materials can pass from one cell to the other. The fusion of these membranes requires lining up of connexin hexamers in the two membranes, and these connexins form the pore through which low-molecular-weight materials diffuse. Chemical synapses can be discrete, meaning that the release and reception of neurotransmitter is highly localized or diffuse. Diffuse chemical synapses usually have a wider gap between the cells and the receptors for the neurotransmitters are more spread out.

Synaptic transmission requires modifications of the pre-synaptic membrane. The pre-synaptic cell has an accumulation of vesicles containing neurotransmitter in the vicinity of the synapse and has an accumulation of proteins necessary for the fusion of these vesicles with the pre-synaptic membrane. This produces an electron-dense area on the pre-synaptic membrane called the **active zone**. The post-synaptic cell is also modified: it has an accumulation of receptors for the neurotransmitter.

Ca^{2+} SIGNALS INITIATE CHEMICAL NEUROTRANSMISSION

There are a variety of neurotransmitters, and their effects on the post-synaptic cell depend on the receptors there. Synaptic transmission follows the same general plan for all of the neurotransmitters. In the pre-synaptic terminal, tiny membrane-bound spheroids sequester the transmitter into an internal compartment, separate from the cytosol in the pre-synaptic terminal. These are **synaptic vesicles**. When an action potential invades the terminus, it triggers a series of events, beginning with increasing intracellular [Ca^{2+}] from depolarization opening voltage-dependent Ca^{2+} channels, which causes the synaptic vesicle to fuse with the pre-synaptic cell membrane, releasing the neurotransmitter into the gap between the cells (see Figure 4.2.7).

VESICLE FUSION USES THE SAME MOLECULAR MACHINERY THAT REGULATES OTHER VESICLE TRAFFIC

Synaptic vesicles appear to come in two major types: small synaptic vesicles (SSVs) and large dense core vesicles (LDCVs). The differences between SSVs and LDCVs are noted in Table 4.2.1. The kinetics of release vary markedly between the two but nonetheless they both appear to use the same machinery that is used for trafficking of vesicles throughout the cell. The mechanism involves an estimated 25 different proteins in the cytoplasm, vesicle membrane, and pre-synaptic membrane and is called the **SNARE hypothesis**. **NSF** (*N*-ethylmaleimide-sensitive factor) is an ATPase that is attached to vesicles by **SNAP** (soluble NSF attachment protein). **Synaptobrevin** (a member of the v-SNARE family; v for vesicle membrane, SNARE for SNAP receptor) binds to vesicles and also binds to **synaptotagmin** on the vesicles. Synaptotagmin binds Ca^{2+} and confers Ca^{2+} sensitivity to vesicle fusion. A trimer of **syntaxin** (a member of a family of t-SNARE; t for target) binds to the pre-synaptic membrane along with **SNAP-25.** The t-SNARE and v-SNARE spontaneously coil up in an exergonic reaction that forces the vesicle towards the target. v-SNARE and t-SNARE proteins interact selectively, which allows for the same general machinery to be used in vesicle trafficking throughout the cell. The

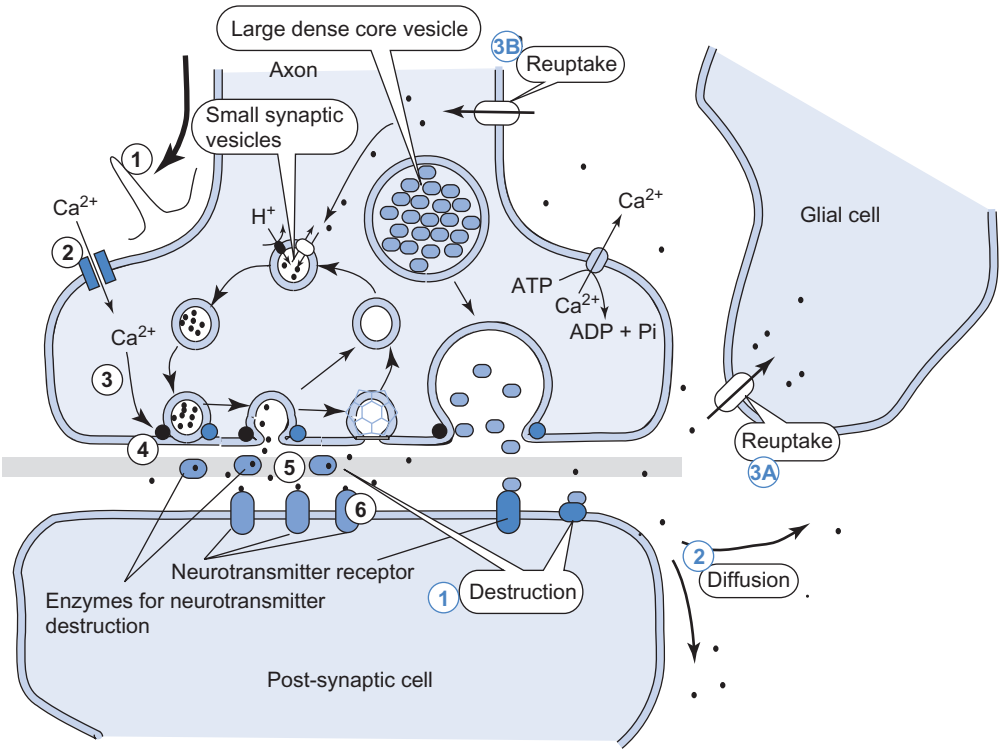

FIGURE 4.2.7 General mechanisms for the origin and shut off of neurotransmission. Neurotransmitters are stored in two types of vesicles: small synaptic vesicles and large dense core vesicles. Both appear to use the same machinery for release of their contents, though the kinetics differs. An action potential that is conducted into the pre-synaptic terminal (1) opens voltage-gated Ca^{2+} channels. (2) This lets Ca^{2+} into the cell and increased cytosolic $[Ca^{2+}]$ (3) binds to synaptotagmin, which causes fusion of vesicles with the pre-synaptic membrane. (4) The neurotransmitter diffuses across the gap (5) and binds to receptors on the post-synaptic cell membrane. (6) The effect of the neurotransmitter depends on the receptor. The neurotransmitter signal is shut off by enzymatic destruction of neurotransmitter (blue 1), diffusion away from the receptors (blue 2), or by reuptake by glial cells or the pre-synaptic cell (blue 3A and 3B).

TABLE 4.2.1 Comparison of Small Synaptic Vesicles (SSVs) with Large Dense Core Vesicles (LDCVs)

Characteristic	SSVs	LDCVs
Size (nm)	50	100–300
EM morphology	Clear particle	Dense core
Neurotransmitters	Acetylcholine, glutamate, glycine, GABA, ATP	Amines (catecholamines, serotonin, histamine), peptides
Release kinetics	0.2 ms after single action potential	>50 ms after repetitive stimulation
Distance from Ca^{2+} channel (nm)	20	300
Vesicle recycling	Local recycling	Slow endocytosis
Location	Made in nerve terminals	Homogeneously distributed

spontaneous fusion is regulated by three other proteins: SM proteins bind to the t-SNAREs, and then complexin activates but clamps the proteins to prevent premature fusion. Lastly, synaptotagmin binds Ca^{2+}, when it rises to signal neurotransmission, and reverses the clamping action of complexin. The coiling of the synaptobrevin and syntaxin is reversed by NSF, which uses the energy of ATP hydrolysis to uncoil the proteins. See Figure 4.2.8.

Ca^{2+} EFFLUX MECHANISMS IN THE PRE-SYNAPTIC CELL SHUT OFF THE Ca^{2+} SIGNAL

Increased intracellular $[Ca^{2+}]$ signals neurotransmitter release. The plasma membrane **Ca^{2+}-ATPase (PMCA)** and a plasma membrane **Na^+–Ca^{2+} exchanger (NCX)** expel the Ca^{2+} that entered over the voltage-dependent Ca^{2+} channel, returning cytoplasmic $[Ca^{2+}]$ to normal and shutting off further neurotransmission.

REMOVAL OR DESTRUCTION OF THE NEUROTRANSMITTER SHUTS OFF THE NEUROTRANSMITTER SIGNAL

Neurotransmitters bind to their receptor by mass action. This principle states that the rate of binding is proportional to the concentration of free ligand (neurotransmitter) and free receptor, and the rate of unbinding or desorption is proportional to the concentration of bound ligand. This is stated succinctly in the equations

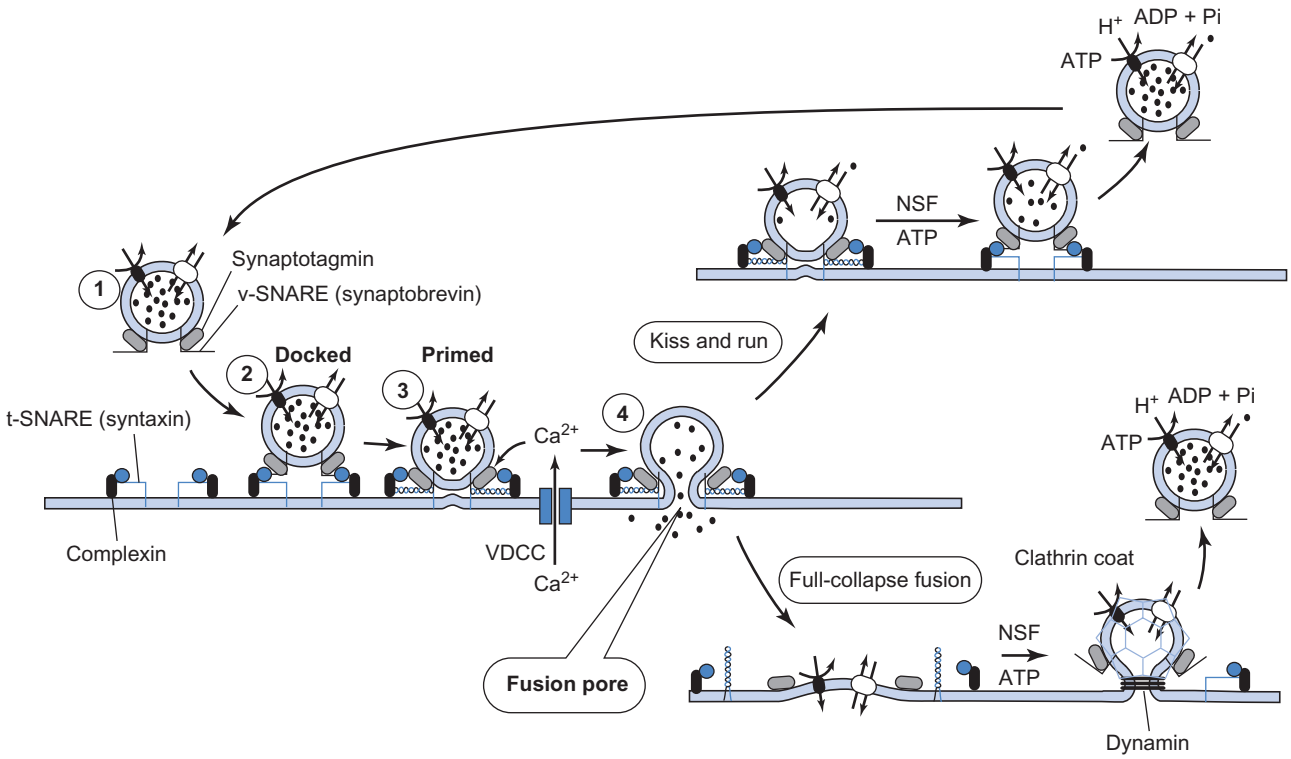

FIGURE 4.2.8 Molecular mechanism for vesicle fusion and recycling. Vesicle membranes have a different composition from the plasma membrane. Synaptobrevin, a v-SNARE (1), interacts with syntaxin, a t-SNARE (2) and coils up, bringing the vesicle close to the plasma membrane (3). This constitutes docking of vesicles and then priming for fusion. Complete fusion is prevented by SM protein Munc18-1 and complexin. Synaptotagmin, bound to the vesicle and interacting with SNAP-25 and syntaxin, binds Ca^{2+} and upon doing so releases the complexin clamp and the vesicles form a fusion pore (4). Recycling of membranes appears to have a fast mode and a slow mode. The fast mode reverses the fusion pore without a full collapse and fusion of the vesicle with the pre-synaptic membrane. When vesicles fully fuse, vesicle membrane is retrieved by endocytotic mechanisms, involving the formation of a clathrin coat and using dynamin to pinch off the endocytotic vesicle. Vesicles reload with neurotransmitter by secondary active transport powered by the vacuolar H^+-ATPase.

$$L + P \overset{k_{on}}{\rightarrow} L \cdot P$$
$$L \cdot P \overset{k_{off}}{\rightarrow} L + P \qquad [4.2.1]$$

Thus, the occupancy of the receptor P with the neurotransmitter L will decrease only when the free ligand concentration falls. Lowering the concentration of free neurotransmitter in the synaptic gap, therefore, will shut off the continued effect on the post-synaptic cell. As shown in Figure 4.2.7, there are three general ways to achieve this end: (1) destruction of the neurotransmitter by degradative enzymes; (2) diffusion of the neurotransmitter away from the post-synaptic receptors; and (3) reuptake of the neurotransmitter either by the pre-synaptic terminal or by other cells.

THE PRE-SYNAPTIC TERMINAL RECYCLES NEUROTRANSMITTER VESICLES

Each action potential results in the fusion of a large number of synaptic vesicles. If the vesicles fully fuse with the pre-synaptic membrane, the vesicle pool becomes partially depleted, the area of the pre-synaptic membrane is increased, and the character of the pre-synaptic membrane changes because the vesicles have a different composition. It appears there are two ways to avoid this problem. First, the vesicles may not fuse completely with the pre-synaptic membrane, but instead "kiss and run": they form a fusion pore that allows neurotransmitter to escape, but the fusion pore is not expanded and instead closes off and the vesicle is released to refill with neurotransmitter. Second, complete fusion of vesicles can be reversed by slow endocytosis involving clathrin coats and dynamin pinching off the endocytosing vesicles. These processes are shown schematically in Figure 4.2.8.

IONOTROPIC RECEPTORS ARE LIGAND-GATED CHANNELS; *METABOTROPIC RECEPTORS* ARE GPCR

The effects of neurotransmitters on the post-synaptic cell are mediated by the receptors and not by the neurotransmitters themselves. The neurotransmitters *activate* the receptors to exert their effects. There are two general classes of receptors. The ionotropic receptors are ligand-gated ion channels, as described in Chapter 2.8, whereas the metabotropic receptors are G-protein-coupled receptors (GPCRs). The ionotropic receptors operate very rapidly, causing membrane potential change within 0.1–2 ms. The metabotropic receptors take longer to activate, but their effects can

remain activated far longer because metabotropic receptors can turn on phosphorylation of channels that remains until they are dephosphorylated.

ACETYLCHOLINE BINDS TO *NICOTINIC RECEPTORS* OR *MUSCARINIC RECEPTORS*

A classic example of receptors that we have already discussed is the **nicotinic receptor** at the neuromuscular junction (see Chapter 3.6). The nicotinic receptor derives its name from its stimulation by **nicotine**. This receptor is a complex of five subunits with the composition $\alpha_2\beta\gamma\delta$. Each of the two α subunits contains a binding site for acetylcholine, the ligand that binds to this receptor. When both α subunits bind acetylcholine, the receptor changes its conformation, opening a large conductance pathway for cations. Because Na^+ is furthest away from its equilibrium potential and its concentration is higher, most of the current when the nicotinic receptor opens is carried by Na^+ influx. The result is a depolarization of the post-synaptic membrane.

Acetylcholine also binds to a class of receptors that are coupled to heterotrimeric G-proteins whose general mechanism was discussed in Chapter 2.8. These are **muscarinic receptors** because **muscarine** is an agonist for this receptor. There are at least five different varieties of muscarinic receptors, labeled M1, M2, M3, M4, and M5. The M1, M3, and M5 receptors are coupled to G-proteins that activate phospholipase C (they use G_q mechanisms), whereas M4 couples to G_i, which inactivates adenylyl cyclase and M2 couples to a K^+ channel and to G_i (see Figure 4.2.9).

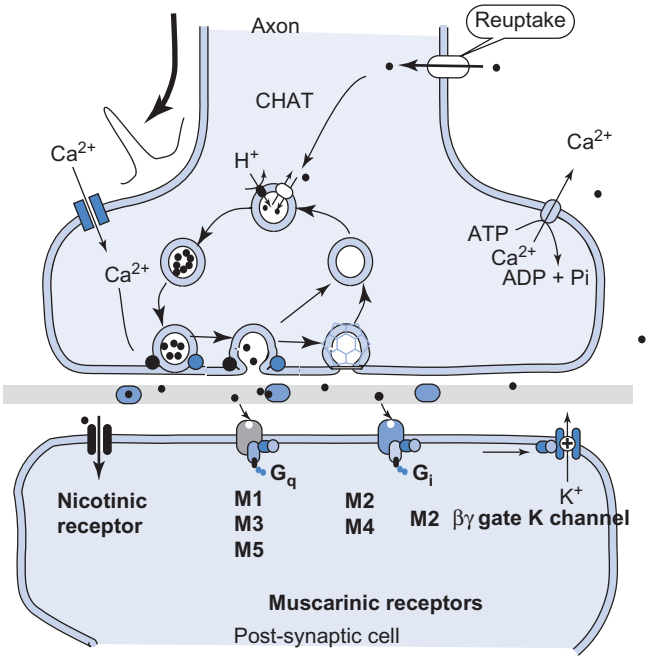

FIGURE 4.2.9 Receptors for acetylcholine. Post-synaptic cells can contain nicotinic receptors or one of five different muscarinic receptors. Nicotinic receptors, of which there are different types, are pentameric ionotropic receptors. All of the M receptors are metabotropic. Acetylcholine is degraded by acetylcholinesterase.

CATECHOLAMINES: DOPAMINE, NOREPINEPHRINE, AND EPINEPHRINE DERIVE FROM TYROSINE

Dopamine, norepinephrine, and epinephrine are all catecholamines, so-named because they consist of catechol, a phenyl group with two adjacent hydroxyl groups and an ethylamine side chain. The synthesis of dopamine (dihydroxyphenylethylamine) begins with the conversion of tyrosine to L-DOPA (dihydroxyphenylalanine) by the enzyme tyrosine hydroxylase. L-DOPA is then converted to dopamine by DOPA decarboxylase, as shown in Figure 4.2.10. Norepinephrine and epinephrine are synthesized from dopamine. Terminals that synthesize norepinephrine must first synthesize dopamine, which is placed in vesicles just like it is in dopamine-secreting terminals. The vesicles contain dopamine β hydroxylase, whereas tyrosine hyroxylase and L-DOPA decarboxylase and PNMT (phenylethanolamine *N*-methyltransferase) are all in the cytoplasm.

DOPAMINE COUPLES TO G_S AND G_I-COUPLED RECEPTORS THROUGH D_1 AND D_2 RECEPTORS

Dopamine released by pre-synaptic terminals crosses the synapse and binds to D_1 or D_2 receptors, both

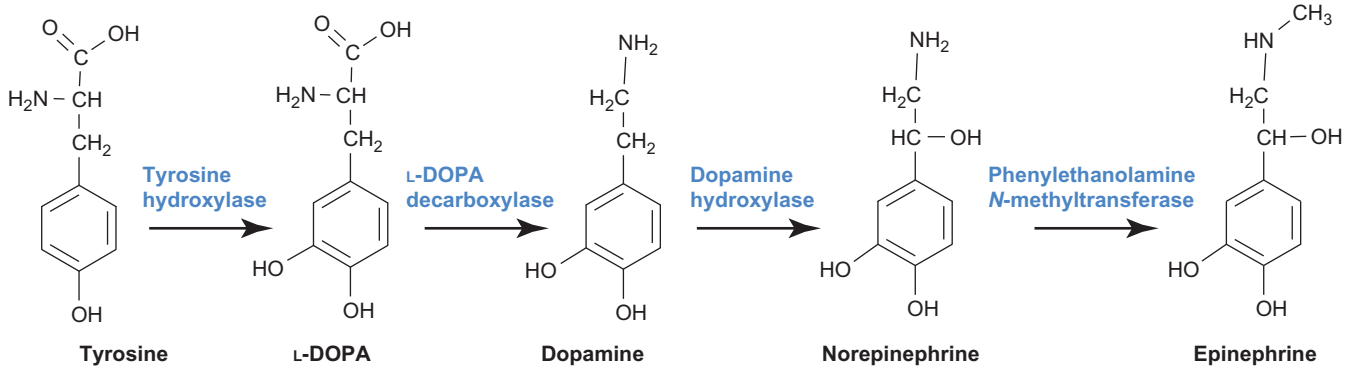

FIGURE 4.2.10 Synthesis of dopamine from tyrosine, and norepinephrine and epinephrine from dopamine.

GPCR; D_1 couples to a G_s mechanism, whereas D_2 couples to a G_i mechanism. Activation of D_2 receptors increases g_K, thereby hyperpolarizing the post-synaptic cell and causing an IPSP. This metabotropic effect develops more slowly and lasts longer than a single IPSP or EPSP. Dopamine can have opposite effects on the post-synaptic cell, depending on which GPCR it expresses (see Figure 4.2.11).

ADRENERGIC RECEPTORS ARE CLASSIFIED ACCORDING TO THEIR PHARMACOLOGY

Epinephrine is a hormone released from the adrenal medulla in response to stress, mediated by sympathetic fibers. The word *epinephrine* derives from *epi*, meaning *above*, and *nephros*, the root word for *kidney*, because the gland sits atop the kidney. Epinephrine is also called **adrenaline**, derived from the name of its gland. For this reason, receptors for both epinephrine and norepinephrine are called **adrenergic receptors**. Ahlquist in 1948 classified the adrenergic receptors as α or β, based on their response to epinephrine, norepinephrine, and isoproterenol, an adrenergic agonist. The β receptors respond to much lower concentrations of epinephrine or norepinephrine than the α receptors. β_1 receptors respond to epinephrine and norepinephrine about equally, whereas β_2 receptors are more sensitive to epinephrine. Propanolol blocks the β receptors; phenoxybenzamine blocks α receptors. All of the β receptors are linked to G_s; α_1 receptors are linked to G_q and α_2 receptors are linked to G_i (see Figure 4.2.12).

GLUTAMATE AND ASPARTATE ARE EXCITATORY NEUROTRANSMITTERS

Transamination reactions in neurons, as well as most other cells, readily interconvert glutamic acid into aspartic acid, and vice versa. Both of these amino acids stimulate the same receptors, and because of the difficulty in distinguishing neurons that use glutamate from those that use aspartate, we classify neurons that use either as a group, the **glutamatergic neurons**. The glutamate in these neurons derives from α-ketoglutarate in the Kreb's Cycle, or from ingested food. The neurons store it in synaptic vesicles and release it into the gap when an action potential invades the nerve terminus. All of the receptors on the post-synaptic cell are ionotropic (see Figure 4.2.13).

The **NMDA receptor**, named for an artificial agonist, ***N*-methyl-D-aspartate**, increases g_{Ca}, the conductance to Ca^{2+}, in response to glutamate binding. The increased g_{Ca} produces an inward current that depolarizes the post-synaptic membrane and therefore makes an EPSP. Prolonged exposure to glutamate leads to pathological increases in neuronal cell $[Ca^{2+}]$ that can kill the post-synaptic cell. This phenomenon is called **excitotoxicity**.

Binding of glutamate to the **AMPA** or **kainate receptors** leads to an increase in g_{Na} and g_K. These receptors are named for their artificial agonists: AMPA is α-amino-3-hydroxy-5-methylisoxazole-4-propionate. Occupancy of these receptors produces an EPSP.

GABA INHIBITS NEURONS

GABA, or **gamma amino butyric acid**, is synthesized from glutamic acid by glutamic acid decarboxylase in

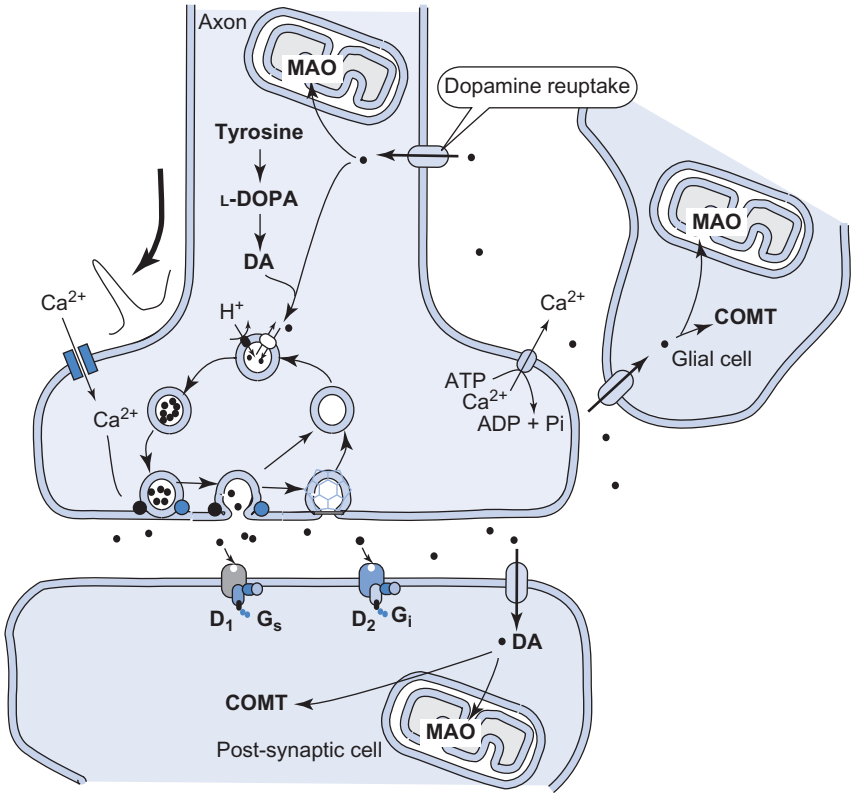

FIGURE 4.2.11 Fate of dopamine in pre- and post-synaptic terminals. Dopamine is synthesized from tyrosine in the pre-synaptic terminal and packaged into vesicles. The action potential opens voltage-gated Ca^{2+} channels on the pre-synaptic membrane that trigger fusion of dopamine-loaded vesicles. Dopamine diffuses across the gap and binds to post-synaptic receptors, which may be either D_1 receptors linked to a G_s protein or D_2 receptors linked to G_i. Dopamine is taken back up by the pre-synaptic cell, post-synaptic cell, or glial cell. It may be recycled by the pre-synaptic cell or degraded by MAO (monoamine oxidase) or COMT (catechol-*O*-methyl transferase). COMT places a methyl group on the 3 OH of the catechol ring; MAO removes the amine group. MAO is mitochondrial; COMT is in the cytosol.

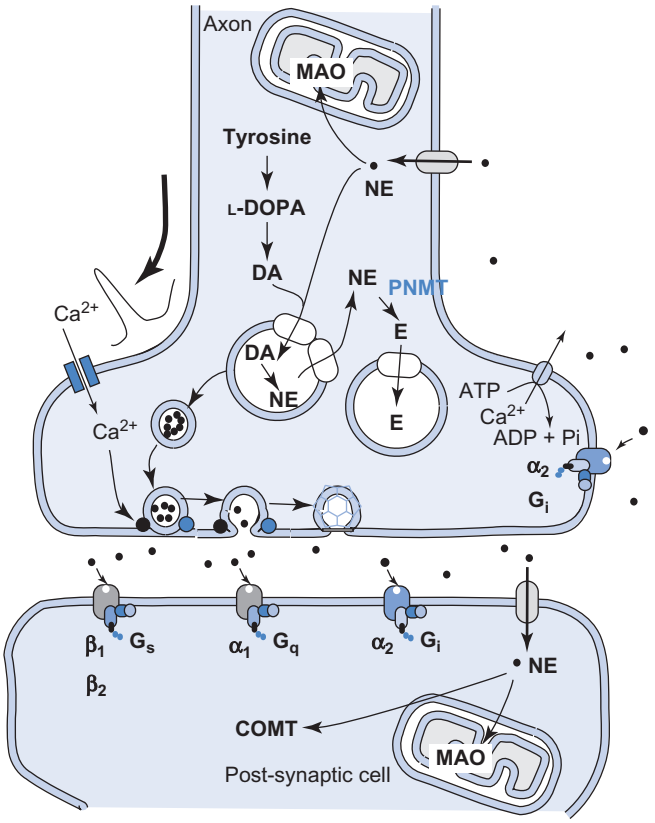

FIGURE 4.2.12 Processing of adrenergic receptors. Norepinephrine is made from tyrosine with dopamine as an intermediate step. It can be released from adrenergic autonomic nerve terminals. Epinephrine is synthesized from norepineprhine and released mainly from the adrenal medulla. Binding to β receptors on the post-synaptic membrane is coupled to a G_s mechanism. There are several different types of β receptors. Binding to α_1 receptors couples to a G_q mechanism that increases IP3 and leads to increased cytosolic $[Ca^{2+}]$. Activation of α_2 receptors is linked to a G_i mechanism. Thus, adrenergic stimulation can be stimulatory (G_s or G_q) in those tissues with the appropriate receptor, or inhibitory (G_i) in cells having those receptors. Like dopamine, norepinephrine is degraded by MAO or COMT.

the pre-synaptic terminal and stored in synaptic vesicles until released. Released GABA binds to $GABA_A$ or $GABA_B$ receptors on the post-synaptic membrane, both producing IPSPs. The $GABA_A$ receptor is an ionotropic receptor and produces a fast IPSP by increasing g_{Cl}. This increases flux of Cl^- into the cell, because $E_m > E_{Cl}$, and this flux makes an outward current (because Cl has a negative charge, current is opposite to Cl flux) that polarizes the cell. Occupancy of the $GABA_B$ receptor produces a slower IPSP because it activates a GPCR that activates a K^+ channel. The increased g_K increases K^+ efflux, a positive current that polarizes the cell away from threshold (see Figure 4.2.14).

SEROTONIN EXERTS MULTIPLE EFFECTS IN THE PNS AND CNS

Serotonin was identified in the serum of mammals in 1946 as a material that had tonic effects on the vasculature, hence its name. It is also known as **5-hydroxytryptamine**, or **5-HT**. It has profound effects on sleep, circadian rhythms, appetite, mood, cognition, reproductive behavior, thermoregulation, and endocrine, cardiovascular, and respiratory function. Serotonin derives from tryptophan. Tryptophan hydroxylase converts tryptophan to 5-hydroxy-tryptophan, and then L-amino acid decarboxylase converts 5-hydroxy-tryptophan to 5-hydroxy-tryptamine, as shown in Figure 4.2.15 and then the cell transports it into synaptic vesicles.

Like all other neurotransmitters, 5-HT works through its receptors, which have been classified into seven families (5-HT_1–5-HT_7) and at least 14 diffferent subtypes. Most of these work through metabotropic receptors, except for 5-HT_3, which is an ionotropic receptor. Figure 4.2.16 illustrates these receptors.

NEUROPEPTIDES ARE SYNTHESIZED IN THE SOMA AND TRANSPORTED VIA AXONAL TRANSPORT

A large variety of neuropeptides are used as neurotransmitters in **peptidergic synapses**. A partial listing is given in Table 4.2.2. These differ from the low-molecular-weight neurotransmitters in that they are often synthesized as larger precursors that are proteolytically cleaved after transport into LDCVs, and they are synthesized in the soma, not in the terminus. They typically bind their receptors with high affinity, and shut-off of the signal is achieved by degradation rather than by uptake by glial cells or pre-synaptic cells. For many years, it was believed that each neuron used a single neurotransmitter, but now it is known that some neurons secrete a low-molecular-weight neurotransmitter and one high-molecular-weight neurotransmitter. The known pairs are listed in Table 4.2.3.

The transport of materials along the axon is called **axonal transport** and it occurs in both directions. Movement from the soma to the axon is called **anterograde transport**, and this is associated with growth of the axon and renewal of synaptic vesicles. **Fast axonal transport** moves materials at 200–400 mm/day; **slow axonal transport** moves materials at 1–2 mm/day. **Retrograde transport** brings worn out parts of the cell back to the soma for destruction, disposal, or recycling. These movements require cytoskeletal elements, **microtubules**, and **microfilaments**, whose structure is described in Chapter 2.1. Materials are carried along microtubule tracts by motor proteins that bind to the tract and "walk" along it, using ATP hydrolysis to power the movement. **Kinesin** is a large protein of 380 kDa that resembles myosin in that it is a dimer with two subunits that each bind to microtubules, a long tail, and an associated light chain. Synaptic vesicles bind to kinesin and are carried when kinesin walks along the tract. Most members of the kinesin family are + directed, meaning that they walk towards the + end of the microtubule (its growing end away from the soma). K1FA kinesin transports synaptic vesicles; K1FB transports mitochondria. **Dynein** is another large protein containing a number of subunits. It carries cargo retrograde, from the + end to the − end of microtubules.

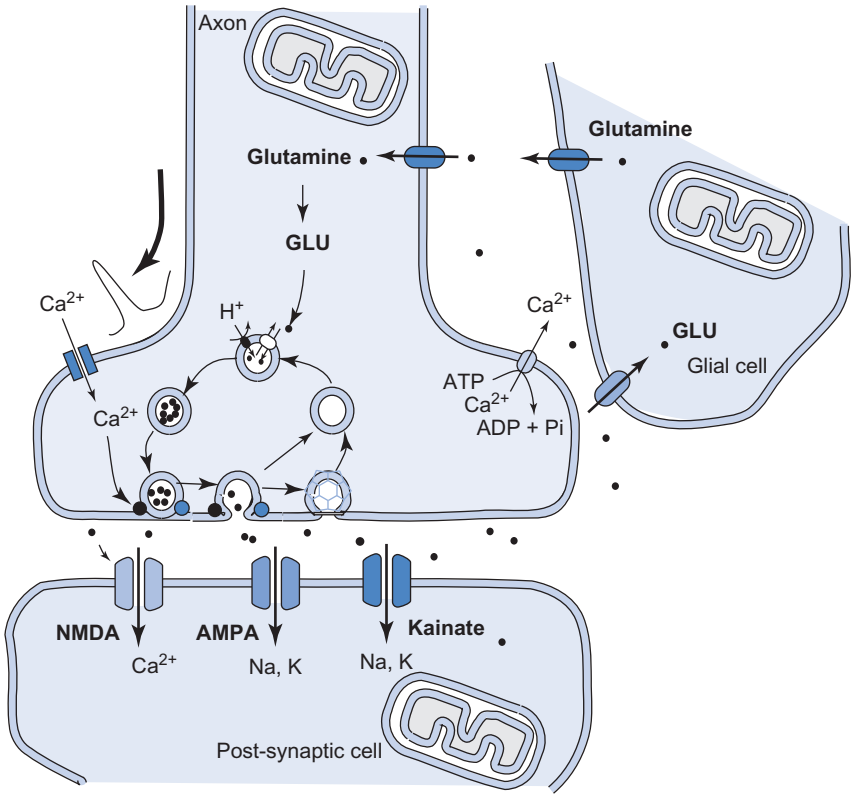

FIGURE 4.2.13 Handling of glutamate at glutamatergic synapses. Glutamate is synthesized from glutamine by glutaminase in the pre-synaptic terminal. The glutamic acid is stored in synaptic vesicles and released in response to an action potential on the pre-synaptic membrane. The released glutamic acid binds to one of its receptors, either the NMDA, AMPA, or kainate variety. Each of these incorporates ion channels and binding of glutamate increases the conductance to some cation, producing an inward current and an EPSP. The released glutamic acid is taken up by glial cells and resynthesized into glutamine by glutamine synthetase.

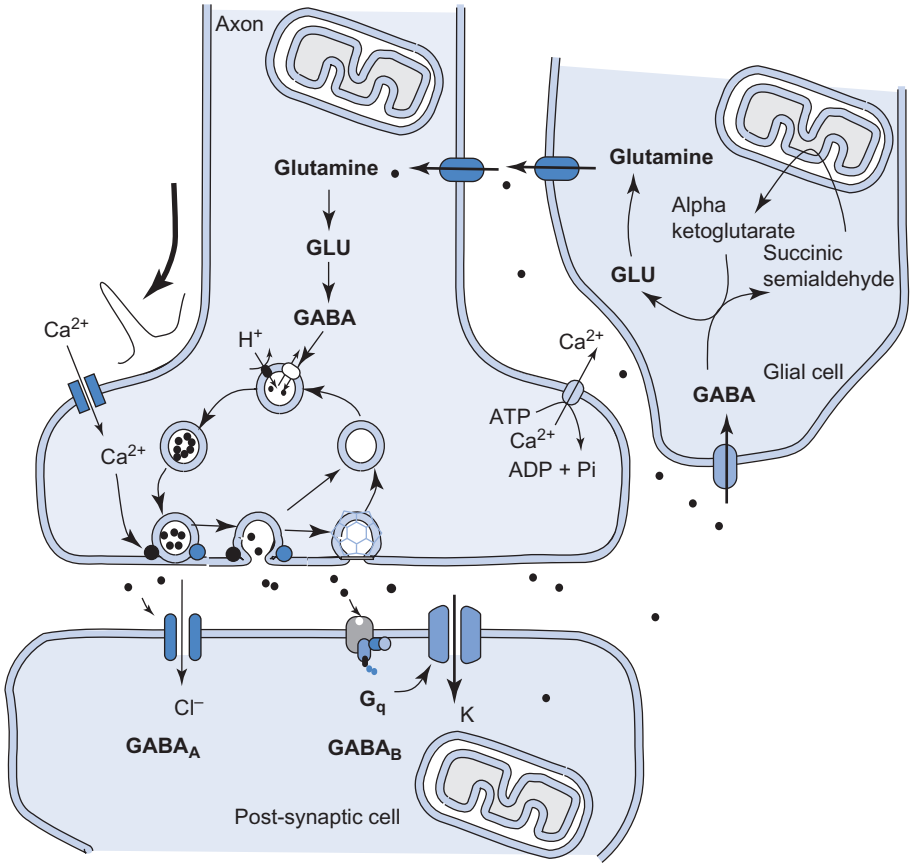

FIGURE 4.2.14 Handling of GABA at GABAergic synapses. Cells synthesize GABA from glutamic acid by glutamic acid decarboxylase and then import the GABA into synaptic vesicles. An action potential in the pre-synaptic terminal increases the local $[Ca^{2+}]$ by increasing Ca^{2+} influx through a voltage-gated channel. This results in fusion of the vesicles with the pre-synaptic membrane and release of GABA into the synapse. GABA diffuses across the gap and binds to $GABA_A$ receptors that increase g_{Cl}, inhibiting the post-synaptic cell. Binding to $GABA_B$ receptors increases g_K indirectly, which also inhibits the post-synaptic cell. The released GABA is taken up by glial cells which convert the GABA to glutamine, which can be taken up by the pre-synaptic terminal to convert it back to GABA.

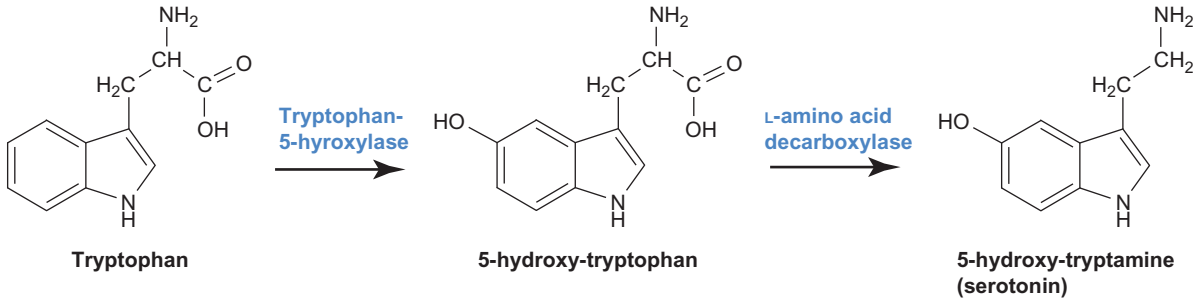

FIGURE 4.2.15 Synthesis of serotonin from tryptophan.

Clinical Applications: Multiple Sclerosis

Multiple sclerosis (MS) is a progressively debilitating disease of the nervous system. Its hallmark is demyelination, the loss of myelin and destruction of the oligodendroglial cells that produce it. The brains of affected persons develop plaques or lesions in seemingly random areas of the white matter in which the myelin is lost. Because the actual areas that are demyelinated vary from person to person, the presenting symptoms also vary considerably. Each affected person develops their own set of symptoms and progresses along individual paths. Patients may first present themselves to their physician with symptoms of numbness, paresthesias (pins and needles), muscle weakness, muscle spasms, spasticity, cramps, pain, blurred vision, slurred speech, loss of balance, nausea, fatigue, depression, incontinence, constipation, inability to swallow, loss of sexual function—the list is nearly endless.

MS is not contagious, but its etiology remains elusive. A favored hypothesis is autoimmune destruction of myelin. What triggers the autoimmune response is also unknown. The progress of the disease is characterized by four patterns: relapsing-remitting MS; secondary progressive MS; progressive relapsing MS; and primary progressive MS. These forms differ in the presence of relapses and the degree of recovery during remission. During periods of MS activity, the brain appears to be involved in an inflammatory response. Leukocytes invade the brain and myelin is stripped from the axons. Oligodendrocytes are killed. However, it is unclear which causes which: does inflammation kill the oligodendrocytes or do dead oligodendrocytes trigger the inflammation? The resulting demyelination alters the propagation properties of the axons, and some axons are also damaged by the inflammation. During this period the affected neurons cannot effectively transmit action potentials. Scar tissue replaces the myelin, and this scarification is the origin of the name, multiple sclerosis. "Multiple" means "many", referring to the many plaques that form; "sclerosis" means "scar forming."

Remission may be accompanied by reduction in inflammation. In the early stages, neurons that have not been damaged can resume their normal functions. Demyelinated nerves may become re-myelinated or the brain may develop new connections to circumvent the damage. In this way normal function can be partially restored. Demyelinated nerves adapt by increasing the number of regenerative Na^+ channels on their surface membrane. This cannot speed action potential conduction velocity, but it can prevent it from failing. If the Na^+ channels were present only at spacings equivalent to the Nodes of Ranvier, and the axon were demyelinated, there might not be enough depolarization left to open the Na^+ channels because of loss of current across the membrane. If the Na^+ channels are closer together, the action potential can still be conducted. Thus the nerve can remain active even if conduction velocity is slowed. For some functions, such as control of movement that requires rapid decision making, reduced conduction velocity greatly and adversely affects function.

SUMMARY

Brain behavior derives from the behavior of brain cells. The set of brain cells consists of neurons and the neuroglia. Neuroglia support, nurture, and protect the neurons, and make up some 90% of the total number of cells in the brain. The neuroglia include ependymal cells, oligodendroglia, astrocytes, and microglia. The ependymal cells make cerebrospinal fluid. The oligodendroglia form the myelin sheaths around axons in the white matter of the brain. The astrocytes help form the blood–brain barrier, take up used neurotransmitters and K^+ ions, and regulate the pH of the extracellular fluid in the brain. The microglia clean up damaged and infected tissue by phagocytosis. In the PNS, Schwann cells make the myelin sheath. Myelin consists of multiple layers of the cell membranes of oligodendroglia or Schwann cells. It insulates the axon. This insulation increases the membrane resistance and decreases the capacitance, both of which speed conduction velocity.

Neurons themselves vary considerably. Somatic sensory cells are pseudounipolar; some sensory cells in olfaction, vision, and hearing are bipolar. The majority of neurons are multipolar. The dendritic fields, size of the soma, and axon branching are highly variable. Most neurons have thousands of synapses. These multiple inputs converge on the cell whereas its output diverges onto other cells.

The synapse is the connection between neurons. There are axodendritic, axoaxonal, axosomatic, dendrodendritic, axoextracellular, and axosecretory synapses. Two

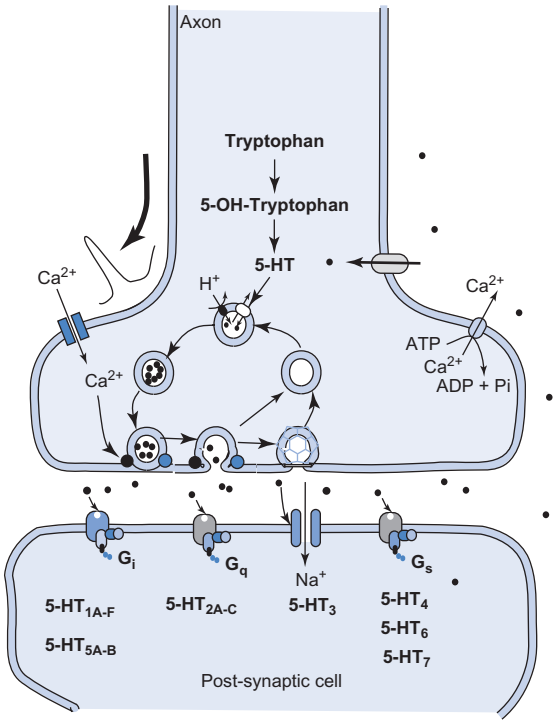

FIGURE 4.2.16 Serotonin receptors. Seven families of serotonin receptors have been identified, with several subtypes of some of these families. Most are metabotropic, working through heterotrimeric GPCRs either through G_i mechanisms (5-HT_1 and 5-HT_5 receptor families), G_q mechanisms (5-HT_2), or G_s mechanisms (5-HT_4, 5-HT_6, and 5-HT_7 families). The 5-HT_3 receptors are ionotropic, increasing conductance to cations nonselectively. In this case, the largest flux should be carried by the Na^+ ion because it is furthest from equilibrium and has one of the highest concentrations. The result is a depolarization of the post-synaptic cell.

main types of synapses are recognized: the electrical synapse and the chemical synapse. The electrical synapse is a gap junction consisting of a field of connexin pores that pass ions and signaling molecules directly from one cell to another without passing through the extracellular fluid. The pores form by aligning one connexin hexamer in one cell with another connexin hexamer in another cell. Chemical synapses have a gap between the cells. Vesicles containing neurotransmitters accumulate on the pre-synaptic side of the synapse, the side from which the signal originates. When an action potential propagates into the terminal of the pre-synaptic cell, voltage-gated Ca^{2+} channels open and Ca^{2+} enters the terminal. The increased local [Ca^{2+}] binds to proteins that attach the vesicles to the pre-synaptic membrane. This triggers fusion of the vesicle with the pre-synaptic membrane, and the vesicles release neurotransmitter into the gap. The neurotransmitter diffuses to the post-synaptic membrane where it binds to its receptors. The Ca^{2+} signal for neurotransmitter release is shut off by pumping Ca^{2+} out of the terminal by the PMCA and the NCX. The neurotransmitter signal to the post-synaptic membrane is shut off by three mechanisms: (1) reuptake of the neurotransmitter by the pre-synaptic membrane or glial cells; (2) destruction of the neurotransmitter by the post-synaptic cell; (3) diffusion away from the synapse. Vesicles that fuse with the pre-synaptic membrane are recycled and loaded back up with neurotransmitter.

The action of the neurotransmitter on the post-synaptic cell depends on the receptor. Ionotropic receptors directly alter the conductance properties of the post-synaptic membrane that produce currents that either

TABLE 4.2.2 Partial Listing of Neurotransmitters with Receptor Types

Neurotransmitter	Receptor	Peptide Neurotransmitter
Acetylcholine	Nicotinic (ionotropic) Muscarinic (metabotropic)	**Opioids** β Lipotropin α MSH α Endorphin β Endorphin Met enkephalin Leu enkephalin Dynorphin A Dynorphin B
Biogenic amines Epinephrine Norepinephrine Dopamine Serotonin Histamine	 Adrenergic β (metabotropic) Adrenergic α,β D_1, D_2, D_4, D_5 5-HT_{1-7} H_{1-3}	
Amino acids Glutamate/Aspartate GABA Glycine	 NMDA, AMPA, kainate $GABA_A$, $GABA_B$	**Gastrointestinal peptides** Cholecystokinin Secretin Substance P Vasoactive intestinal polypeptide
Purines Adenosine ATP		
Gases CO NO		**Hypothalamic peptides** LHRH Oxytocin TRH Somatostatin Vasopressin Corticotrophin

TABLE 4.2.3 Examples of Co-Localization of Low-Molecular Weight Neurotransmitters and Neuropeptides

Low-Molecular-Weight Neurotransmitter	Neuropeptide
Acetylcholine	Vasoactive intestinal polypeptide
Dopamine	Enkephalin
	Cholecystokinin
Norepinephrine	Enkephalin
	Somatostatin
Serotonin	Substance P
	TRH (thryotropin-releasing hormone)

depolarize (EPSP) or hyperpolarize (IPSP) the post-synaptic cell. Metabotropic receptors are linked to longer-lasting changes in membrane conductance through signaling pathways such as cyclic AMP and protein kinase A, or PLC and IP3. Metabotropic effects take longer to produce and last longer than ionotropic mechanisms. Each neurotransmitter has its own set of receptors and receptor mechanisms.

Materials move from the soma to the terminus, and back again to the soma, by fast and slow axonal transport. These occur over microtubule and microfilament tracts using motor proteins that attach cargo. Kinesins are generally + directed motor proteins, traveling to the + end of microtubules away from the soma. Dyneins generally transport material from the + end to the − end.

REVIEW QUESTIONS

1. Name the four types of glial cells. What do ependymal cells do? What do astrocytes do? What do oligodendroglial cells do? What do microglia do?
2. What is a myelin sheath? What cells make it in the CNS? In the PNS? What happens if myelinated cells become demyelinated?
3. What is a pseudounipolar neuron? A bipolar neuron? A multipolar neuron? What is meant by "convergence of inputs"? What is meant by "divergence of output"?
4. What is a synpase? What is the pre-synaptic cell? What is the post-synaptic cell? Are synapses bidirectional? What is an electrical synapse? Is it bidirectional?
5. How does a small synaptic vesicle differ from a large, dense core vesicle? Are they present simultaneously in a single synapse?
6. What is meant by "kiss and run" synaptic vesicle fusion? Could synaptic vesicle fusion occur in the absence of extracellular Ca^{2+}?
7. What is an ionotropic receptor? What is a metabotropic receptor?
8. Acetylcholine binds to what kinds of receptors? Which are ionotropic? Which are metabotropic? How do M1, M3, and M5 receptors work? What does M2 do? M4?
9. How can dopamine have different effects on post-synaptic cells? What mechanism do D_1 receptors use? D_2?
10. What amino acids is used to make dopamine? Serotonin? Norepinephrine? Epinephrine? GABA?
11. Is glutamate generally inhibitory or excitatory? Why? How about GABA? Why?
12. Where are neuropeptides synthesized? How do they get to the nerve terminals?
13. What is anterograde axoplasmic transport? What is retrograde axoplasmic transport? What motor proteins are generally used in each?