Hypothalamic Modulation of Thermoregulation

The hypothalamus also plays a central role in coordinating thermoregulatory responses and behavior patterns related to this [310]. Afferent input for this regulatory function is from temperature-sensitive neurons in the brain and particularly within the hypothalamus as well as from peripheral thermoreceptors in the skin, abdomen, peritoneum, and spinal cord. The information from all these sources is relayed centrally to the coordinating nuclei in the hypothalamus and other locations to result on autonomic nervous system, behavioral, and neuroendocrine response geared to maintain core body temperature within a narrow preset "normal" range. Thyroid hormones (both LT4 and LT3) are important effector mediators of this normal regulative effect, and their absence in the clinical syndrome of myxedema coma is typically among other features characterized by dramatic hypothermia.

While thermosensitive neurons are virtually ubiquitous in the hypothalamus, the most important sensory locations are the medial and lateral portions of the PON, portions of the anterior hypothalamus including the perifornical region, and the dorsomedial nucleus (DMN) [311–313]. Reduced temperature sensing in the PON results in increased heat generation by induction of the shivering reflex and initiation of non-shivering thermogenesis induced by sympathetic nervous neuron activation of UCP-1 brown adipose tissue (BAT) and by increased metabolic activity in skeletal muscle and other organs. Furthermore, cooling sensing in the PON and other hypothalamic thermo-sensors also induce various heat retention responses including cutaneous vasoconstriction and redirection of blood flow from peripheral to central core depots as well as behavioral responses geared to increased heat generation including moving to warmer places, increased layered clothing, and increased caloric intake. In some animals (though not clearly in humans), there is also an activation of the HPT axis with increased thyroid hormone-induced thermogenesis [314–316]. Contrawise warming in the PON induces opposite behavioral and autonomic responses including hyperventilation and panting in some animal species, increased sweating, cutaneous vasodilatation, UCP-1 inhibition in BAT, and behavioral response to encourage increased heat loss [311]. The PON has both warm and cold thermosensitive neurons, but the warm thermosensitive neurons are dominant and more numerous in resting environmental states. Typically PON lesions result in anomalies of heat dissipation resulting in hyperthermic clinical states [312]. While the full details of the chemical mediators of the hypothalamic cold and warm neurosecretory responses are still not fully elucidated, Table 5.3 details some of the most prominent mediators thus far identified.

Body temperature in humans in steady state is associated with an intrinsic diurnal rhythm with peak temperature in the late afternoon and early

Table 5.3 Chemical mediators of hypothalamic and CNS thermoregulatory response

Chemical mediators of hypothalamic and CNS-related thermoregulatory signaling	
Hypothermic mediators	Hyperthermic mediators
Estrogens	GABA
Angiotensin 2 (AG2)	Opioid peptides[a]
Acetylcholine (ACH)	Progesterone
CCK	CRH
Dopamine	Prostaglandins
α-MSH	TRH (+ T4 and T3)
Noradrenaline (norepinephrine)	5HT
Opioid peptides[a]	UCP-1
Neurotensin	Irisin
Somatostatin	Endotoxin[b]
Substance P	Lipopolysaccharide (LPS)[b]
ADH (vasopressin)	Tumor necrosis factor-α (TNF-α)[b]
	Interleukin-1 (IL-1)[b]
	Interleukin-6 (IL-6)[b]
	Other proinflammatory cytokines[b]

[a]The variable thermogenic effects of opioid peptides are dependent on the specific peptide(s) involved (viz., endorphins, dynorphins, or enkephalins whether met or leu subtypes) and the receptor types they mediate their actions through (mu, μ; delta, δ; or kappa, κ)

[b]These mediators are only relevant to pathologic states of systemic infections or chronic inflammation and not to steady-state physiologic homeostatic regulation

evenings, while the nadir is in the early morning soon after waking up from sleep. This diurnal rhythm is mainly modulated by the SCN. The SCN has extensive projections to the PON, thus enabling thermo-sensing cross talk to regulate the diurnal rhythm [317, 318]. The set point for body temperature regulation is also sensitive to sex steroidal milieu with the core body temperature typically reaching a nadir just prior to the midcycle LH surge and then rising during the luteal phase of the menstrual cycle mediated by progesterone [319–321]. Estrogen appears to be the major mediator of the midcycle temperature dip which it initiates by stimulation of the heat dissipation response neurons in the PON. Progesterone has the opposite effect on these same neuronal groups of the PON [322–324]. Expectedly, the hypoestrogenic milieu of the human postmenopausal state increases central hypothalamic thermic responses resulting in the well-known menopausal vasomotor syndrome of hot flashes which are also typically well ameliorated with exogenous estrogen administration via defined estrogen replacement regimens [325, 326]. Also notable is that the vasomotor hot flashes are most prevalent in the afternoon and early evenings when the superimposed diurnal rhythm is associated with peaks related to neurosecretory stimulation from the SCN's circadian pacemaker [325, 326]. The fact that some postmenopausal women with hot flashes have a positive clinical response to clonidine (a centrally acting α-2 adrenergic agonist) suggests a possible role for catecholamines in mediating the vasomotor responses [327].

The recent recognition that adult humans have significant depots of BAT as demonstrated by FDG PET imaging demonstrated capacity of transformation of some white adipose tissue (WAT) to BAT under certain humoral and environmental stimuli in addition to the recognition of the intermediate fat tissue depot; beige adipose tissue (BeAT) has opened up another exciting area of investigation into the thermoregulatory and energy expenditure modulatory effects of the hypothalamus [328–331]. There is suggestion that the small amount of BAT present in adult humans (a few grams) when stimulated to induce thermogenesis by UCP1-dependent means is able to increase total energy expenditure by up to 20%. Animal models lacking this capacity have an obese phenotype suggesting that beyond its role in thermogenesis and energy expenditure, BAT may also have a role in long-term weight management as well [328, 332, 333]. BAT activation physiologically occurs in the setting or cold ambient temperatures and involves a sympathoexcitatory pathway that involves gamma-aminobutyric acid (GABA) release in the PON thermo-sensor and the VMN of the hypothalamus [334]. In addition there appears to be a unique hypothalamic-mediated neurosecretory pathway from the VMN for inducing the beige transformation of WAT that appears mediated via the sympathetic nervous system [335]. There is also some evidence suggesting that brain GLP-1 expressed primarily in the VMN plays a central role both in the browning and beige transformation of WAT but also in BAT-induced thermogenesis. This GLP-1 effect appears to be mediated via AMPK [331, 336–339].

The hyperpyrexic response associated with infections and other systemic inflammatory states represents a unique situation where the normally tightly regulated temperature set point is upregulated for survival benefit of the organism so as to optimize recovery mechanisms from the immunomodulatory system while making the organism as inhospitable as possible for infective agents [340, 341]. This unique pathophysiologic response is achieved by upregulation of the body temperature set point in the thermo-sensors of the PON. This is apparently mediated by endotoxin and other proinflammatory cytokines like tumor necrosis alpha (TNF-α) and interleukin-6 (IL6). These mediators act via receptors in the vascular endothelial cells and subendothelial microglia of the OVLT. This consequently results in activation of the hypothalamic cyclooxygenase activity with increased production of prostaglandin E2 (PGE2) [342–344].

Finally it is also worthwhile to be aware of the potential role that irisin (the relatively recently identified adipo-myokine produced by both adipocytes and skeletal muscle) may have in modulation of thermogenesis by its central action on as

yet unclear hypothalamic nuclei targets. Its roles in centrally mediated reduction in caloric intake as well as modulation of the HPG axis at the hypothalamic level are also still in the early stages of full elucidation [345–352].

Hypothalamic Mediation of Circadian Rhythms

Circadian rhythms are genetically encoded cyclic physiologic functions, systems, and/or behavior patterns generated by internal mechanisms within the living entity. In mammals including humans, the hypothalamus is the most important modulator of such systems [353, 354]. The circadian regulatory system consists of an endogenous rhythm generator which functions akin to the cardiac pacemaker. This is sometimes referred to as the endogenous clock (aka zeitgeber), a photosensitive sensor system to encode light and dark and to thus link the endogenous clock to the time of day. In humans this is mediated mainly via the retinal photoreceptors (predominantly the cones). The afferent neuronal circuit linking the external environment to the endogenous clock is the retino-hypothalamic pathway, while efferent effector pathway from the endogenous clock is myriad and variable resulting in various modified physiologic functions and behavioral responses. The major endogenous clock in mammals (humans included) as earlier indicated is the hypothalamic SCN. The neurons of the SCN have autonomous synchronously repetitive neuronal firing mediated by local GABA release [355, 356]. Bilateral SCN lesions result in disruption of normal circadian rhythmicity characterized by disrupted sleep-wake cycling on abrogation of the typical daily routines associated with feeding, drinking, and the diurnal rhythms of melatonin and several adenohypophyseal hormones. This disruption can then be corrected by subsequent SCN transplantation [357–360]. While the full details of the genetic and molecular underpinnings of the SCN's neuronal cells endogenous pacemaker capacity are not completely understood at present, among the identified so-called "Clock" genes that are involved in this are the Period (PER), Clock, Cryptochrome (CRY), and Bmal genes [353, 354]. The SCN has two major cellular subgroups: a ventrolateral and a dorsomedial group. The ventrolateral SCN neurons receive the majority of the SCN's afferent inputs which are predominantly via the retino-hypothalamic pathway. These neurons' main neurotransmitter products are pituitary adenyl cyclase-activating peptide (PACAP) and nitric oxide [353, 354, 361]. The ventrolateral SCN neurons also receive afferent inputs from the intergeniculate leaflet of the thalamus and the midbrain raphe. These sets of afferent neurons utilize GABA, NPY, and 5HT as their main neurotransmitters. These inputs are important in modulating SCN pacemaker variability based on day-night oscillations. The dorsomedial SCN neuronal cells receive the bulk of their afferent input from the limbic system as well as from other hypothalamic nuclei [362, 363]. The efferent neurons of the two nuclear subgroups also have unique neurotransmitters. While the dominant ventrolateral nuclei neurons mainly release VIP, gastrin-releasing peptide, and GABA, the dorsomedial nuclei neurons mainly release arginine vasopressin, AG2, somatostatin, prokineticin 2, and GABA [354, 363, 364].

The SCN has three major diencephalic projections: (a) the hypothalamic subparaventricular zone (SPVZ), (b) the PVN, and (c) the medial and lateral tuberal hypothalamus.

From the SPVZ there are projections to the PON, and as expected these mediate circadian regulation of body temperature set points and food-dependent energy intake [354, 363, 364]. Additional efferent projections from the SPVZ extend to the dorsomedial nucleus of the hypothalamus, midline thalamus, midbrain reticular formation, and basal forebrain. These are involved in modulation of food intake, rest vs movement, sleep-wake cycling, and various pituitary hormone secretions based on light and photic stimuli.

The afferents to the PVN are GABA producing and are mainly involved in melatonin production pineal gland as previously discussed [363, 365, 366]. Beyond melatonin's well-documented role in modulating sleep-wake cycling,

it also has important immunomodulatory effects and is of considerable importance in reproductive functioning behavior among animals with seasonal breeding patterns though this is largely unimportant in humans [367–371]. The PVN projections from the SCN also appear to be central in the circadian night-day alteration of various adenohypophyseal hormone secretory patterns.

The afferents to the medial and lateral tuberal hypothalamus from the SCN are mainly to the VMN, the AN, and the lateral hypothalamic area. These projections are presumed to mainly regulate circadian secretion of neuroendocrine tuberoinfundibular and neurohypophyseal hormonal secretions.

Figure 5.17 provides a schematic overview of the main elements of the hypothalamic circadian regulatory network.

Hypothalamic Modulation of the Sleep-Wake Cycle

The sleep-wake cycle is one of the most important circadian rhythms and is closely regulated by various hypothalamic nuclei. More in-depth description and detailing of the role of the hypothalamus in this will be covered in a separate chapter of this volume. The following provides a basic overview and outline of the elements involved in the hypothalamus' regulatory input into sleep and wakefulness.

While wakefulness is characterized by asynchronous rapid low-voltage beta wave EEG-displayed cerebral cortical activity, the sleep state is more synchronized and organized into stages forms 1 to 4 based on depth of subconsciousness and progressive slowing and increase in amplitude of the detected cortical activity. While stage 1 sleep is characterized by alpha waves, stage 2 is characterized by spindle waves and k-complexes, while stage 3 and 4 sleep are characterized by high-voltage, low-frequency delta waves. States of partial arousal not associated with wakefulness can occur in the course of sleep and are characterized by asynchronous low-voltage electrical cortical activity akin to the beta waves associated with wakefulness. These are theta waves and are also apparent often soon after sleep initiation. Sleep architecture is further subcategorized depending on the absence or presence of rapid eye movement into rapid eye movement (REM) sleep or non-rapid eye movement (N-REM) sleep. While REM sleep is associated with loss of muscle tone except for respiratory and inner ear muscle activity, N-REM sleep is associated with normal muscle tone and an increased depth of subconsciousness during sleep [372, 373].

The sleep-wake cycle's neuronal regulation involves a balanced coordination between diencephalon basal forebrain and the mid-rostral brainstem. These dual systems subserve states of rest (sleep) versus arousal (wakefulness). There are thus "sleep"- and "wakefulness"-promoting centers. The main sleep center is in the PON and includes neurons in the ventrolateral portions of the PON that have GABA and galanin as their main neurosecretory products [374]. A secondary sleep center has been identified in the midline thalamus (aka the visceral or limbic thalamus) mainly in the dorsomedial and reticular thalamic nuclei [375, 376]. Wakefulness centers include the ascending reticular system of Moruzzi and Magoun [377]. The system consists of two major subdivisions: a monoaminergic and a cholinergic producing set of neuronal nuclei. These are located in the mesencephalic (limbic midbrain) and pontine reticular formation. The monoaminergic system of neurons includes the locus coeruleus which produces noradrenaline, the medial and dorsal raphe which produces 5HT, and the parabrachial nucleus that produces glutamate. In addition, neurons from the ventral periaqueductal gray which produce dopamine are included in this group.

The cholinergic group of neurons which are located in the pontine tegmentum include the laterodorsal and pedunculopontine tegmental nuclei.

Other wakefulness centers have been demonstrated in the tuberomamillary nucleus (producing histamine), nuclei of the lateral hypothalamus, and prefornical area that produce orexin, hypocretin, and MCH. Other less prominent but never-

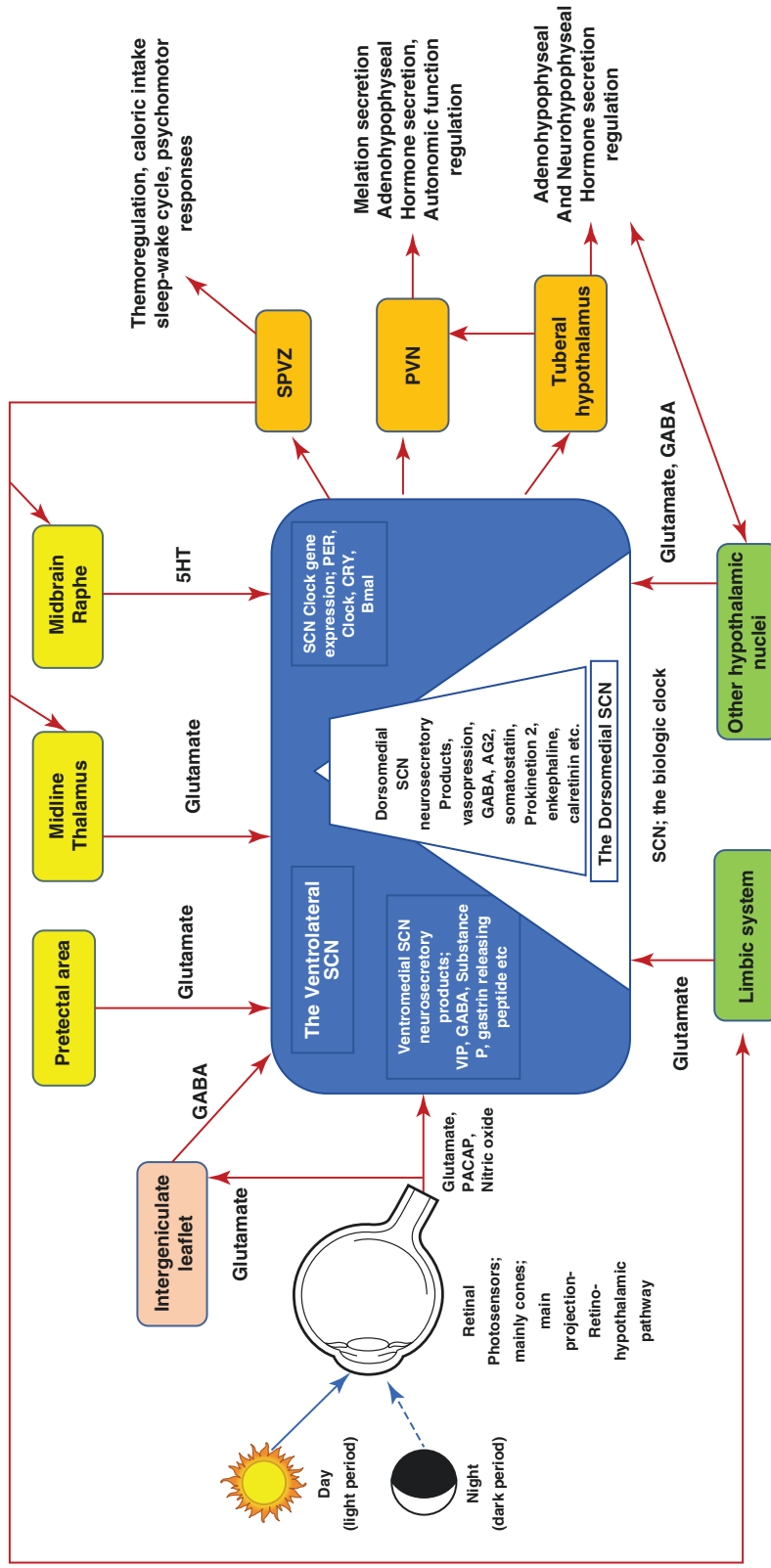

Fig. 5.17 Schema of the hypothalamic circadian regulatory system

theless notable "wakefulness centers" include cholinergic- and GABA-producing neurons of the basal forebrain (aka nucleus basalis of Meynert), portions of the PON, medial septal nucleus, and the nucleus of the diagonal band of Broca [373].

The main sleep center in the PON has efferent neuronal connections with the wakefulness centers in the posterior hypothalamus via the medial forebrain bundle and serves to enable intimate interaction and coordination between sleep and wakefulness cycling. In addition, neuronal connections from the secondary sleep center in the dorsomedial thalamus and reticular formation travel via the medial forebrain bundle to the PeVN and PON as well as to the mesopontine tegmental nuclei.

The wakefulness centers also have efferent outputs of note. These again utilize the medial forebrain bundle, and there are two main such projections: a dorsal route that is mainly cholinergic and GABA secretory as well as a ventral route. The dorsal route projects mainly to the intralaminar and reticular thalamic nuclei and from there diffusely to the cerebral cortex. The ventral route is mainly aminergic and glutamine secreting arising mainly from pontine and mesencephalic nuclei and projects diffusely to the cerebral cortex.

Other Behavioral Modulatory Responses of the Hypothalamus

The hypothalamus plays roles in various other behavioral responses and patterns. This has been aptly demonstrated by various lesional and stimulatory experiments of various hypothalamic nuclei mostly in animal models. More in-depth discussion of these effects and the relevant clinical significance to human behavior and psychopathology will be covered in other chapters of this book. Suffice it to indicate that portions of the medial hypothalamus appear integral to controlling motivated behavior patterns including defensive behavior. Fos labeling has helped identify a group of hypothalamic nuclei in this regard referred to as the "behavior control column" that are integral to expression of both innate and conditioned defensive behavior patterns [378–380]. Antipredatory defensive behavior has been demonstrated in various animal models with activation of the anterior hypothalamic nucleus, dorsomedial portion of the VMN, and ventrolateral portions of the premamillary nucleus [381–384]. The premamillary nucleus appears to play a critical role in such defensive behavior as destructive lesions of the nucleus abrogate such behaviors [384, 385]. The dorsal periaqueductal gray is an additional important relay station for mediating fear response behaviors [386–388].

The hypothalamus also has a role in the phenotypic behavior response of "social defeat" and "docility." Animal models demonstrating this behavioral phenotype have been shown to have activated hypothalamic nuclei in sexually dimorphic locations including the PON, the ventrolateral portions of the VMN, and the ventral premamillary nucleus [389, 390]. These nuclei are also involved in modulating and regulating other social behaviors including sexual and aggressive behaviors.

Neuroendocrinology of the Pituitary Axis

Introduction/History

Early recognition for the role of the hypothalamus as a site for integration of endocrine, autonomic, and behavioral responses can be dated to the second to eighteenth centuries A.D [391]. The pituitary gland derives its name from the Greek ptuo and Latin pituita, meaning phlegm, reflecting its nasopharyngeal origin. Galen in the second century AD hypothesized that nasal phlegm originated from the brain and drained via the pituitary gland [391]. Andreas Vesalius in the sixteenth century included the first anatomical depiction of the infundibular-pituitary stalk. In 1733, Morgagni recorded the absence of adrenal glands in an anencephalic neonate, providing early evidence for a developmental and functional connection between the brain and the adrenal glands [392]. In 1778, Sommering introduces

the term "hypophysis." In 1849, Claude Bernard set the stage for advances in neuroendocrinology by demonstrating that central lesions to the area of the fourth ventricle resulted in polyuria [392]. In 1948, Geoffrey Harris, the father of modern neuroendocrinology, showed that the anterior pituitary is regulated by the hypothalamus via the hypophyseal portal system [392]. It is now clear that with the hypothalamus, the pituitary orchestrates function of endocrine glands including the thyroid, adrenal, and gonads. The pituitary stalk serves as an anatomic and functional connection to the hypothalamus. Preservation of the hypothalamic-pituitary axis is critical for anterior pituitary control of sexual function and fertility, linear and organ growth, lactation, stress responses, energy, appetite, and temperature regulation and secondarily for carbohydrate and mineral metabolism.

In general, hypothalamus can be considered the coordinating center of the endocrine system. It consolidates signals derived from upper cortical inputs, autonomic function, environmental cues such as light and temperature, and peripheral endocrine feedback. In turn, the hypothalamus delivers precise signals to the pituitary gland, which then releases hormones that influence most endocrine systems in the body that form the hypothalamic-pituitary axis.

Blood Supply

The hypothalamic hormones are small peptides that are active only at the relatively high concentrations achieved in the pituitary portal blood system. Their small size and lack of known binding proteins results in rapid degradation and very low concentrations in the peripheral circulation. Therefore, the unique blood supply of the hypothalamic-pituitary axis is essential to its function. It is why the pituitary gland enjoys an abundant blood supply derived from several sources. Both the anterior lobe and posterior lobe of the pituitary have the same venous drainage, the anterior and posterior hypophyseal veins. The venous plexus empties into the petrosal sinuses and then into the peripheral circulation via the internal jugular veins [393]. Thus, venous blood in the petrosal sinuses has a relatively high concentration of pituitary hormones and is a useful site to catheterize and sample when assessing pituitary function [391]. But they both have individual arterial supplies. The anterior pituitary gland receives arterial supply from the superior hypophyseal artery (a branch of the internal carotid artery). This vessel first forms a capillary network around the hypothalamus; blood from this network is then transported to a secondary capillary plexus surrounding the anterior pituitary known as the hypothalamo-hypophysial portal system [391]. This structure allows the hypothalamus to communicate with the anterior pituitary via the release of neurotransmitters into the bloodstream. The infundibulum and posterior pituitary gland receive a rich blood supply from many arteries; the major vessels are the superior hypophyseal artery, infundibular artery, and inferior hypophyseal artery.

Anatomy

The *hypothalamus* rests in the sella turcica at the base of the brain, below the third ventricle and above the optic chiasm and pituitary gland. This location is the intersection of the cortex, the cerebellum, and the brainstem [391]. A number of nuclear groups and fiber tracts are recognized in the hypothalamus; they are organized into three major regions including the lateral, medial, and periventricular hypothalamus, each having distinct morphological and functional features. The medial and periventricular subdivisions of the hypothalamus contain a high density of neuronal cell bodies organized into nuclear groups that are crucial for the regulation of the anterior and posterior pituitary gland. Some groups serve as relay centers for highly differentiated neural information coming from the neocortex, limbic system, and autonomic sensory centers in the brainstem of specific homeostatic behaviors such as thirst, hunger, thermoregulation, the sleep-wake cycle, and reproductive behavior. The lateral hypothala-

mus occupies the largest portion of the hypothalamus by volume and has relatively fewer neurons compared to the medial hypothalamus. But the lateral hypothalamus does interact with a massive fiber system, medial forebrain bundle (MFB), through this fiber system that information from the medial forebrain (amygdala, hippocampus, septum, olfactory system, neocortex) and the brainstem is carried to the medial and periventricular hypothalamic subdivisions [391].

One of the most important regions in the hypothalamus, essential for regulation of the pituitary gland, is the median eminence. It is a midline structure located in the basal hypothalamus ventral to the third ventricle and adjacent to the AN [391]. All hypophysiotropic hormones converge there before they are conveyed to the pituitary gland. The median eminence is one of seven circumventricular organs situated as midline structures in the walls of the lateral, third or fourth ventricles. These circumventricular organs contain a rich capillary plexus and have a fenestrated endothelium rendering the structures outside of the blood-brain barrier. This morphologic feature allows the secretion of brain-derived products into the peripheral circulation and/or makes circumventricular organs targets for blood-borne information which can then be transmitted to the brain [391].

Pituitary Gland

The adult human pituitary weighs approximately 600 mg (range 400–900 mg) and measures approximately 13 mm in the longest transverse diameter, 6–9 mm in vertical height, and about 9 mm anteroposteriorly. It is thus the size of average pea [394]. The pituitary gland is comprised of the anterior lobe and posterior lobe along with the pituitary stalk, which connects the median eminence to the pituitary gland. The posterior lobe of the pituitary gland is smaller than the anterior lobe and embryologically derives from the neural primordia as an outpouching from the floor of the third ventricle, a direct anatomic extension of the central nervous system. The posterior pituitary is composed primarily of unmyelinated axons and axon terminals as well as specialized glial cells called pituicytes [391]. The anterior pituitary derives from the oral ectoderm as Rathke's pouch, first seen by the third week of pregnancy. The anterior lobe contains three subdivisions named pars distalis, pars intermedia, and pars tuberalis. The pars distalis makes up the bulk of the anterior pituitary and is responsible for the secretion of anterior pituitary hormones into the peripheral circulation. The pars intermedia lies between the pars distalis and the posterior pituitary, representing what remains of the original Rathke's pouch cleft and is considered vestigial [391]. Other important boundaries to the pituitary gland are the cavernous sinus laterally, which contain the internal carotid artery surrounded with sympathetic fibers, and the cranial nerves III, IV, V, and VI.

The anterior pituitary is composed of nests of cuboidal cells organized near venous sinusoids lined with a fenestrated epithelium where secretory products are collected. Classically, there are five cell types and six secretory products of the anterior pituitary gland: somatotrophs (growth hormone), lactotrophs (prolactin), corticotrophs (adrenocorticotropic hormone), thyrotropes (thyroid-stimulating hormone), and gonadotrophs (luteinizing hormone and follicle-stimulating hormone). However the anterior pituitary can also synthesize numerous other nonclassical peptides and substances that are important for paracrine and/or autocrine control of anterior pituitary secretion and/or cell proliferation under defined physiological conditions [391].

Table 5.4 details the other nonclassical peptides and other chemical mediators thus far identified to be produced by the anterior pituitary gland.

Physiology of Anterior Pituitary Hormone

Prolactin (PRL)

Physiology Prolactin (PRL) is synthesized in lactotroph cells which makes up 15–25% of func-

Table 5.4 List of nonclassical peptides and other chemical mediators from the anterior pituitary: adenohypophysis

List of nonclassical peptides and substances produced by anterior pituitary	
Substances	Cell types
Peptides	
Activin B, inhibin, follistatin	F, G
Aldosterone-stimulating factor	UN
Angiotensin II (angiotensinogen, angiotensin I)	—
Converting enzyme, cathepsin B, renin	C, G, L, S
Atrial natriuretic peptide	G
Corticotropin-releasing hormone-binding protein	C
Dynorphin	G
Galanin	L, S, T
Gawk (chromogranin B)	G
Growth hormone-releasing hormone	UN
Histidyl-proline diketopiperazine	UN
Motilin	S
Neuromedin B	T
Neuromedin U	C
Neuropeptide Y	T
Neurotensin	UN
Protein 7B2	G, T
Somatostatin 28	UN
Substance P (substance K)	G, L, T
Thyrotropin-releasing hormone	G, L, S, T
Vasoactive intestinal polypeptide	G, L, T
Growth factors	
Basic fibroblast growth factor	C, F
Chondrocyte growth factor	UN
Epidermal growth factor	G, T
Insulin-like growth factor I	S, F
Nerve growth factor	UN
Pituitary cytotropic factor	UN
Transforming growth factor alpha	L, S, G
Vascular endothelial growth factor	F
Cytokines	
Interleukin-1 beta	T
Interleukin-6	F
Leukemia inhibitory factor	C, F
Neurotransmitters	
Acetylcholine	C, L
Nitric oxide	F

C corticotropin, *F* folliculostellate cell, *G* gonadotroph, *L* lactotroph, *S* somatotroph, *T* thyrotroph, *UN* unknown

tioning anterior pituitary cells. Human PRL gene, located on chromosome 6, arose from a common ancestral gene, which gave rise to PRL, growth hormone, and placental lactogen-related proteins [395]. PRL-expressing cells appear to arise from GH-producing cells. The identification of PRL was elusive because human GH is highly lactogenic and active in bioassays used to isolate and measure PRL. GH is present in human pituitary glands in much higher concentrations (5–10 mg) than PRL (approximately 100 μg) [396]. Occasional mammosomatotroph cells co-secrete both PRL and GH, often stored within the same granule. Prolactin structure is a 199–amino acid polypeptide containing three intramolecular disulfide bonds. It circulates in the blood in various sizes: monomeric PRL ("little prolactin"; 23 kDa), dimeric PRL ("big prolactin"; 48–56 kDa), and polymeric forms (also known as "big, big prolactin"; >100 kDa) [397]. The monomeric form is the most bioactive PRL. In response to TRH, the proportion of the monomeric form will increase. Monomeric PRL is cleaved into 8- and 16-kDa forms and the 16-kDa variant is antiangiogenic. A glycosylated form is less biologically active than little PRL [398]. PRL receptor gene is a member of the cytokine receptor superfamily, localized to chromosome 5p13, creating receptor with an extracellular domain, a hydrophobic transmembrane domain, and an intracytoplasmic region homologous to the GH receptor [399]. PRL receptor dimerization occurs in both ligand-dependent and ligand-independent manners, a single PRL molecule binding to both components of the receptor dimer for formation of the trimeric ligand-receptor complex and subsequent activation by phosphorylation of intracellular Janus kinase/signal transducers (JAK-STAT) [400]. PRL receptors are expressed in many tissues from the pituitary, liver, adrenal cortex, kidneys, prostate, ovary, testes, intestine, epidermis, pancreatic islets, lung, myocardium, brain, and lymphocytes and most recognizable in breast tissue.

Regulation Prolactin (PRL) regulation is under the inhibitory control of dopamine, which is produced by the tuberoinfundibular (TIDA) cells and the hypothalamic tuberohypophyseal dopaminergic system [401]. Dopamine reaches the lactotrophs via the hypothalamic-pituitary portal

system and inhibits PRL secretion by binding to the type 2 dopamine receptors on pituitary lactotrophs. Prolactin participates in negative feedback by increasing tyrosine hydroxylase activity and thereby dopamine synthesis in the TIDA neurons [402]. Several other factors influence PRL gene expression, including estrogen, dopamine, thyrotropin-releasing hormone (TRH), and thyroid hormones [392]. Many factors have been shown to inhibit PRL synthesis and secretion which are endothelin-1, transforming growth factor beta 1 (TGF-β1), fibroblast growth factors (FGF), vasoactive intestinal polypeptide (VIP), growth hormone-releasing hormone (GHRH), histamine, serotonin, calcitonin, and opiates [392].

Secretion Prolactin (PRL) is cleared rapidly, with a calculated disappearance half-life ranging from 26 to 47 min. PRL secretion occurs episodically in 4–14 secretory pulses over 24 h , each lasting 67–76 min, with the highest levels achieved during sleep and the lowest occurring between 10 am and noon [403]. Prolactin levels decline with age in both men and women. In older men, less PRL is produced with each secretory burst. Postmenopausal women have lower mean serum PRL levels and PRL pulse frequency than do premenopausal women, suggesting a stimulatory effect of estrogen on both these parameters [404].

Function PRL is essential for human survival, because it is responsible for milk production during pregnancy and lactation. Additional biologic functions include reproductive and metabolic effects, mammary development, and melanin synthesis [405]. Serum PRL concentrations rise to 10 times normal during pregnancy. Active lactation is due in part to estrogen and progesterone levels and elevation of PRL levels after delivery. Suckling increases milk production after parturition and is essential for continued lactation. In the absence of suckling, PRL concentrations return to normal by 7 days postpartum. Amenorrhea and infertility result from PRL-mediated inhibitory effects on hypothalamic gonadotropin-releasing hormone (GnRH) neurons and on the pituitary to reduce secretion of the gonadotropins, LH, and FSH, resulting in a reduction in both amplitude and frequency of LH pulses [406].

Growth Hormone (GH)

Physiology Growth hormone (GH) is a single-chain polypeptide hormone consisting of 191 amino acids, which is synthesized, stored, and secreted by somatotroph cells. GH is the most abundant anterior pituitary hormone as somatotroph cells constitute up to 50% of the total anterior pituitary cell population and they are located predominantly in the lateral wings of the anterior pituitary gland. The pituitary gland contains a total of 5–15 mg of GH. Human growth hormone (hGH) genome locus spans approximately 66 kb and contains a cluster of five highly conserved genes located on the long arm of human chromosome 17q22–24 [407]. It encodes the many forms of hGH and human chorionic somatomammotropin (hCS); one is hGH-N. The hGH-N gene is selectively transcribed in pituitary somatotrophs and codes for a 22-kDa (191-amino acid) protein which is the predominate GH variant, accounting for 75% of pituitary GH secretion [407]. But 10% of pituitary GH is a 20-kDa variant lacking amino acid residues formed from alternate slicing. Circulating GH molecules comprise several heterogeneous forms: 22- and 20-kDa monomers, an acetylated 22-kDa form, and two desamino GH molecules. The 22-kDa peptide is the major physiologic GH component, while the 20-kDa GH has a slower metabolic clearance [408]. GH elicits intracellular signaling through a peripheral growth hormone receptor (GHR), initiating a phosphorylation cascade involving the JAK-STAT pathway. GHR is a 620-amino acid 70-kDa protein of the class I cytokine/hematopoietin receptor superfamily consisting of an extracellular ligand-binding domain, a single membrane-spanning domain, and a cytoplasmic signaling component [409]. JAK2 (tyrosine kinase) activation leads to phosphorylation of intracellular signaling molecules, signal-transducing activators of transcription proteins

(STATs 1, 3, and 5), and critical signaling components for GH action [410].

Regulation Growth hormone synthesis and release are under control of a variety of hormonal agents, including growth hormone-releasing hormone (GHRH), somatostatin, ghrelin, IGF-1, thyroid hormone, and glucocorticoids. The somatotroph cell expresses specific receptors for growth hormone-releasing hormone (GHRH), GH secretagogues, and somatotropin release-inhibiting factor (SRIF) receptor subtypes 2 and 5, which all mediate GH secretion. Hypothalamic SRIF and GHRH are secreted in independent waves and interact together with additional GH secretagogues to generate pulsatile GH release. GH secretion is further regulated by IGF-1, which participates in a hypothalamic-pituitary peripheral regulatory feedback system [411]. Norepinephrine, insulin-induced hypoglycemia, clonidine, arginine administration, and exercise all facilitate GH secretion [412]. Emotional deprivation and endogenous depression suppress GH secretion. Acute glucocorticoid administration stimulates GH secretion, but chronic steroid treatment inhibits GH. Hypothyroidism impaired GH response to stimulation and normalized when thyroid status is restored. Gonadal steroids regulate GH secretion and GH action in men and women. Nutrition plays a major role in GH regulation. Malnutrition increases GH secretion, whereas obesity decreases GH secretion. These nutritional effects occur acutely, exemplified by fasting state [413].

Secretion GH secretion is episodic and exhibits a diurnal rhythm with approximately two thirds of GH secretion produced at night by the onset of slow-wave sleep. This accounts for 70% of daily GH secretion [414]. Normal GH secretion is characterized by secretary episodes separated by troughs of minimal basal secretion during which GH is undetectable. GH concentration is highest in the fetal circulation peaking at approximately 150 μg/L, and neonatal levels are lower (~30 μg/L) reflecting the negative feedback control by rising levels of circulating IGF-1. GH output falls to a stable level during childhood (prepubertal state levels 200–600 μg/day), rising to peak at a twofold to threefold level at the peak of puberty (1000–1800 μg/day) [412]. GH output declines exponentially in both sexes at the young adulthood transition, declining to one quarter of the values achieved in late puberty. The decline in GH status occurs by a change in pulse amplitude rather than frequency. Adiposity accounts for a significant component of declining GH output with increasing age [398].

Function GH is the most abundant hormone in the adult pituitary gland, and GH functions as a major metabolic hormone. Metabolic actions of GH promote fat metabolism by enhancing lipolysis and fatty acid oxidation and regulate lipoprotein metabolism by enhancing low-density lipoprotein (LDL) clearance [415]. GH enhances glucose uptake and utilization in cells and suppresses glucose oxidation and utilization while enhancing hepatic glucose production [416]. GH reduces protein oxidation and stimulates protein synthesis. Growth hormone (GH) stimulates the production of insulin-like growth factor 1 (IGF-1), also called somatomedin C; it is a primary mediator of the effects of growth hormone (GH) systemically [411]. IGF-1 stimulates systemic body growth and has growth-promoting effects on almost every cell in the body, especially the skeletal muscle, cartilage, bone, liver, kidney, nerve, skin, hematopoietic, and lung cells.

Adrenocorticotropic Hormone (ACTH)

Physiology Corticotroph cells comprise about 20% of functional anterior pituitary cells; they are clustered mainly in the central median pituitary wedge. They are the earliest detectable human fetal pituitary cell type, appearing by the eighth week of gestation. These cells produce POMC peptide which is the precursor for ACTH, which acts on the adrenal glands to induce synthesis and secretion of adrenal steroids. Proopiomelanocortin (POMC) is a 266-amino acid pre-prohormone molecule encoding ACTH (1–39), β-lipotropin (LPH), and endorphins. The 8-kb human POMC gene is located on chromo-

some 2p23 [417]. It consists of three exons, first exon encodes a leader sequence, the second encodes the signal initiation sequence along with N-terminal residues of the precursor peptide, and the third exon encodes most of the mature peptide sequences including ACTH and β-LPH [418]. The POMC gene is expressed in pituitary and nonpituitary tissues including the brain, skin, placenta, gonads, gastrointestinal tissues, liver, kidney, adrenal medulla, lung, and lymphocytes. Corticotroph expression is determined by the pituitary promoter interaction (upstream) with exon 1, whereas peripheral expression of the short POMC mRNA is determined by exon 3 (downstream) promoter [419]. Multiple signals act to activate POMC gene expression, including corticotropin-releasing hormone (CRH), cytokines, arginine vasopressin (AVP), catecholamines, and vasoactive intestinal peptide (VIP), cAMP, activator protein-1 (AP1), and glucocorticoids [420]. The CRH type 1 receptor is predominantly expressed on the corticotroph, and receptor activation increases cAMP, protein kinase A, and CREB induction of CRH-binding protein (CRHBP) leading to POMC transcription [421]. After transcription POMC required several post-translational modifications before hormone secretion, including removal N-terminal signal sequence, glycosylation via an *O*-linkage, and serine phosphorylation [422]. POMC cleaved by prohormone convertase 1 (PC1) and prohormone convertase 2 (PC2) into ACTH, melanocyte-stimulating hormone, β-lipotropin (LPH), and endorphins. PC1 is most abundant in the pituitary and hypothalamus, whereas PC2 is present in the CNS, skin, and pancreatic islets but is absent in the pituitary. PC1 expression results in cleavage of POMC limited to four sites, with ACTH being a major product. In the hypothalamus and CNS, both PC1 and PC2 allow coordinated proteolysis, resulting in the generation of smaller fragments such as melanocyte-stimulating hormone (α-, β-, and γ-MSH), β-endorphin, and corticotropin-like intermediate lobe peptide (CLIP) [422].

Function ACTH is a polypeptide of 39 amino acids with a molecular weight of 4.5 kDa. Full-length ACTH is the only POMC-derived peptide with adrenocorticotroph function; it is the ligand of the melanocortin receptor type 2 receptor (MC2R) [392]. MC2R activation results in production of adrenal glucocorticoids, androgenic steroids, and mineralocorticoids. ACTH signals via adenyl cyclase to regulate P450 enzyme transcription of cortisol, aldosterone, 17-hydroxyprogesterone, and, to a lesser extent, adrenal androgens [423].

Regulation ACTH regulation involves at least three tiers of control: First, the brain and hypothalamus release regulatory molecules (including CRH, vasopressin, and dopamine) that directly regulate corticotroph function. Second, intrapituitary cytokines and growth factors act locally to regulate ACTH. Third, glucocorticoids maintain regulatory feedback control of corticotroph secretion by rapidly inhibiting hypothalamic CRH and pituitary ACTH secretion [392]. A tightly controlled immuno-neuroendocrine interface regulates the ACTH response to peripheral stressors, like pain, infection, inflammation, hemorrhage, hypovolemia, trauma, psychological stress, and hypoglycemia. These signals vary in ability to generate ACTH secretion and glucocorticoid response to ACTH.

Secretion ACTH is secreted with both circadian periodicity and ultradian pulsatility under the control of the suprachiasmatic nucleus [392]. This centrally controlled pattern is influenced by peripheral corticosteroids, given chronic glucocorticoid exposure (>24 h) with lead to HPA suppression persisting for days or longer. The circadian pattern of ACTH secretion typically begins at about 4 am, peaking before 7 am, with both ACTH and adrenal steroid levels reaching their nadir between 11 pm and 3 am [392]. In this 24-hour diurnal cycle, periodic ACTH secretory bursts occur at a frequency of 40 pulses per 24 h, with amplitude rather than frequency modulation which contributes to diurnal changes in ACTH [424]. ACTH circadian rhythm is controlled by visual cues and the light-dark cycle and is centrally controlled by CRH. CRH signal determines ACTH response, continuous signal desensitizing the ACTH response while a pulsatile CRH signal

restoring cortisol secretion. Endogenous and exogenous stress, including hypoglycemia, act centrally to increase ACTH pulse amplitude [425]. Daily ACTH secretion is higher in males, who also exhibit higher pulse frequency and peak amplitudes.

Gonadotropins Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

Physiology Gonadotroph cells secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH); it is part of the hypothalamic-pituitary-gonadal (HPG) axis. Gonadotroph cells comprise about 10–15% of the functional anterior pituitary cells [392]. LH and FSH act on the ovaries and testes to direct gametogenesis and sex steroid hormone synthesis. The synthesis and secretion of LH and FSH are under complex regulation by hypothalamic input (gonadotropin-releasing hormone, or GnRH), by positive and negative feedback from gonadal sex steroid and peptide hormones, and by paracrine modulation from local factors produced within the pituitary gland. The four heterodimeric glycoprotein hormones, LH, FSH, TSH, and hCG, share structural homology, having evolved from a common ancestral gene. While both the homologous LH and FSH molecules are co-secreted by gonadotrophs, their regulatory mechanisms are not similar. The αGSU, LHβ, and FSHβ subunits are encoded by different genes, located on chromosomes 6, 11, and 19. The LH/CGβ gene cluster comprises seven genes, one gene encodes LHβ, one encodes CGβ, and the remainder are pseudogenes. The LHβ and CGβ genes have different promoters and transcriptional start sites. LHβ includes a 24-amino acid signal peptide followed by a 121-amino acid mature protein. The FSHβ gene, on chromosome 11, is organized similarly to the other glycoprotein hormone β genes, encoding a mature peptide of 111 amino acids, with 2 glycosylation sites, and like LHβ, it is expressed only in gonadotrophs. The heterodimeric structure of the subunit of LH and FSH is essential for biologic activity. Disulfide linkages within each subunit result in a tertiary structure that allows and maintains noncovalent heterodimerization, forming the ultrastructure of the mature folded molecule to facilitate specific ligand-receptor interaction [426].

Regulation LH and FSH secretion patterns and in general the hypothalamic-pituitary-gonadal (HPG) axis are mediated primarily via GnRH, paracrine intrapituitary factors (primarily activin and follistatin), and peripheral feedback (both gonadal sex steroids and gonadal peptide hormones) [392]. Hypothalamic control of gonadotropin secretion occurs primarily through actions of GnRH. The mechanisms that regulate GnRH secretion have been provided by the study of genetic abnormalities that manifest as GnRH deficiency, defects in GnRH secretion, and defects in GnRH action, all of which lead to pubertal disorders or infertility. Conversely, a genetic defect in MKRN3 was noted to cause premature reactivation of GnRH secretion leading to precocious puberty [427]. Many neurotransmitters directly or indirectly modulate GnRH secretion, including norepinephrine, dopamine, serotonin, γ-aminobutyric acid (GABA), glutamate, opiates, neuropeptide Y (NPY), and galanin. Glutamate and norepinephrine provide stimulatory drive, whereas GABA and opioid peptides are inhibitory [392]. Kisspeptins, neurokinin B (NKB), and substance P are key to modulate GnRH secretion. Three gonadal peptides (inhibins, activins, and follistatin) are selective for FSH in terms of their effects on gonadotropins and serve as an additional mechanism for the differential control of FSH and LH. Inhibins, originating in the gonads and acting on the pituitary downregulate FSH synthesis and inhibit FSH secretion [428]. Activins act locally in the pituitary as autocrine/paracrine factors and play an important role to enhance FSH biosynthesis and secretion [428]. Follistatin, an activin-binding protein, inhibits activin action by interfering with activin binding to its receptor [429]. Leptin, a product of peripheral adipose tissue, is a positive regulator of the HPG axis and enables a pivotal link between body fat and reproduction [430]. Nutritional, metabolic, stress, and circadian inputs all appear

to act through these peptides to modulate GnRH, gonadotropin secretion, and the activity of the HPG axis. Gonadal steroid hormones (estrogens, progesterones, and androgens) all have effects on gonadotropins which occur both directly at the level of the gonadotroph and indirectly via effects at the hypothalamus that modulate GnRH secretion.

Secretion GnRH secretion into the hypophyseal portal circulation is pulsatile, resulting in episodic stimulation of the gonadotroph. GnRH signaling initiates with recognition by its receptor, GnRHR. GnRHR activation increases calcium mobilization and stimulates influx of extracellular calcium to induce pituitary LH and FSH secretion [431]. The patterns of GnRH signaling (amplitude, frequency, and contour) are important as each of these characteristics can influence gonadotroph responses allowing for two functionally distinct gonadotropins to be differentially regulated by a single hypothalamic-releasing hormone. The characteristic secretory episodes for LH and FSH indicate daily production rates of 1000 IU and 200 IU, with a half-life of 90 and 500 min for each respective β-subunit [432], with FSH having a longer circulating half-life than that of LH.

Function The primary targets of FSH and LH are the gonads; therefore the effects differ in the male and female. In female, FSH acts on FSH receptors in granulosa cells to facilitate follicular growth and estradiol biosynthesis. In response to FSH, follicles convert androstenedione to estradiol by aromatase activity [433]. FSH also controls granulosa cell production of inhibin during the follicular phase and induces LH receptor expression in granulosa cells of large preovulatory follicles. FSH also initiates the recruitment of the next generation of follicles for subsequent cycles. LH is a major regulator of ovarian steroid synthesis. LH stimulates estrogen production by promoting synthesis of androgen precursors in theca cells, which then diffuse into neighboring granulosa cells, where they are aromatized into estrogens under the control of FSH [434]. The midcycle LH surge initiates the rupture of the ovulatory follicle and ovulation and induces conversion of the follicle wall into the corpus luteum. LH helps to sustain luteinization by stimulating progesterone synthesis [433].

In male, LH acts on LH receptors in Leydig cells to induce intratesticular testosterone synthesis. FSH binds to FSH receptors on Sertoli cells and stimulates the production of inhibins, androgen-binding protein, androgen receptor, and other proteins. FSH mediates the maturation of spermatids into mature spermatozoa in concert with testosterone [435].

Thyroid-Stimulating Hormone (TSH)

Physiology Thyroid-stimulating hormone (TSH) is made by the thyrotroph cells, which comprise approximately 5% of the functional anterior pituitary cells. They are situated predominantly in the anteromedial areas of the gland. They are smaller than the other cell types and are irregularly shaped. TSH is a glycoprotein hormone comprising a 28-kDa heterodimer of two noncovalently linked α- and β-subunits. The tertiary TSH structure comprises three hairpin loops separated by central disulfide bonds [436]. The 13.5-kb α-subunit gene is located on chromosome 6 and comprises four exons and three introns. The α-subunit is common to TSH, LH, FSH, and hCG, but its regulation is uniquely cell-specific; upstream promoter elements are required for thyrotroph-specific expression [437]. The 4.9-kb TSH β-subunit gene located on chromosome 1 comprises three exons and two introns; it is unique and confers specificity of action [437]. Production of the mature heterodimeric TSH molecule requires complex cotranslational glycosylation and folding of nascent α- and β-subunits [438].

Regulation The thyrotropin-releasing hormone (TRH) neuron plays a central role in determining the set point of the hypothalamic-pituitary-thyroid axis by regulating pituitary TSH release [439]. Three main neuronal groups mediate the effects on hypothalamic TRH neurons: First is adrenergic input from the medulla

in response to the effects of cold exposure, as catecholamines increase the set point for inhibition of TRH gene expression by T3 [440]. The second group, TRH neurons, receive projections from the arcuate nucleus and contain two leptin-responsive groups: POMC system and NPY/agouti-related protein (AGRP) system regulating energy homeostasis [440]. Third, the hypothalamic dorsomedial nucleus projects to the paraventricular nucleus which represents alternative pathways by which leptin acts to regulate TRH neurons [440].

Intrapituitary TSH is stored in secretory granules and the mature hormone is released primarily in response to hypothalamic TRH. Both α- and β-TSH subunit gene transcriptions are induced by TRH. Feedback regulation by thyroid hormones on TRH and TSH is elaborated through a complex system of paracrine control. The effects of thyroid hormones are mediated by thyroid hormone receptors (TRs). TRs exist as two major isoforms, TRα and TRβ. TRα is the key isoform responsible for T3-mediated negative-feedback regulation by hypophysiotropic TRH neurons [441]. The local availability of T_3 is determined by deiodinase 2, which generates T3 from circulating thyroxine (T4) [439].

Other factors affecting TSH: Somatotropin release-inhibiting factor (SRIF) inhibits TSH pulse amplitude and blocks the nocturnal TSH surge directly at the pituitary level [442]. Dopamine infusions suppress TSH pulse amplitude by 70% and abrogate the nocturnal TSH surge; however prolonged use of dopamine agonists, however, does not result in hypothyroidism [443]. Certain medications, such as glucocorticoids and NSAIDs, also play a role in suppressing TSH [444].

Secretion Daily TSH production is approximately 100–400 mU with a calculated circulating half-life of approximately 50 min [445]. Secretion rates are enhanced up to 15-fold in hypothyroidism and are suppressed in hyperthyroidism. The degree of TSH glycosylation determines both metabolic clearance rate and bioactivity, and in hypothyroidism, the molecule appears highly sialylated, enhancing bioactivity [438]. TSH secretion is pulsatile with the low pulse amplitudes along with long TSH half-life result in modest circulating variances; it is amplified in hypothyroidism and abrogated in critical illness [446]. Secretory pulses every 2–3 h are interspersed with periods of tonic, nonpulsatile TSH secretion. Circadian TSH secretion peaks between 11 pm and 5 am, mainly due to increased pulse amplitude that is not sleep-entrained [447]. The 24-hour TSH secretion is stable and robust and not influenced by sex, body mass index, and age [448].

Function Hypothalamic-pituitary-thyroid system plays a critical role in development, growth, and cellular metabolism with thyroid hormone. TSH induces thyroid hormone synthesis and release and maintains trophic thyroid cell integrity.

Posterior Pituitary and Stalk

Anatomy

The posterior pituitary or neurohypophysis is composed of the pars nervosa (also known as the neural or posterior lobe), the infundibular stalk, and the median eminence. The infundibular stalk is surrounded by the pars tuberalis, and together they constitute the *hypophyseal stalk*. The pituitary stalk serves as an anatomic and functional connection to the hypothalamus by connecting the pituitary gland to the median eminence of the hypothalamus. The posterior pituitary is not glandular in nature like the anterior pituitary. It is neural tissue that is made up by the conglomeration of distal axon terminals from the hypothalamic magnocellular neurons. The cell bodies of these neurons are located in paired SON and paired PVN of the hypothalamus. During embryogenesis neuroepithelial cells of the lining of the third ventricle mature into magnocellular neurons and migrate laterally to and above the optic chiasm forming the SON and to both walls of the third ventricle to form the PVN [449]. Axons of the SON join axons of the PVN and course to the basal hypothalamus where they join

the axons from the other side and course through the infundibular stalk to the axon terminals in the posterior pituitary.

Axon terminals of the magnocellular neurons contain neurosecretory granules, membrane-bound packets of precursor hormones stored for subsequent release. The precursor proteins traverse the endoplasmic reticulum and the Golgi apparatus to be packaged in secretory granules [450]. The neurosecretory granules then travel along microtubules down the long axons through the stalk of the infundibulum to the posterior pituitary where the granules are stored. During transport, peptide enzymes (peptidases) within the neurosecretory granules cleave the prohormone into the hormone: vasopressin (ADH) or oxytocin, the carrier protein (neurophysin), and (for vasopressin) the glycopeptide. Blood supply for the posterior pituitary comes directly from the inferior hypophyseal arteries and branches of the posterior communicating and internal carotid arteries. The drainage is into the cavernous sinus and internal jugular vein.

The hormones of the posterior pituitary, oxytocin and vasopressin, are for the most part synthesized in individual hormone-specific magnocellular neurons, within the paraventricular nuclei and supraoptic nuclei, allowing stimulation of hormone-specific neurons. The supraoptic nucleus magnocellular neurons mainly produce vasopressin, around 80–90% and virtually all axons projecting to the posterior pituitary [449]. The organization of the paraventricular nuclei, however, is much more complex. There are five subnuclei and parvocellular divisions that synthesize other peptides, such as corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), somatostatin, and opioids [451–453]. The parvocellular neurons project to the median eminence, brainstem, and spinal cord, where they play a role in a variety of neuroendocrine autonomic functions [380]. The SCN, which is located in the midline at the base of and anterior to the third ventricle, also synthesizes vasopressin and controls circadian rhythms as well as seasonal rhythms [451].

Posterior Pituitary Hormones: Synthesis and Secretion

Vasopressin and oxytocin are nonapeptides that are synthesized in the cell bodies of the magnocellular neurons as part of a larger precursor molecule consisting of 6-amino acid ring with a cysteine-to-cysteine bridge and a 3-amino acid tail [454]. The hormones consist of the precursor molecule and a hormone-specific neurophysin and for vasopressin a glycopeptide. Subsequently the precursor molecule is packaged in neurosecretory granules and cleaved to the products during transport to the posterior pituitary. When a stimulus for secretion of vasopressin or oxytocin acts on the appropriate magnocellular cell body, an action potential is generated and propagates down the long axon to the posterior pituitary. The action potential causes an influx of calcium, which induces neurosecretory granules to fuse with the cell membrane, extruding the contents of the neurosecretory granule into the perivascular space and later into the capillary system of the posterior pituitary. Thus, there is coordination of stimulated release of hormone, transport of hormone, and synthesis of new hormone. The control of hormone synthesis is at the level of transcription. Stimuli for secretion of vasopressin or oxytocin also stimulate transcription and increase the mRNA content in the magnocellular neurons. When synthesis is turned off, transport stops, and when synthesis is increased, transport is upregulated [455].

Antidiuretic Hormone (ADH)/ Vasopressin

The physiologic regulation of vasopressin synthesis and secretion involves two systems: osmotic and pressure/volume. There are separate systems at the level of the receptors on the end organs of response. The V_{1a} receptors on blood vessels are distinct from V_2 receptors on renal collecting duct epithelia. V_2 receptors also regulate the nontraditional action of vasopressin to stimulate factor VIII and von Willebrand fac-

tor production. A third receptor, V_{1b}, is responsible for the nontraditional biologic action of vasopressin to stimulate ACTH secretion from the anterior pituitary and has been found in numerous peripheral tissues and areas of the brain [456].

Physiology of Volume and Pressure Regulation

Vasopressin is the main hormone involved in the regulation of water homeostasis and osmolality along with thirst. The renin-angiotensin-aldosterone system (RAAS) is mainly responsible for the regulation of blood pressure and volume [450]. Vasopressin plays a smaller role in regulation of blood pressure and volume when compared to the RAAS. High-pressure arterial baroreceptors are located in the carotid sinus and aortic arch, and low-pressure volume receptors are located in the atria and pulmonary venous system [457]. The afferent signals from these receptors are carried to the brainstem through cranial nerves IX and X. Volume/pressure regulation by vasopressin operates through V_1 receptors on blood vessels. When blood pressure is low and volume is low, activation of V_1 receptors causes contraction of vascular smooth muscle to raise blood pressure and constrict intravascular volume around the available fluid volume, to effectively increase plasma volume and reestablish the inhibition of secretion of vasopressin. Baroreceptors and volume receptors normally inhibit the magnocellular neurons causing decreased secretion of vasopressin. The opposite is true for a decrease in tonic inhibition, blood pressure or volume, will result in stimulation of the magnocellular neurons and release of vasopressin.

Vasopressin's action at the kidney to retain water will help replace volume, but to a lesser extent when compared to the RAAS which is the major hormonal regulation for volume control by stimulating sodium reabsorption in the kidney. This is in part due to volume/baroreceptor responses which are much less sensitive than are the osmoreceptors. The lesser response is attributed to the fact that changes in blood volume and central venous pressure have little effect to increase vasopressin as long as arterial pressure is maintained by alternative regulatory mechanisms such as RAAS and sympathetic reflexes [457]. A decrease in volume or pressure of around 10–15% is necessary before there is a measurable increase in plasma vasopressin. By counterregulatory effects increases in pressure and central volume will decrease vasopressin secretion [458].

Physiology of Osmotic Regulation

The primary receptors for sensing changes in osmolality are located in the brain. Experimental brain lesions in animals have strongly implicated cells in the OVLT and areas of the anterior hypothalamus near the anterior wall of the third cerebral ventricle as the primary osmoreceptors [454]. Surgical destruction or patients with brain damage affecting the OVLT have inability to maintain normal osmolality due to abolished vasopressin secretion and thirst responses to hyperosmolality but no alteration in their responses to hypovolemia [459]. In contrast, destruction of the magnocellular neurons of the SON and PVN eliminates dehydration-induced secretion of vasopressin but does not alter thirst, indicating that osmotically stimulated thirst is generated at a site proximal to the magnocellular cells.

Extracellular fluid (ECF) osmolality is predominantly determined by sodium concentration. Osmolality varies from 280 to 295 mOsm/kg H_2O in normal subjects, but in any individual it is maintained within a narrower range by three different mechanisms: sensitive response of plasma vasopressin to changes in plasma osmolality, the sensitive response of urine osmolality to changes in plasma vasopressin, and then the gain in the system by the response of urine volume to change in plasma vasopressin [454]. Basal plasma vasopressin is in the range of 0.5–2 pg/mL. As little as a 1% increase or decrease in plasma osmolality will cause a rapid increase or decrease of vasopressin released from the store of hormone in the

posterior pituitary [460]. Rapid metabolism of vasopressin is also characteristic of the hormone, which circulates in plasma with a half-life of approximately 15 min, and this allows rapid changes in levels of vasopressin in plasma. In humans a direct linear relationship exists between plasma osmolality and plasma vasopressin. The opposite is true for the relationship of plasma vasopressin to urine volume. Thus, small increases in plasma osmolality produce a concentrated urine, and small decreases produce a water diuresis.

The kidney conserves water by the combined functions of the loop of Henle and the collecting duct. The loop of Henle generates a high osmolality in the renal medulla via the countercurrent multiplier system. Vasopressin acts in the collecting duct and increases water and urea permeability, allowing osmotic equilibration between the urine and the hypertonic medullary interstitium. The net effect of this process is to extract water from urine from the medulla, through interstitial blood vessels, the vasa recta resulting in increased urine concentration and decreased urine volume. The antidiuretic effect of vasopressin occurs when binding to V_2 receptors on the epithelial principal cells of the renal collecting tubule. Binding activates adenylate cyclase, increasing cyclic adenosine monophosphate (cAMP), which then stimulates protein kinase A. This process leads to phosphorylation and activation of aquaporin 2 and movement of the water channels into the luminal membrane. In addition to shifting water from the collecting duct into the hypertonic inner medulla and concentration of urine, binding also promotes activation of the V_2 receptor increasing the synthesis of aquaporin 2 and the permeability of aquaporin 2 to water [461]. Aquaporins 3 and 4 are constitutively synthesized and are expressed at high levels in the basolateral plasma membranes of principal cells, where they are responsible for the high water permeability of the basolateral plasma membrane [462, 463]. Dissociation of vasopressin from the V_2 receptor allows intracellular cAMP levels to decrease, and the water channels are then reinternalized, terminating the increased water permeability. The aquaporin-containing vesicles remain just below the apical membrane and can be quickly shuttled into and out of the membrane in response to changes in intracellular cAMP levels. This mechanism allows minute-to-minute regulation of renal water excretion in response to changes in ambient levels of vasopressin in plasma.

During prolonged periods of dehydration (at least 24 h), long-term regulation of collecting duct water permeability occurs in response to chronically elevated levels of circulating vasopressin. Persistently elevated levels of vasopressin upregulate synthesis of aquaporin 2 and aquaporin 3 water channels in the collecting duct principal cells, thus achieving maximum permeability and water conservation. In response urine volume can be reduced to a minimum but not eliminated. To maintain water homeostasis, water must also be consumed to replace the obligate urinary and insensible fluid losses. This is regulated by thirst. Similar to vasopressin, thirst can be stimulated by increases in osmolality of the ECF or by decreases in intravascular volume.

Oxytocin

The classic roles of oxytocin are smooth muscle activation promoting milk let-down with nursing and uterine myometrial contraction at parturition [450]. Difficulty to carry studies in pregnant women and human tissue makes physiologic regulation of oxytocin secretion and function a less well-known subject when comparing humans to other mammals. All mammals secrete oxytocin to stimulate milk let-down associated with nursing, unique characteristic among all mammals. The milk-producing unit of the breast is the alveolar system in which clusters of milk-producing cells are surrounded by specialized myoepithelial cells. Oxytocin receptors are localized on glandular cells of alveoli which synthesize milk. Glandular cells are surrounded by myoepithelial specialized cells that are connected to ductules and then ducts that lead to the nipple. Oxytocin in the systemic circulation acts on these receptors to cause myoepithelial contraction along with shortening and widening of the ducts

to causing milk secretion and enhancing flow. During lactation sucking at the breast triggers an afferent signal that is transmitted from the mechanoreceptors or tactile receptors in the breast to the spinal cord ascending to the oxytocinergic magnocellular neurons in the supraoptic nucleus and the paraventricular nucleus, where neurotransmitters trigger oxytocin secretion. Pulsatile release of the hormone produces a pulsatile pumping action on the alveoli, promoting maximum emptying of milk from the alveoli [464].

Oxytocin also plays a role in parturition, mainly uterine contraction during expulsion stage. During early labor, upregulation in the uterus of oxytocin receptor mRNA occurs, and oxytocin receptor numbers increase [465, 466]. Oxytocin receptors are prominent in the fundus of the uterus, where they stimulate myometrial contraction, and in decidual cells, where they stimulate the production of prostaglandins. At parturition increased oxytocin activity in the fundus will push the fetus toward the cervix, which is thinned and relaxed by the effects of prostaglandins.

Figures 5.18 and 5.19 provide a pictorial view of the various anatomic subsections and blood supply organization of the pituitary gland.

Other Aspects of the Hypophysis Cerebri

Comparative anatomical studies between various mammals as well as other vertebrates and human pituitary glands have provided some insight into other less well-understood and appreciated sections of the pituitary gland. Furthermore noted age-related differentials between fetal, neonatal, childhood, adult, and geriatric configurations of human pituitary have also provided additional insight in this regard [467–469].

The hypophysis (pituitary) is connected to the hypothalamus via the pituitary stalk which has a neurohypophyseal component: *the infundibulum*. This is a sheath of projecting axons from several hypothalamic nuclei as previously detailed above. The pituitary stalk however also has an adenohypophyseal component which forms and encircling tube around the infundibulum and is called the *pars tuberalis*. There is some suggestion that the pars tuberalis may have a specialty function beyond being a more superiorly located location for anterior pituitary hormonal secretory cells. It appears to in addition serve as the primary transducer for long-term internal timers and is sometimes referred to as the "circannual clock" (as opposed to the SCNs established role as the

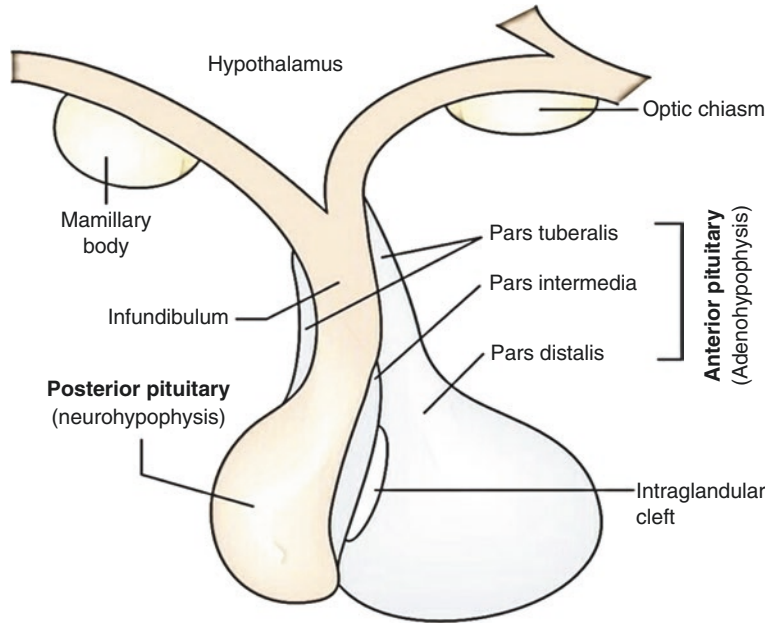

Fig. 5.18 Pictorial of the human pituitary gland; hypophysis cerebri

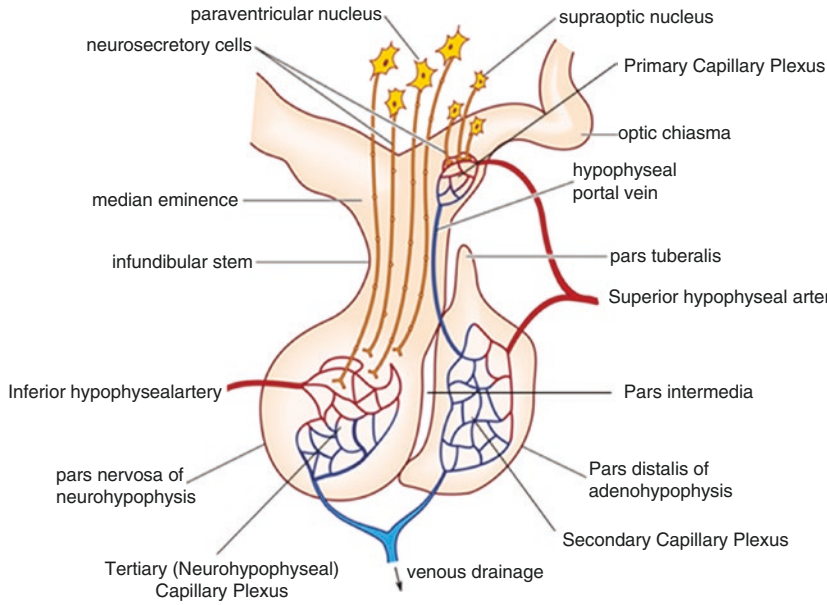

Fig. 5.19 Schema of the blood supply of the pituitary gland

circadian biologic clock center) [470]. In this capacity the pars tuberalis appears to play a role in establishing and regulating seasonal rhythmicity of various autonomic and other physiologic functions [470–473].

The *pars intermedia* is the small sliver of tissue that lies between the adenohypophysis and neurohypophysis. It contains three main groups of cells: chromophobes, basophils, and colloid lining secretory cells that line several colloid-filled cysts which are vestiges of the developmental Rathke's pouch [467–473]. Human fetal pituitary glands as well as the pituitary from fish and amphibians produce MSH in abundance. While this is important for proper skin pigmentation development in human fetuses in the lower vertebrates, it has a more complex and important role in adult animals including environmental-induced skin pigmentation for camouflage purposes as well as for playing a role in sexual and reproductive mating behaviors. In human adults however, it is typically vestigial or completely absent, and it is unclear that it has any significant physiologic functional role in adults. The cells of the pars intermedia are highly metabolically active and especially demonstrable in bovines demonstrate a triphasic cyclic activity routine characterized by (a) resting cellular phase, (b) desquamation with autolysis, and (c) cellular regeneration. The desquamated cuboidal secretory cells produce the colloid which fills the colloid cysts present in the pars intermedia, and from here the colloid is drained by the extensive capillaries traveling between the neuro- and adenohypophysis with subsequent venous drainage via the inferior pituitary venules.

To varying degrees human pituitary glands can also demonstrate a well-defined *interglandular cleft* that lies between the pars intermedia and the adenohypophysis. It is a true glandular lumen lined with secretory cuboidal cells. While well defined in some mammals and in the fetal pituitary, its presence in adult humans is variable and when excessive can induce pathology due to local mass effect and is then referred to as Rathke's cleft cysts which will be discussed in more depth in other chapters. The exact functional significance of any of the colloid of the interglandular cleft to adult human physiology remains unresolved.

Concluding Remarks

This chapter has attempted to give a comprehensive overview of the roles that the hypothalamus and pituitary play in the normal regulation of various voluntary and autonomic functions and behavior patterns and has sought to show the close integration between specialized neuronal and endocrine functions between the various cells and nuclei of both organs. As a unit the hypothalamic-pituitary axes serve as the highest center of systemic endocrine oversight and modulation.

While our knowledge of this complex system has grown significantly, there still remain unresolved questions from a molecular through cellular to anatomic level of inquiry as regards various aspects of the structure and function of this system. Even better understanding of the interactions between the hypothalamic-pituitary axes and its upward projections to the thalamus, limbic system, cerebellum, and neocortex as well as its downward projections to the midbrain, spinal cord, peripheral nervous system, and systemic circulation will have great implications for improving therapeutics in a wide range of clinical disciplines.

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Part II

Pathobiology and Dysfunction of the Hypothalamus

6 Imaging Aspects of Pathologies of the Sella, the Pituitary Gland, and the Hypothalamus

Manuel Schmidt and Arnd Doerfler

Introduction

Imaging of the sellar region, the pituitary gland, and the hypothalamus is quite challenging since there are large vessels, subarachnoid space, bone, and air-filled cavities in close neighborhood. Varieties of pathologies arise in the central skull base due to adjacent neuronal, vascular, and endocrine structures in this anatomical region. The pituitary gland itself is a very small-volume organ. High-quality imaging necessitates high contrast and spatial resolution to depict very subtle pathologies. Additionally, anatomic variations can hamper differential diagnosis. Magnetic resonance imaging is the modality of choice providing multiplanar high-contrast images of the pituitary gland, the hypothalamus, and the adjacent structures. Computed tomography is used only as supplementary, i.e., when information about the osseous anatomy needs to be obtained or to exclude or visualize calcifications.

Located in the pituitary fossa (Fig. 6.1), the pituitary gland can be morphologically and functionally divided into two parts – the anterior (adenohypophysis) and posterior (neurohypophysis) lobes. Embryologically, the distal part of the adenohypophysis arises from the epithelium of Rathke's pouch, an invagination of the roof of the oropharyngeal membrane. As part of the brain, the neurohypophysis is composed of the stalk (infundibulum) and the neural lobe (infundibular process). The pars intermedia, derived from the posterior wall of Rathke's pouch, is located in-between the anterior and posterior lobes and is usually not seen in MRI. The posterior lobe of the pituitary gland and the pituitary stalk receive their blood supply from the superior and inferior hypophyseal branches of the internal carotid artery, whereas the anterior lobe receives its blood supply from penetrating capillary loops from the portal vessels of the hypophyseal-portal circulation, respectively.

The adenohypophysis is producing a variety of hormones, i.e., prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). In addition, prohormone precursors of corticotropin (ACTH) and melanocyte-stimulating hormone are secreted, respectively. Thus, lesions of the adenohypophysis may cause hormonal deficiency resulting in a variety of clinical symptoms. The posterior pituitary lobe has no independent secretory function and receives vasopressin (ADH) and oxytocin from the hypothalamic neurons through capillaries for storage. In newborns up to 3 months of age, both anterior and posterior pituitary lobes exhibit hyperintensity on T1-weighted imaging [1, 2]. With further age, the adenohy-

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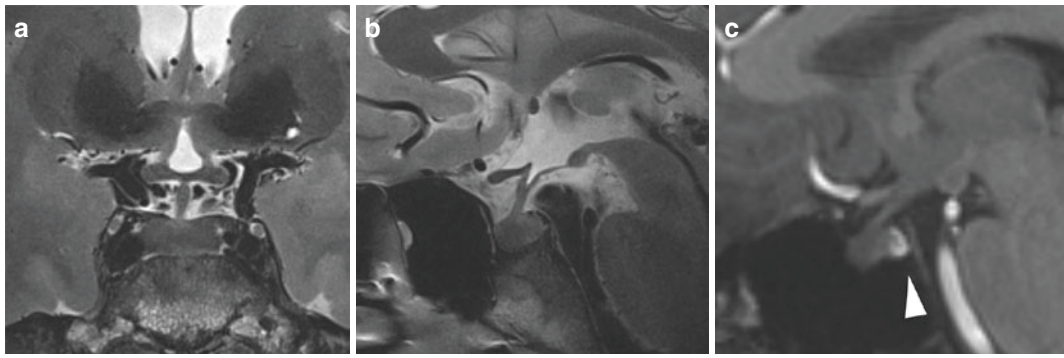

Fig. 6.1 Normal hypophysis. Coronal and sagittal T2w TSE (**a** + **b**). Sagittal T1w native (**b**). Note the bright signal of the normal neurohypophysis in T1w (**c**, arrow)

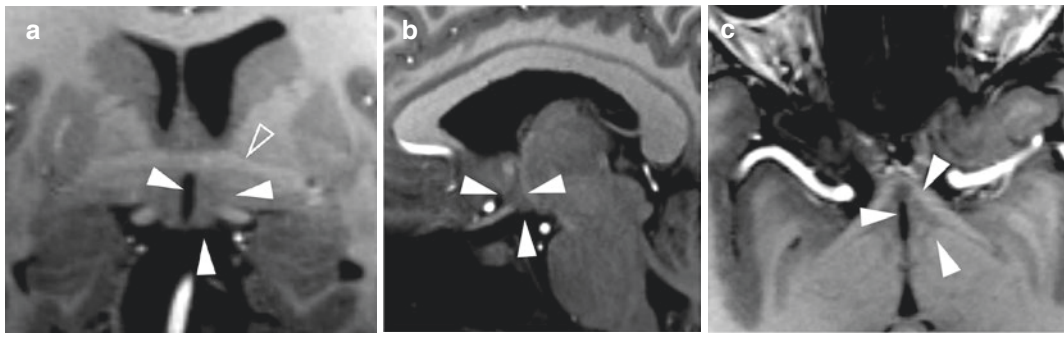

Fig. 6.2 Normal hypothalamus (arrows), hypointense to the adjacent structures on T1w. Ultrahigh resolution T1w MP2RAGE (0.6 mm isotropic voxels). The anterior commissure can be clearly delineated as superior border (**a**, coronal reformation, empty arrow). Medial border is the third ventricle, while there is no distinct lateral border. Superior and posterior border is the thalamus (**b** and **c**, sagittal and axial reformations)

pophysis loses its hyperintensity gradually, whereas the neurohypophysis remains hyperintense [3] (Fig. 6.1b). Experimental studies have shown that the high signal intensity of the posterior lobe is caused by accumulated neurosecretory granules containing ADH. Thus, in patients with a central diabetes insipidus, the high signal of the posterior lobe is absent, returning after appropriate medical substitution [4].

As the name suggests, the hypothalamus is anatomically located below the thalamus (Fig. 6.2). It is intimately associated with both the limbic system and the pituitary gland. Its boundaries are in part not clearly defined:

- Superior: between the anterior and posterior commissures; thalamus
- Anterior: lamina terminalis, with optic chiasm at the lower border and anterior commissure above
- Medial: third ventricle
- Posterior: a line running antero-inferiorly from the posterior commissure to the mammillary bodies; thalamus
- Lateral: no distinct border
- Inferior: infundibular stalk, tuber cinereum, and mammillary bodies

Imaging Techniques

A standard MRI protocol for examination of the pituitary and parasellar region consists of thin sliced (max. 2 mm) sagittal and coronal T1-weighted images with and without application of contrast medium (Table 6.1). Angulation of the coronal images should be parallel to the pituitary stalk. Thin sliced, sagittal T2-weighted images can be added for evaluation of cystic

Table 6.1 Possible protocol for MR imaging of the sella

	Description
MRI characteristics	Field strength of 1.5 T or 3 T (Tesla), slice thickness of 1.5–2 mm, small field of view (FoV), high matrix and in-plane resolution, ideally 0.5 × 0.5 mm
	T2-weighting (T2w) in coronal orientation, parallel to pituitary stalk (sagittal T2w localizer); additionally at least one plane in axial or sagittal orientation
	T1-weighting (T1w) native in coronal and sagittal orientation
	T1w coronal and sagittal after administration of i.v. contrast agent (e.g., 0.05 mmol/kg bodyweight (microadenoma) and 0.1 mmol/kg bodyweight (macroadenoma) of gadobutrol, respectively)
	3D T1 MPRAGE or 3D T1 SPACE+Gd volume dataset with 1 mm isotropic voxels
Dynamic hypophysis (T1w + Gd)	Flow rate: 2 ml/s
	Time of injection: start of the second dynamic measurement
	Duration of dynamic measurement: max. 30 s
	Number of measurements: 6–8
	Sequence: coronal T1w turbo-spin-echo or T1w VIBE (GRASP or TWIST)
	Voxel size: 0.5 × 0.5 × 2 mm
	Flush: 20 ml NaCl-Flush with a flow rate of 2.0 ml/s

lesions. We administer half of the standard dose of Gd-DTPA (0,05 mmol/kg) to search for microadenomas. In dynamic sequences after rapid injection of contrast medium, a diminished enhancement of microadenomas may be seen. Studies of normal pituitary tissue have also shown an earlier enhancement of the posterior lobe, due to the direct blood supply of the neurohypophysis via hypophyseal branches of the internal carotid artery. Adenomas also have direct arterial blood supply similar to the neurohypophysis. Exploiting this pattern of blood supply, some microadenomas can only be diagnosed using dynamic T1-weighted images. Additionally, there should be one scan covering the whole brain (T2w or FLAIR).

Computed tomography (CT) may become important when supportive information concerning bony structures or calcifications is required. CT is used in extensively growing pituitary adenomas, invading the sphenoid sinus, nasal cavity, or the skull base. Additionally, the anatomy of the sphenoid sinus can be evaluated as a precursor to transsphenoidal surgery. To exclude acute pituitary hemorrhage, CT may still be helpful in the emergency situation.

Nowadays, conventional radiography is no longer important in the diagnostic workup of pituitary adenomas. Adenomas are usually very slow-growing lesions, resulting in a vertical and horizontal enlargement of the bony pituitary fossa (balloon sella) with no demineralization. Asymmetric growth of pituitary adenomas may lead to a double outline of the sellar fundus in the lateral view. Thinning, destruction, or dorsal shift of the dorsum sellae might also occur. In patients with central Cushing's disease, if no adenoma is visible in MRI, selective inferior petrous sinus venous blood sampling is a highly specific technique that might be helpful in the diagnosis and especially lateralization of the microadenoma and might guide selected surgical resection.

Developmental Lesions of the Sella and the Hypothalamus

Rathke's Cleft Cyst

Most sellar epithelial cysts are remnants of derivates of the Rathke's cleft and arise in the region of the pars intermedia. They are relatively common incidental findings at autopsy (up to 30%) and usually remain asymptomatic [5]. Location is usually intrasellar, between the anterior and posterior pituitary lobes (Fig. 6.4c). Occasionally, they can occur in the suprasellar region, anterior to the infundibulum. Symptoms may result from

mass effect resulting in headache, endocrine dysfunction, or visual impairment due to compression of the optic chiasm.

Differentiation from craniopharyngioma is very important. Histologically, these lesions can be distinguished by the composition of their walls. Rathke's cleft cysts can contain mucinous or serous fluid and thus return variable signals in MRI. Cysts containing serous fluid are typically hypointense, whereas mucoid cysts show hyperintensity on T1-weighted images [5, 6]. Sometimes differentiation from acute hemorrhage can be difficult. Clinical symptoms and follow-up imaging are helpful in this setting.

Arachnoidal Cysts

While suprasellar arachnoidal cysts usually present with symptoms due to the local mass effect in children, the rare intrasellar arachnoidal cysts are regarded as acquired and may become symptomatic later in life [7–9]. Clinical symptoms may include increased intracranial pressure, hormone deficiency, gait disturbance, and visual impairment. Arachnoidal cysts arise from herniation of an arachnoidal diverticulum through an incomplete diaphragma sellae. Although usually indistinguishabe from Rathke's cleft cysts, they typically displace the anterior lobe and the infundibulum posteriorly [8]. On MRI, a focal mass with CSF signal intensity might be seen.

Ectopic Posterior Lobe

An ectopic posterior lobe is usually found in diagnostic imaging studies for growth hormone deficiency [10–13]. It is thought to be a developmental anomaly, rather than a residuum of traumatic (birth) incidents. Patients become conspicuous with an isolated growth hormone deficiency or multiple anterior pituitary lobe hormone deficiencies. On T1-weighted images, the ectopic posterior lobe is typically seen as a small nodule with characteristic high signal at the median eminence in the floor of the third ventricle [14–16] (Fig. 6.3). Sometimes, a tender pituitary stalk can only be seen after contrast enhancement.

Dermoid and Epidermoid Tumors

Both dermoid and epidermoid tumors are benign, slow-growing congenital lesions which result from inclusion of epithelial elements during embryogenesis. They may cause mass effect in the sellar, parasellar, or suprasellar region resulting in visual disturbance or endocrine dysfunction and consist of less than 2% of all intracranial neoplasms. Both lesions are often hypointense in T1- and hyperintense in T2-weighted images. Depending upon fat and calcium content, dermoid tumors can also show a hyperintense signal in T1 [17, 18]. For epidermoid tumors, diffusion-

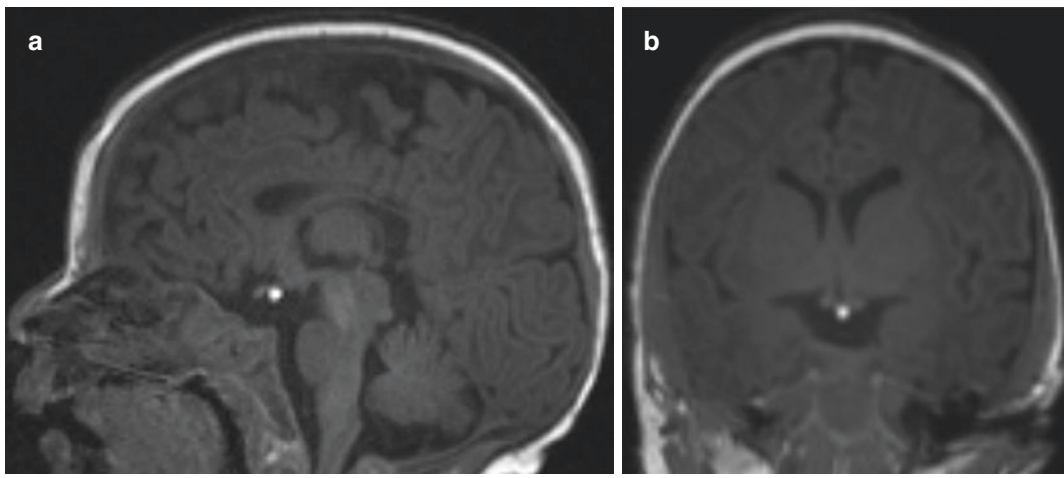

Fig. 6.3 Ectopic posterior lobe of the pituitary gland with bright signal in T1w. Sagittal (**a**) and coronal T1w (**b**)

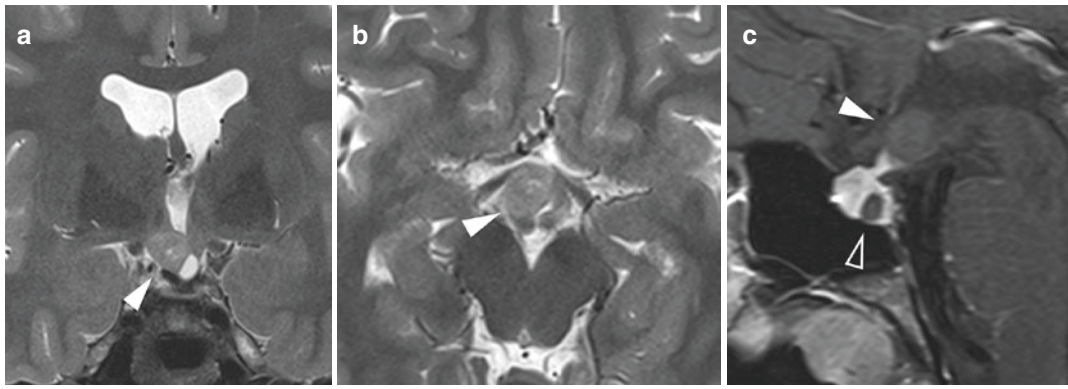

Fig. 6.4 Typical hamartoma of the tuber cinereum. Note the iso- to slight hyperintense signal with regard to the cortex in T2w (**a**, **b**). No enhancement in T1w + Gd (**c**). Secondary finding: Rathke's cleft cyst (empty arrow)

weighted images can be helpful, typically showing a markedly increased signal.

Hypothalamic Hamartomas

Hypothalamic hamartomas are of neuronal origin and represent congenital heterotopias usually located within the tuber cinereum. They usually affect children, who present with precocious puberty and epileptic seizures (gelastic seizures) [19]. Characteristically, MRI and CT show a rounded expansion of the tuber cinereum, best seen in coronal and sagittal images. Hamartomas are iso- to hyperintense to the cerebral cortex in T2-weighted images and isointense to the cortex in T1w images (Fig. 6.4). Because they are rarely larger than 1–2 cm in diameter, little mass effect is seen [20, 21].

Neoplasms of the Sella and the Hypothalamus

Pituitary Adenomas

Pituitary adenomas are benign epithelial lesions and account for about 10–15% of all intracranial tumors and thus represent the most common intrasellar pathology. In unselected autopsy series, the estimated incidence is up to 27%. Using the size as a criteria, adenomas larger than 10 mm are classified as macroadenomas, whereas tumors smaller than 10 mm are referred to as microadenomas (Fig. 6.5.). Classification concerning endocrine function distinguish hormone secretive from nonsecreting (nonfunctional) adenomas.

Prolactin-secreting adenomas are the most common secretive tumors and account for about 30% of all pituitary adenomas. Clinical manifestations in women are secondary amenorrhea, galactorrhea, and infertility [22]. In men, loss of libido and impotence can occur [23, 24]. Because of the varying symptoms, prolactinomas in men are often diagnosed at a later stage. Acromegaly in adults and gigantism in children are the cardinal symptoms of growth hormone-producing adenomas [25]. Incidence peak lies in the fifth life decade, causing growth of the feet and hands as well as coarsening of facial features like the nose and chin. Retrospective studies indicate that mortality is approximately doubled relative to the general population, mostly due to cardiovascular events [26, 27]. Their insidious onset often leads to significant delays in diagnosis.

About 5–10% of pituitary tumors cause elevated glucocorticoid levels (ACTH-producing adenomas). Overproduction leads to the stigmata of Cushing's disease, including diabetes, hypertension, osteoporosis, easy skin bruisability and striae rubrae, truncal obesity, moon facies, amenorrhea, impotence, and a generalized weakness. In children, growth retardation is a common

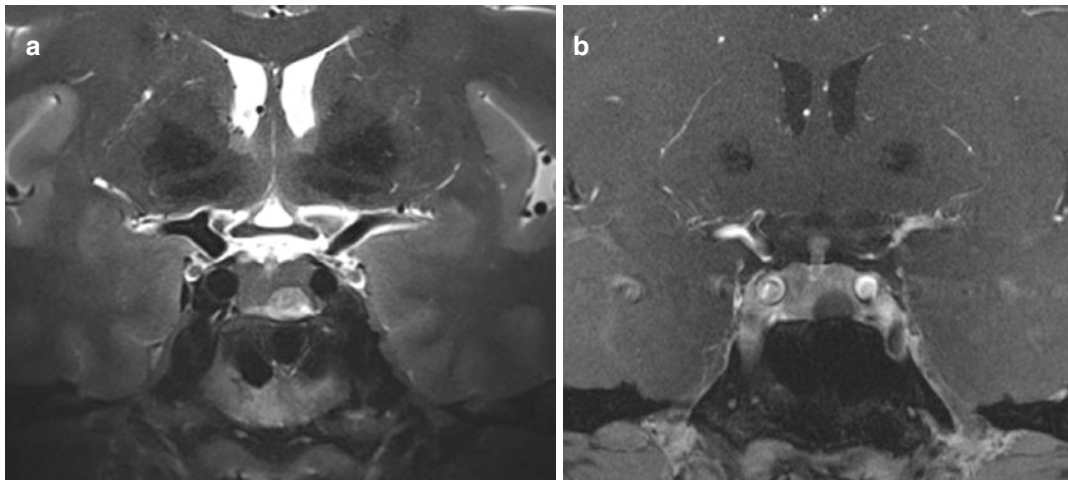

Fig. 6.5 Typical microadenoma (histologically prolactinoma), hyperintense in T2w, in the left aspect of the pituitary gland. Coronal T2w (**a**) and T1w + Gd (**b**)

manifestation [28]. Treatment can either be surgically or conservative with neuromodulatory drugs (i.e., bromocriptine) [29]. Patients with Cushing's syndrome that are treated surgically with bilateral adrenalectomy can develop an aggressive ACTH-producing adenoma (Nelson tumor) in about 15% [30, 31] due to the lack of the negative feedback loop.

Thyroid-stimulating hormone-producing adenomas occur in <1%, leading to hyperthyroidism [32]. Aberrant secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) is very rare, causing symptoms such as hypogonadism. About 10% of all adenomas are mixed tumors, out of which 75% are macroadenomas.

Nonfunctioning adenomas are the second most common tumors, comprising 25–30% of pituitary adenomas. The majority are macroadenomas that often grow to a significant size, causing visual field defects, hydrocephalus, or other mass effects. Parasellar infiltration into the cavernous sinus occurs in 40%, rarely leading to cranial nerve palsies [33, 34]. Cranial nerve palsy in combination with a sellar mass rather points towards metastasis or ophthalmoplegic aneurysm [35, 36].

Microadenomas are best evaluated in coronal images and usually appear hypo- or isointense relative to normal pituitary tissue on unenhanced T1-weighted images [3, 37]. On T2w images they often appear hyperintense. After contrast administration, due to an earlier and more intense enhancement of normal pituitary tissue, the microadenoma usually remains hypointense. Indirect radiologic features of microadenomas may be a one-sided elevation of the diaphragm or lapse of the pituitary fossa. In dynamic sequences after rapid injection of contrast medium, a diminished enhancement of the adenoma may be seen [38–41]. Studies of normal pituitary tissue have also shown an earlier enhancement of the posterior lobe, due to the direct blood supply of the neurohypophysis via hypophyseal branches of the internal carotid artery. Using fast T1-weighted images, some microadenomas demonstrate an early arterial enhancement, occurring simultaneously as enhancement of the posterior lobe [42]. However, compared with normal pituitary tissue, most microadenomas display a slightly lower signal intensity.

Macroadenomas are also best evaluated with MR imaging. These tumors usually extend beyond the sella and often show infiltration of the cavernous sinus, the sphenoid sinus, or the clivus. Compression of the optic chiasm and encasement of the internal carotid artery can be present [43]. Cavernous sinus invasion often restricts complete surgical tumor resection. In contrast to parasellar meningiomas, encasement of the internal carotid artery rarely causes luminal compromise in pitu-

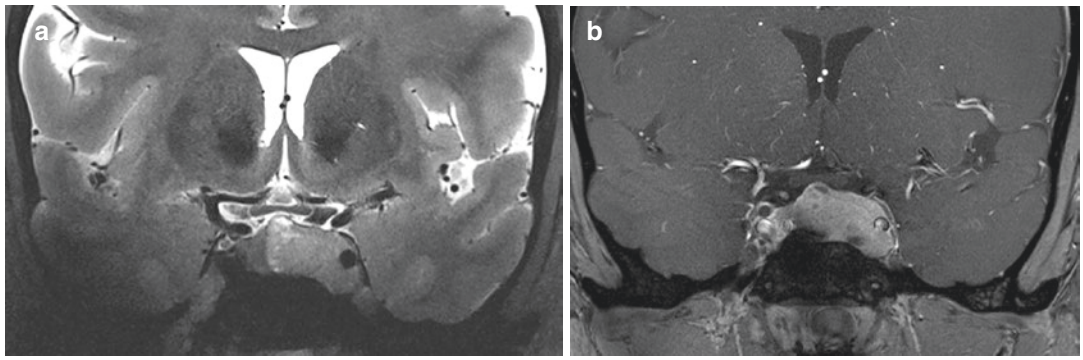

Fig. 6.6 Typical left sided macroadenoma with infiltration of the cavernous sinus und compression of the oculomotor nerve. Coronal T2w (**a**) and T1w + Gd (**b**)

itary adenomas. In about 94% macroadenomas lead to enlargement of the bony pituitary fossa (Fig. 6.6).

Intratumoral hemorrhage of macroadenomas occurs in up to 10–15% of incidental pituitary adenomas [44]. Medical treatment with bromocriptine and pregnancy are typical predisposing factors associated with pituitary apoplexy and hemorrhage [45, 46]. Primary pituitary hemorrhage may also occur traumatically, after surgery, after viral diseases or radiation, or during delivery. Acute hemorrhagic infarction of a pituitary adenoma is referred to as pituitary apoplexy with an impressive clinical presentation, i.e., acute onset of headache, vomiting, ophthalmoplegia, and visual loss [47, 48]. Rarely, meningism, loss of consciousness, or seizures can occur.

Other Pituitary Neoplasms

Primary tumors of the posterior lobe of the pituitary, e.g., pituicytomas or gangliogliomas, are very rare lesions.

Pituitary metastases most commonly arise from the common cancers such as breast, thyroid, or bronchogenic cancer and occur in approximately 3% of terminally ill patients [49]. Only about 5–15% of these patients become symptomatic [36]. Metastases tend to arise within the posterior lobe of the pituitary or the pituitary stalk and spread to the anterior lobe of the pituitary. Typical MRI findings include a relatively small enhancing pituitary lesion and lack of sella enlargement. Bony destruction may occur. Third nerve palsy in combination with a sellar mass rather points towards metastasis or ophthalmoplegic aneurysm and is unlikely in the case of adenoma. Rarely, pituitary adenomas can transform to pituitary carcinomas (0,1–0,5% of all pituitary tumors) [50, 51]. They are locally destructive and can metastasize to intracranial and intraspinal sites via CSF pathways. Hepatic, bronchial, bone, and lymphatic spread are also reported.

Hypothalamic Glioma/Optic Pathway Glioma

Sometimes the distinction between optic pathway gliomas and hypothalamic gliomas is not clear. In cases where a tumor is confined to the optic nerve, it can be referred to as optic nerve glioma. Often, however, they are either centered on or extend to involve the chiasm and optic radiations. In such cases, they are difficult to distinguish from hypothalamic gliomas, and such a distinction is arbitrary in most cases. In these cases, the term hypothalamic-optochiasmatic glioma should be used. Generally, the term optic pathway glioma is favored, recognizing that there may be involvement of the hypothalamus.

Optic pathway gliomas are relatively uncommon tumors, with a variable clinical course. They are often seen in the setting of neurofibromatosis type I (NF1) and are frequently bilateral.

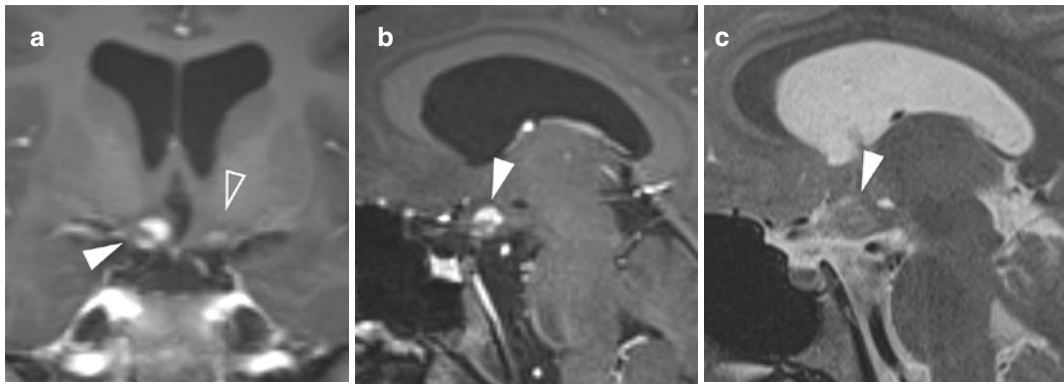

Fig. 6.7 Vividly enhancing mass of the right hypothalamus, extending along the optic tract (**a** and **b**, coronal and sagittal T1w + Gd). Hyperintense signal in T2w (C, sagittal). Note the small enhancing secondary manifestation in the contralateral hypothalamus (empty arrow)

Histologically, the majority are pilocytic astrocytomas. They are characterized on imaging by an enlarged optic nerve. These tumors usually return low signal on T1w and high signal on T2w images, enhancement of contrast agent is often vivid but variable (Fig. 6.7). A widely accepted classification of optic pathway gliomas is the Dodge classification [52]. This simple classification divides the tumors into three groups based on anatomical localization: stage 1, optic nerves only; stage 2, chiasm involved (with or without optic nerve involvement); and stage 3, hypothalamic involvement and/or other adjacent structures.

Optic pathway gliomas demonstrate variable clinical and radiological progression. In patients with NF1, it is not unusual for these tumors to be clinically quiescent, with little progression over some years. In others, the tumors are more aggressive (Fig. 6.8) and extend along the optic pathways; therefore, treatment depends on the clinical situation.

Meningiomas

Meningiomas of the sellar region (cavernous sinus, planum sphenoidale, diaphragma sellae, clinoid process) account for 20–30% of all intracranial meningiomas. They are benign, slow-growing tumors that can reach considerable size at the time of diagnosis.

To distinguish meningiomas from neurinomas, dynamic contrast enhancing MRI sequences are useful, since meningiomas usually show early enhancement, while neurinomas present gradual enhancement [53, 54].

Due to an en plaque growth pattern often associated with a "dural-tail," demarcation from pituitary macroadenomas is usually possible. Pure intrasellar meningiomas are very rare and may be hard to distinguish from adenomas [55, 56]. They usually originate from the dorsum sellae. When invading into the cavernous sinus, meningiomas tend to constrict the carotid lumen, unlike adenomas, which are thus mostly easily distinguishable [43, 57–59]. They often cause hyperostosis at the sites of bony attachment.

Craniopharyngioma

Craniopharyngioma is an important differential accounting for approximately 3% of all intracranial tumors. Usually slow growing, craniopharyngiomas arise from squamous epithelial cell rests of Rathke' pouch [60]. Craniopharyngiomas may be divided into adamantinomatous or squamous-papillary histological types [61]. In children they make up about 5–10% of all intracranial neoplasms, being the third frequent tumor after medulloblastoma and astrocytoma. Patients usually present with headache, visual impairment, hydrocephalus, or hypopituitarism. Although suprasellar

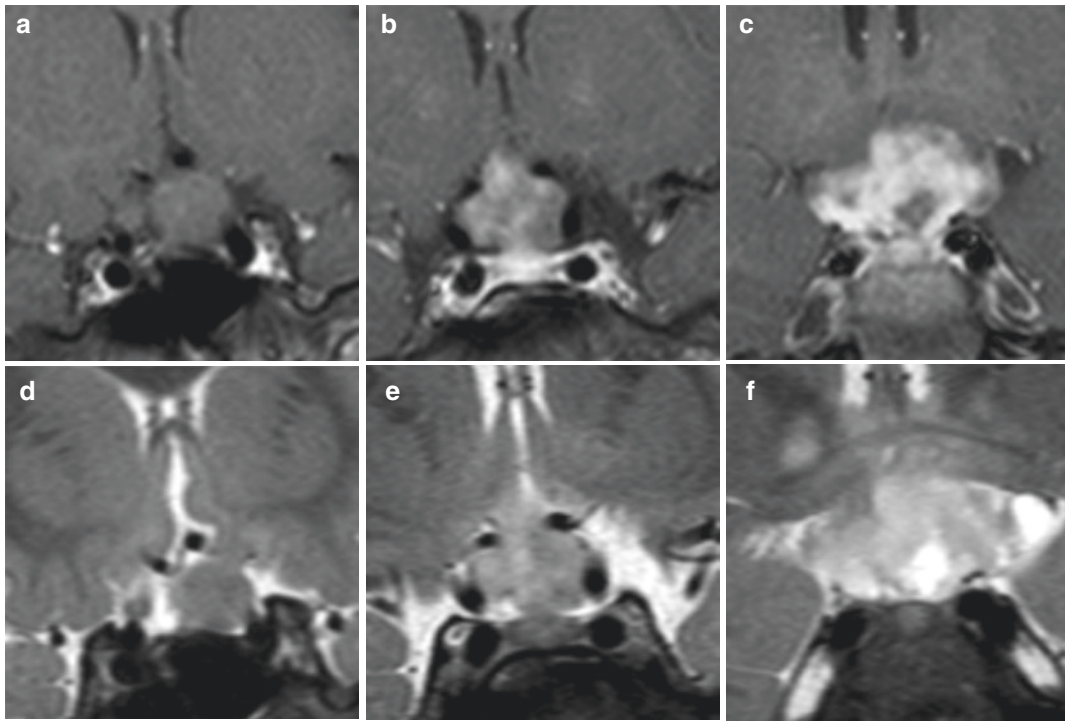

Fig. 6.8 T1w + Gd (**a** + **b** + **c**). T2w fat-sat (**d** + **e** + **f**). Partly enhancing, T2w hyperintense mass of the optic chiasm, extending along the left optic nerve (**a**). Diffuse infiltration of the hypothalamus. Patient with neurofibromatosis I

in origin, about 50% extend into the sella. The suprasellar component of the tumor may induce edema to spread along the optic tract [62, 63]. In CT and MRI craniopharyngiomas have a typical heterogeneous appearance with cystic and solid components (Fig. 6.9) and frequently (approximately 93%) abundant calcifications [61, 64] (Table 6.2). The solid tumor portions as well as the cyst wall enhance usually after contrast administration.

Germ Cell Tumors

Intracranial germinomas occur most frequently in the pineal and suprasellar region but can also have a primary intrasellar origin [65, 66]. Occasionally, these tumors can extend and involve the sella turcica and mimic pituitary macroadenoma. Germinomas usually show prominent contrast enhancement and present well-defined margins. Individual case reports describe sellar lesions that radiologically cannot be differentiated from pituitary adenomas, such as chondrosarcomas, granular cell tumors [67, 68], gangliocytomas [69, 70], fibrosarcomas [71, 72], hemangiopericytomas [73], esthesioneuroblastomas [74], melanomas [75], ependymomas [76], or lymphomas [77].

Schwannoma/Neurinoma

Nerve sheath tumors in the parasellar region are very rare lesions and usually arise from the trigeminal nerve (V1/V2) or the third, fourth, and sixth cranial nerve [78]. Neurinomas are slowly growing tumors. Expansion through the superior orbital fissure or the oval and round foramen has been described. On MRI they show an intense (usually heterogeneous) contrast enhancement [79, 80].

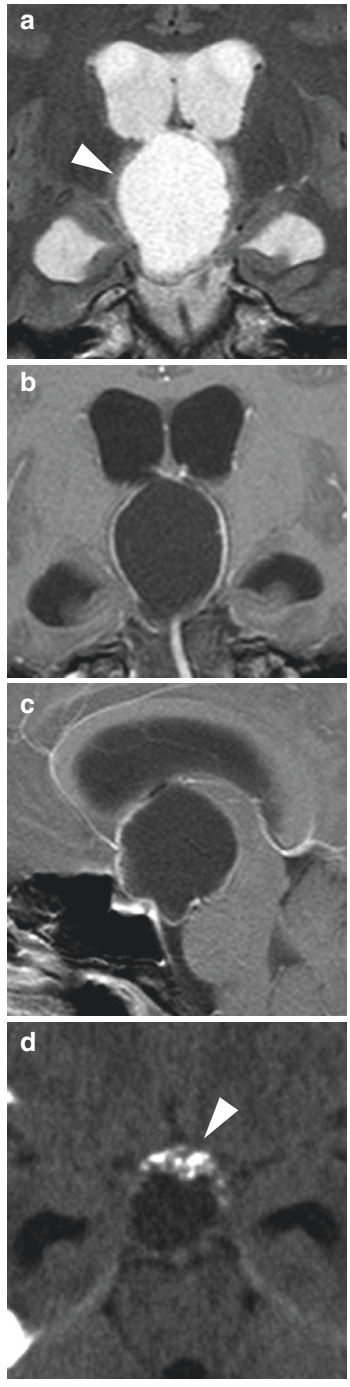

Fig. 6.9 Large cystic mass with hyperintense signal in T2w (**a**, coronal) and suprasellar epicenter. Thin, enhancing cyst wall (**b** and **c**, coronal and sagittal, T1w + Gd). Peripheral calcifications (**d**, axial CT). Obstructive hydrocephalus is present due to compression of die third ventricle and the midbrain/aqueduct (**c**). Neuropathology revealed adamantinomatous craniopharyngioma

Neoplasms Involving the Clivus

Neoplasms in the clival region can include chordoma, chondrosarcoma, hemangiopericytoma [81], meningioma, lymphoma [82], plasmacytoma, paraganglioma [83], or metastasis. With an incidence below 1%, chordoma and chondrosarcoma are even rarer than malformative tumors [84]. Clival chordomas are slow-growing tumors arising from the remnants of the primitive notochord. It shows no age or sex predilection and usually causes bony destruction and can reach considerable size at the time of diagnosis. This extracranial tumor is heterogeneously hyperintense on T2-weighted images and shows a marked contrast enhancement. Chondroma is another bone-destructing, nodular/lobular tumor that tends to undergo mucinous, cystic regression and calcification. It most commonly arises from cartilaginous remnants in the area of the foramen lacerum. Imaging findings are similar to those in chordoma. Clival tumors tend to extend posteriorly into the prepontine cistern [85–88].

Neoplasms Involving the Sphenoidal Sinus

Mucoceles are the most common space-occupying lesions of the sphenoid sinus. The pathogenesis relates to obstruction of the sphenoid ostium (secondary mucocele) or mucous retention cyst expansion (primary mucocele). In CT, a nondestructive mass, causing a thinning and bulging of the bony sinus walls, may be seen. The sellar part can mimic a para- or suprasellar mass. MRI better demonstrates the wall-enhancing fluid-filled lesion [89–91] . Rarely, inverted papillomas arising from the ethmoidal sinus can extend to the sphenoid sinus.

Table 6.2 Imaging features of craniopharyngiomas and macroadenomas

	Craniopharyngioma	Macroadenoma
Calcifications	90%	1–2%
Localization	Suprasellar (rarely purely intrasellar)	Intrasellar epicenter (may extend supra-/parasellar)

Vascular and Inflammatory Lesions of the Sella and the Hypothalamus

Aneurysms

Aneurysms of the sellar region usually originate from the cavernous or supraclinoid portions of the internal carotid artery and account for about up to 10% of all cerebral aneurysms. In selected cases they can mimic other supra-, para-, or intrasellar lesions [92]. MR angiography (time-of-flight or contrast enhanced) is useful in differentiating tumor from aneurysms (Fig. 6.10). Usually, the aneurysm itself can be sufficiently visualized by noninvasive imaging. These aneurysms may cause hypopituitarism or, in case of rupture, may also lead to (subarachnoid) hemorrhage in up to 15% [93].

Cavernous Sinus Thrombosis

Thrombosis of the cavernous sinus is a rare condition and often secondary to iatrogenic or septic etiologies [94, 95]. On MRI, enlargement of the cavernous sinus with internal filling defects and incomplete enhancement of the sinus may be noted, along with a diffusion restriction in the case of a (sub-)acute thrombus [96] (Fig. 6.11). Additionally, periorbital edema, exophthalmos, or dilatation of the superior ophthalmic vein can occur.

Inflammatory and Infectious Lesions

Sarcoidosis, a systemic disease featuring multiple noncaseating granulomas, may involve the central nervous system in about 5% of cases. Predilection sites are the basal leptomeninges especially the sellar and suprasellar region, such as the pituitary stalk, optic chiasm, and the hypothalamus, respectively [97] (Fig. 6.12). Since radiological differentiation from other disease such as lymphocytic hypophysitis is often impossible, clinical history and time course are of great importance.

Lymphocytic hypophysitis is a rare autoimmune inflammatory disease most often seen in women in the peri- or postpartum period. Clinical symptoms usually include diabetes insipidus, amenorrhea, hypopituitarism, headache, and visual impairment favorably responding to steroid therapy [98–100]. MRI usually demonstrates thickening of the pituitary stalk in combination with an intense contrast enhancement [101].

Granulomatous hypophysitis can occur with fungal infections, tuberculosis [102], sarcoidosis [103], Langerhans cell histiocytosis, and Wegner's granulomatosis [104] and accounts for approximately 1% of sellar masses. The typical radiological appearance is similar to that of lymphocytic hypophysitis [105, 106].

Pituitary abscess can be primary or secondary due to an adenoma or to surgical procedure [107]. Spread of gram-positive bacteria from the sphenoid sinus is the usual source of infection, but rare infectious disease such as toxoplasmosis [108] or cryptococcosis has been described. Typical MRI findings are those of a round sellar mass with ring enhancement. Furthermore, meningeal enhancement due to concurrent meningitis may help distinguishing pituitary abscess from pituitary adenoma [109–111].

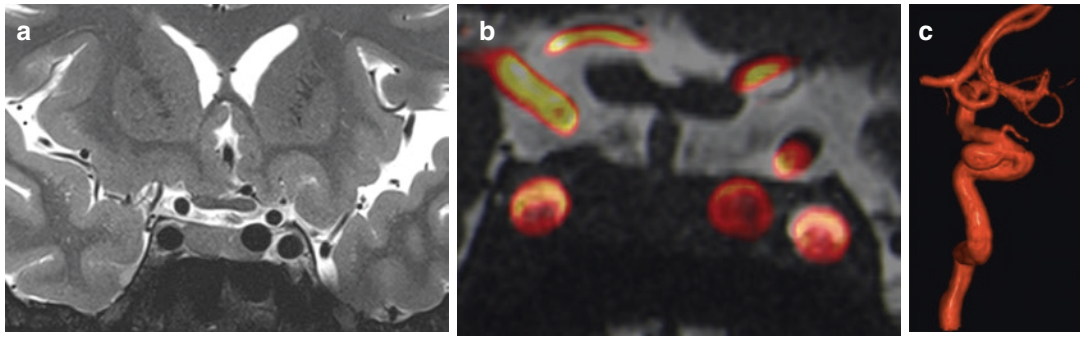

Fig. 6.10 Left infraophthalmic, saccular aneurysm of the ICA. Medially, the aneurysm reaches the pituitary body; cranially it slightly elevates the diaphragma sellae. Coronal Tw2 (**a**) and fusion of ToF-angiography with 3D T2w CISS (**b**). VRT reconstruction of ToF-angiography showing the saccular aneurysm (**c**)

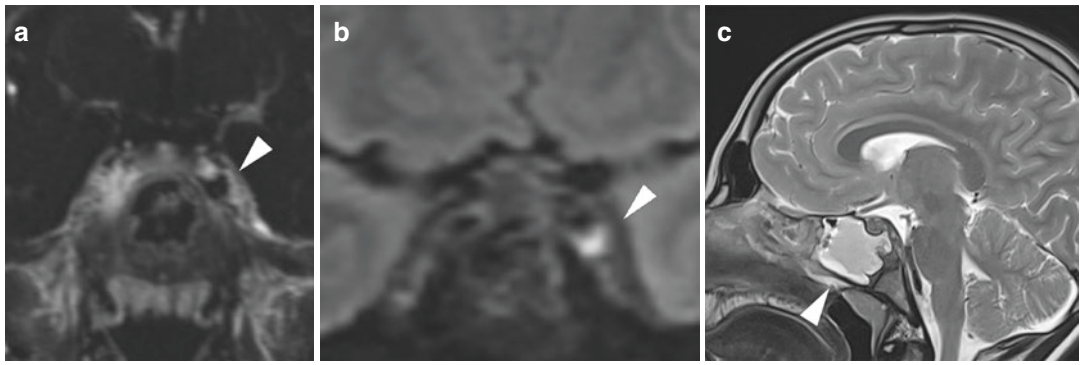

Fig. 6.11 Filling defect in the left cavernous sinus (**a**) and corresponding diffusion restriction of the acute thrombus (**b**). Thrombosis was presumably secondary due to sinusitis sphenoidalis (**c**)

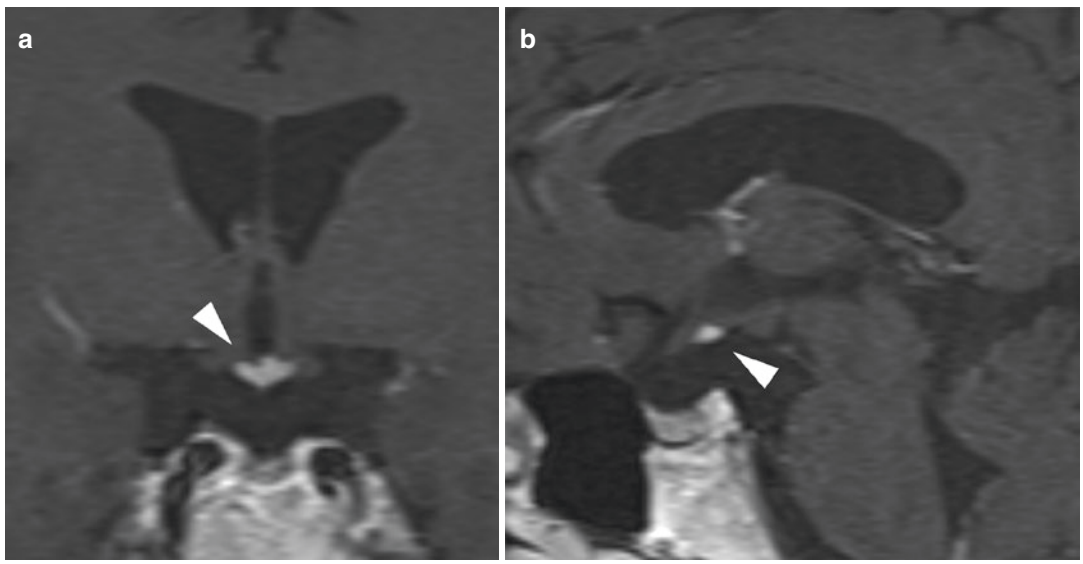

Fig. 6.12 Neurosarcoidosis. Vivid contrast enhancement of the tuber cinereum (**a** and **b**, T1w + Gd coronal and sagittal). Distant leptomeningeal enhancement frontal (not shown). Skin biopsy revealed sarcoidosis

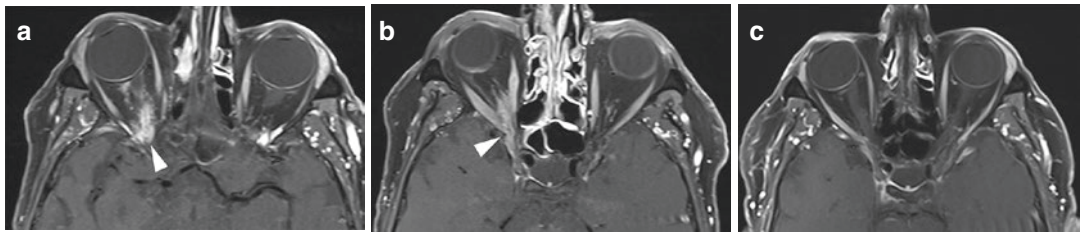

Fig. 6.13 Contrast enhancement extending to the right cavernous sinus with thickening of the adjacent lateral and medial rectus muscle (**a** and **b**, T1w + Gd). The inflammatory changes have fully resolved after 6 months and therapy with steroids (**c**)

Tolosa-Hunt/Orbital Apex Syndrome

Tolosa-Hunt syndrome is a painful, recurrent ophthalmoplegia that usually responds favorably to steroid medication. It is essentially a diagnosis of exclusion. Associated with granulomatous inflammatory changes at the cavernous sinus and the superior orbital fissure, it can frequently strike various cerebral nerves located within this area [112]. Contrast-enhanced MRI shows an asymmetrical expansion and enhancement of the orbital apex extending to the cavernous sinus [113–115] (Fig. 6.13) and may also lead to thickening of the orbital muscles as well as cause secondary thrombosis of the cavernous sinus.

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Neurological Syndromes of the Hypothalamus

7

Christopher Morgan Smith, Rima El-Abassi, and David Chachkhiani

Introduction

The hypothalamus is a small, but crucial and unique, structure of the brain that has many functions, including homeostatic mechanisms (i.e., hunger, thirst, circadian rhythms), endocrine hormone production, autonomic control, and limbic regulation. One can recall its function with the mnemonic "HEAL" (Homeostasis, Endocrine, Autonomic, Limbic) [1]. However, in this chapter, rather than its function, we will be discussing the *dysfunction* of the hypothalamus and many of the consequential clinical syndromes of hypothalamic dysregulation.

Recall from Part I, Chap. 4, that there are three major regions of the hypothalamus – supraoptic, tuberal, and mamillary regions. Despite the very small size of the hypothalamus, these regions encompass many key nuclei including the paraventricular nucleus, supraoptic nucleus, dorsomedial nucleus, posterior nucleus, anterior nucleus, lateral nucleus, mammillary body, arcuate nucleus, suprachiasmatic nucleus, ventromedial nucleus, and preoptic nucleus. It is important to take note of key hypothalamic nuclei responsibilities to best understand their dysfunction. As we will see, any insult to these cramped regions and nuclei can produce profound neurological changes.

Neuro-structural Syndromes – *Neurovascular Ischemia/Infarct/Trauma*

The etiology of structural insults to the CNS can vary including neurovascular lesions, vasculopathies, trauma, inflammatory processes, infectious processes, tumors/malignancy, electrolyte/metabolic disturbances, congenital defects, and neurodegenerative disorders. One of the most common neurological insults is neurovascular lesions, or stroke.

The arterial blood supply of the hypothalamus largely comes from the branches of the circle of Willis. Almost every nuclear group within the hypothalamus receives its arterial supply from multiple blood vessels and/or branches of local vessels. The ventral supraoptic region obtains its blood supply from the tubero-optic branch of the internal carotid artery, the dorsal aspect of the supraoptic region gets its blood supply from the branches of the anterior cerebral artery, while the preoptic areas receive its blood supply via the anterior communicating artery. The paraventricular, lateral, and dorsomedial nuclear regions obtain its supply from the posterior communicating artery. The lateral and median tuberal nuclei are supplied by the cir-

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Table 7.1 Hypothalamic nuclei and correlating functions

Hypothalamic nuclei	Function
Preoptic n.	Thermoregulation
Suprachiasmatic n.	Circadian rhythms; sleep
Anterior n.	Thermoregulation; reduction in temperature
Paraventricular n.	Oxytocin release, ADH release
Supraoptic n.	Thirst, ADH release
Periventricular n.	Autonomic regulation, metabolism, growth, reproduction
Arcuate n.	Appetite regulation
Ventromedial n.	Appetite regulation, reproduction
Posterior hypothalamic n.	Autonomic regulation, thermoregulation
Mammillary n.	Memory
Lateral hypothalamic n.	Hunger, thirst, arousal

cuminfundibular plexus. Finally, the mammillary bodies are supplied by the posterior cerebral arteries distal to the bifurcation of the basilar artery as well as the posterior communicating arteries. Interestingly, the vessels that supply the deepest nuclei enter more superficially [2].

Figure 7.1 demonstrates many of the arteries responsible for supplying the hypothalamus [3]. Any insult to the aforementioned arteries can give rise to hypoperfusion and ischemia to its area of blood supply. As many of these vessels are notably small vessels, a single lesion may not be enough to infarct the correlating hypothalamic tissues; however, a more proximal lesion can produce devastating effects.

In review of some of the important hypothalamic regions and nuclei (Table 7.1 demonstrates major hypothalamic nuclei and correlating function), remember that the anterior and posterior hypothalami are important in autonomic functions such as temperature regulation. The posterior hypothalamus is responsible in increasing body temperature when the body temperature is reduced. As the anterior region (preoptic n.) aids in reducing an overheated body temperature and the posterior hypothalamus (posterior n.) is useful in the hyperthermic effects, an imbalance between the two opposing forces can yield an abnormal baseline body temperature. Considering the anterior communicating artery supplies the preoptic area, obstruction in blood flow through the anterior communicating artery can lead to infarct, which would produce an overall hyperthermic effect.

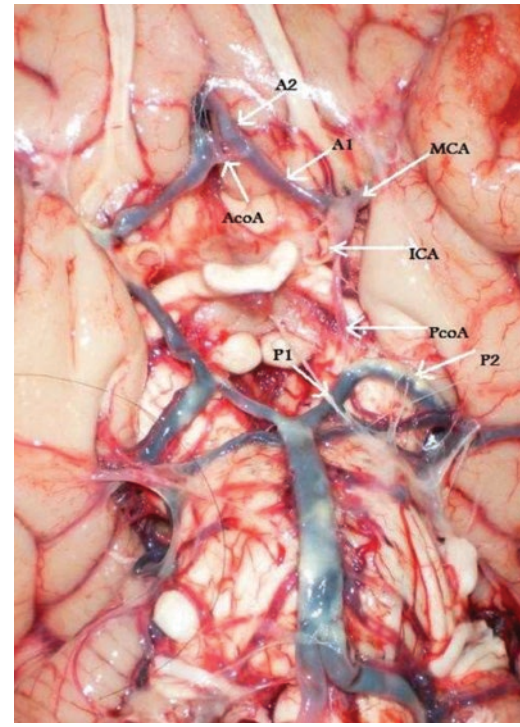

Fig. 7.1 Circle of Willis. Labeled are some of the arteries responsible for supplying the hypothalamus. Anterior cerebral arteries (A1)(A2); posterior cerebral arteries (P1) (P2) near their origin; posterior communicating artery (PcoA); and anterior communicating artery (AcoA) [3]

Demyelinating Disorders: *Multiple Sclerosis and Neuromyelitis Optica*

One of the more well-known neurological demyelinating disorders is multiple sclerosis. Multiple sclerosis is defined by the American Academy of Neurology as a chronic disorder characterized by inflammation and demyelination of the central nervous system associated with variable degrees of axonal and neuronal damage [4]. Multiple sclerosis classically affects CNS white matter, or neuronal fiber bundles. Demyelination of these fibers within or near the hypothalamus can produce autonomic and endocrine abnormalities and

mood disorders in individuals living with multiple sclerosis. The hypothalamus, however, frequently appears normal on neuroimaging, despite clinical evidence of hypothalamic involvement and confirmation on necropsy studies [5].

Clinically, hypothalamic dysfunction in multiple sclerosis can present similarly to those with neurovascular or structural lesions. Thus, it is important to note that autonomic features and sleep disturbances are common among multiple sclerosis patients. Parenteral glucocorticoids (i.e., methylprednisolone) may be considered the drug of choice in patients presenting with acute demyelinating lesions in multiple sclerosis, and the hypothalamo-pituitary-adrenal axis (HPA) is crucial in the production of intrinsic glucocorticoids. Demyelinating lesions to the HPA may impede innate steroidal production and theoretically increase the susceptibility and severity of future multiple sclerosis flares. When compared to controls, few studies have shown that patients living with multiple sclerosis showed significantly higher neuronal activation in production of corticotropin-releasing hormone (CRH) [6].

Neuromyelitis optica spectrum disorder (NMOSD), previously known as Devic's disease, is a similar process to multiple sclerosis in that it is an inflammatory demyelinating disease of the central nervous system and can easily be mistaken for multiple sclerosis (Table 7.2 demonstrates major differences between NMOSD and MS). NMOSD is an aggressive demyelinating process associated with episodic optic neuritis, transverse myelitis, and serum biomarkers: aquaporin-4 (AQP4)-IgG and myelin oligodendrocyte glycoprotein (MOG)-IgG. The transverse myelitis seen in NMOSD is typically more longitudinally extensive involving 3 or more vertebral segments of the spinal cord. Episodic intractable nausea, vomiting, or hiccups are also a feature of NMO with area postrema irritation or involvement [4].

Prior to the discovery of the AQP4-Ab in 2004, Devic's disease was largely considered to have an absence of brain involvement. However, with advancing studies, certain discoveries may prove otherwise. In fact, hypothalamic lesions may be more prevalent in neuromyelitis optica than multiple sclerosis; however, this claim is under study [7]. AQP4-Ab has a sensitivity of ~60% and a specificity of 98% on tissue-based assay [8]. Patients who have AQP4-Ab positive NMOSD with hypothalamic lesions had symptoms of ataxia, intractable hiccups/nausea, SIADH, and encephalopathy, which were more common than those without hypothalamic lesions.

Table 7.2 Clinical comparison between neuromyelitis optica and multiple sclerosis

	Neuromyelitis optica (Devic's disease)	Multiple sclerosis
AVG. age of onset	40s	30s
Brain involvement	Brain MRI is typically nonspecific	Multiple periventricular white matter lesions (Dawson's fingers)
Optic nerve involvement	Mostly unilateral, however can be bilateral as well; outcome is typically poor	Mostly unilateral with favorable recovery
Spinal cord involvement	Longitudinally extending (>3 vertebral segments)	Smaller lesions
Associated antibody	Associated with serum NMO antibody	Associated with oligoclonal bands in CSF
Overall impairment	Functional impairment after attack is usually severe	Usually less severe outcome

Limbic Encephalitis

The limbic system is a collection of brain structures that aid in many functions including homeostasis, olfaction, memory, and emotion (mnemonic – "HOME") [1]. Interestingly, these structures are thought to be resultant of evolutionary change as they may have played an important role in survival. Key structures of the limbic system include the hypothalamus, hippocampus, amygdala, thalamus, septal nuclei, olfactory cortex/bulb, limbic cortex, and basal

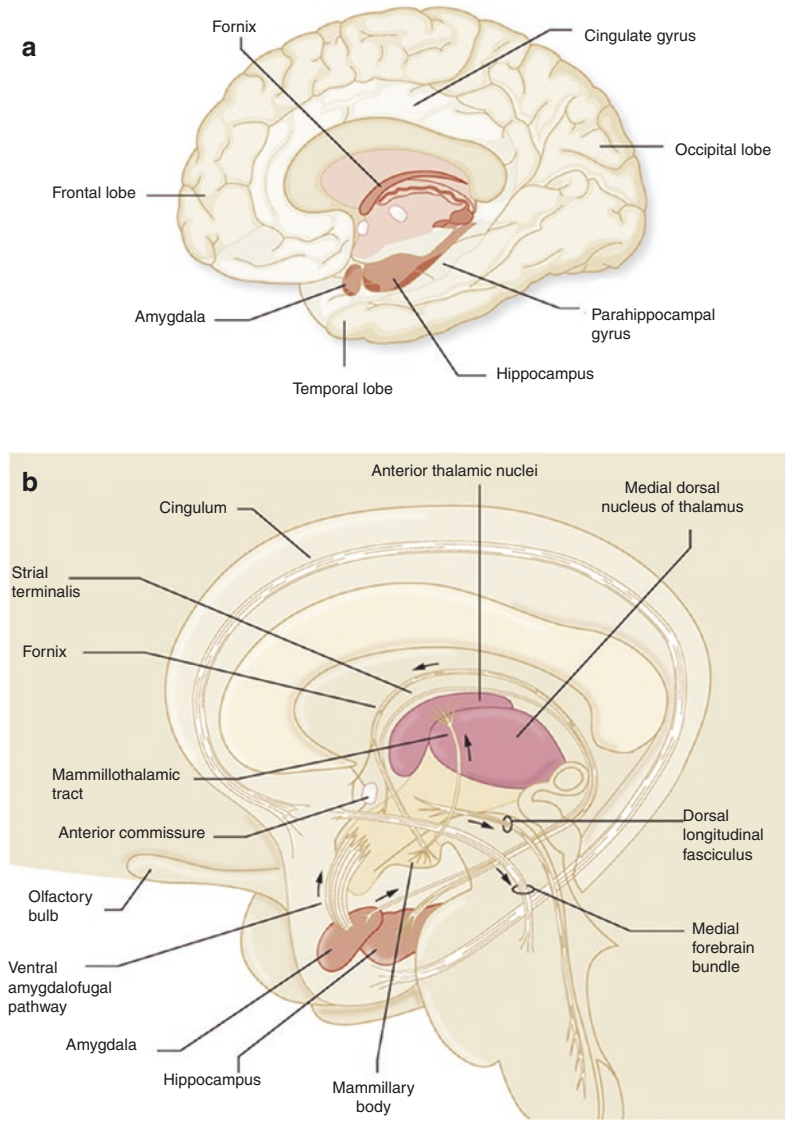

Fig. 7.2 Limbic structures and cortical pathways. (Source: Ropper AH, Samuels MA, Klein JP: *Adams and Victor's Principles of Neurology, Tenth Edition*: www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved)

ganglia. Figure 7.2 depicts a visual representation of many of the limbic system structures [9].

Limbic encephalitis is a neurological disorder in which the limbic system is affected by inflammation and consequently dysfunction. Limbic encephalitis classically presents as short-term memory loss, agitation, cognitive impairment, and seizures. Involvement of the hypothalamus may also include presenting symptoms of sleep disturbances, fatigue, narcolepsy, hyperthermia, weight gain, sexual dysfunction, autonomic dysfunction, and hormonal dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Most causes of inflammation to the limbic system include infectious or autoimmune etiology. There is insufficient data to suggest a prevalence or incidence rate of limbic encephalitis.

Autoimmune forms of limbic encephalitis are further categorized into paraneoplastic limbic encephalitis and non-paraneoplastic limbic encephalitis. Between the two subsets of autoimmune encephalitis, non-paraneoplastic limbic encephalitis is much more common [10]. Non-paraneoplastic limbic encephalitis is caused by circulating antibodies recognizing self-antigens located on or near the limbic system.

Table 7.3 Known antigens associated with autoimmune encephalitis

Intracellular antigens	Neuronal-surface proteins
GAD 65 – glutamic acid decarboxylase	Caspr2 – contactin-associated protein 2
CRMP5 – collapsin response mediator protein 5	LGI-1 – leucine-rich glioma-inactivated 1
Ma1/2 – Ma proteins widely throughout a normal brain	DDPX – dipeptidyl-peptidase-like protein 6
DNER – Delta/Notch-like epidermal growth factor	GFAP – glial fibrillary acidic protein
	Neurexin-3-alpha – synapse membrane proteins
	IgLON5 – a cell surface adhesion molecule

Table 7.4 Autoimmune encephalitis antibodies with associated clinical features

Antibody	Associated clinical features
Anti-NMDA	Memory loss, psychosis, seizures, insomnia, dyskinesias
Anti-Ma2	LE, daytime sleepiness, ophthalmoplegia
Anti-Hu	Sensory neuropathy, LE, cerebellar ataxia
Anti-VGCC	Cerebellar ataxia
Anti-LGI1	LE, faciobrachial dystonic seizures, different epileptic seizures
Anti-GABA-A	Refractory seizures, status epilepticus, cognitive and behavioral changes
Anti-GABA-B	LE, seizures, opsoclonus-myoclonus
Anti-Caspr2	LE, cerebellar ataxia, neuromyotonia
Anti-AMPA	LE, bipolar features, seizures
Anti-IgLON5	Parasomnias, chorea

LE limbic encephalitis

Potential threatening antibodies have been identified to target antigens that play a crucial role in signal transmission in the central nervous system. Table 7.3 details some of the major intracellular antigens and proteins involved in the etiopathogenesis of this form of encephalitis. Intracellular antigens (GAD54, CRMP5, Ma1, Ma2, DNER), extracellular neuronal cell-surface proteins (Caspr2, LGI-1, DDPX, GFAP, neurexin-3-alpha, IgLON5) and receptors (NMDAR, AMPAR, GABAbR, GABAaR, mGluR), and others (MOG, AQP4).

Most non-paraneoplastic limbic encephalitides result from antibodies attacking cell surface proteins or receptors, instead of the intracellular foci. Some of the well-established foci include LG1, CASPR2, AMPA receptor, GABA(A/B) receptor, AMPA receptor, and NMDA receptor. Receptor antibodies can alter receptor functioning and receptor density in synapses [11].

Table 7.4 details the major autoantibodies and their associated clinical presenting symptomatology and signs in the spectrum of autoimmune encephalitis.

Voltage-gated potassium channels (VGKC) were once believed to be a major antigen associated with limbic encephalitis. The VGKC complex is the combination of LGI1 and CASPR-2 with voltage-gated potassium channels. Patients with LGI1-antibody positivity are more likely to have features of limbic encephalitis and seizures (Table 7.3 shows autoimmune encephalitis antibodies associated with clinical features), while patients with CASPR2-antibody positivity were more likely to experience symptoms of limbic encephalitis with neuromyotonia, dysautonomia, and neuropathic pains.

The N-methyl-D-aspartate (NMDA) receptor is a glutamate receptor that allows cations (positively charged ions) to flow through the neuronal cell membrane allowing for depolarization. The NMDA receptor aids in synaptic receptor down-/upregulation and memory. Anti-NMDA receptor encephalitis has a higher prevalence in women compared to men but can be seen in children as well [12]. Clinical symptoms may include hallucinations (auditory/visual), agitation, impaired consciousness, seizures, motor dysfunction, and autonomic dysfunction. Anti-NMDA receptor antibodies can also be associated with psychiatric conditions like schizophrenia [12], and caution should be used when considering a diagnosis of NMDA-receptor encephalitis. The alpha-amino-3-hydroxy-5-methyl-isoxazolepropionic acid (AMPA) receptor is an ionotropic transmembrane receptor that, when activated, induces NMDA receptor activity. Antibodies against the AMPA receptor typically target the glutamate receptor (GluR1, GluR2) subunits. The AMPA receptors are also expressed widely throughout the CNS, including the hypothalamus.

Glucagon-like peptide-1 (GLP-1)-expressing neurons in the hindbrain have been found to project to the paraventricular nucleus of the hypothalamus and aid in the regulation of food consumption by enhancing AMPA receptor expression. Anti-AMPAR encephalitis is a paraneoplastic process in 64% of cases, and malignancy screening should be considered. The typical presenting features are limbic encephalitis or psychosis, and the prognosis and treatment response largely depend on detection of tumors and onconeural antibodies [13].

Another important paraneoplastic limbic encephalitis to mention in special regard to the hypothalamus is anti-Ma2 encephalitis. Anti-Ma2 limbic encephalitis differs from the classical presentation of paraneoplastic limbic encephalitis. This subtype of paraneoplastic encephalitis often presents with diencephalic or brainstem dysfunction. In one study of 34 patients with confirmed anti-Ma encephalitis, excessive daytime sleepiness was seen in 32% of patients, and 34% had additional abnormalities seen in hormonal testing or MRI findings that indicated hypothalamic involvement [14]. Notably, in both anti-Ma1 and anti-Ma2 encephalitis, tumors can be an underlying factor and must be screened for particularly of the testes. Immunosuppressive therapy and oncological treatments have been shown to improve outcomes [14].

The first step in approaching limbic encephalitis is its diagnosis and malignancy screening. Treatment and prognosis of autoimmune limbic encephalitis vary largely on the time of diagnosis, type of antibody, comorbidities, and associated malignancies. Diagnosis can be very challenging as patients often present with nonspecific signs and symptoms. Treatment options can include supportive therapy, glucocorticoids, IVIG, plasma exchange, or immunomodulatory therapies (i.e., azathioprine, mycophenolate, etc.).

Migraine

Migraine is a neurological disorder that most commonly presents as recurrent severe headaches. There are classically four main phases of migraine – migraine aura, premonitory phase, headache phase, and the postdrome [15]. The International Classification of Headache Disorders, Third Edition (ICHD-3), defines migraine aura as recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Migraines can be with or without aura. About 20–40% of patients with migraines report some form of aura. Roughly 90% of migraine auras are reportedly visual symptoms, and ~ 10% are sensory, language, and/or motor symptoms (usually in addition to visual symptoms) [15]. The typical duration of migraine aura is 30 minutes; however, it can last anywhere from a few minutes to 4 hours. The etiology of migraine auras is currently unknown, but interestingly, one theory is that visual auras are a consequence of a higher neuron-to-astrocyte ratio in the visual cortex [15]. Figure 7.3 offers another theory of migraine etiology by means of electrophysiological hyperexcitability extending to nerves and glial cells called *cortical spreading depression* [15].

The premonitory, or prodromal, phase is newly defined as a period of nonpainful symptoms which precede the onset of migraine headache usually by hours to a few days. The most common symptoms of the premonitory phase include fatigue, mood changes, and yawning; however, symptoms can largely be categorized as cognitive changes, homeostatic alterations, and sensory sensitivities. Following the premonitory phase, the headache phase of migraines is typically a severe, unilateral headache with associated nausea, vomiting, photophobia, and phonophobia lasting 5–72 hours. Finally, the postdrome phase is the time between resolution of migrainous headache and at which point the patient feels he/she is back to baseline. Similar to the premonitory phase, symptoms constitute non-headache symptoms, most commonly fatigue, lack of concentration, and neck stiffness [16].

One study in 2016 showed evidence that neuropeptide Y may play as a key component in migraines and trigeminovascular activation [16]. Neuropeptide Y is a naturally secreted substance by the hypothalamus that is involved in various

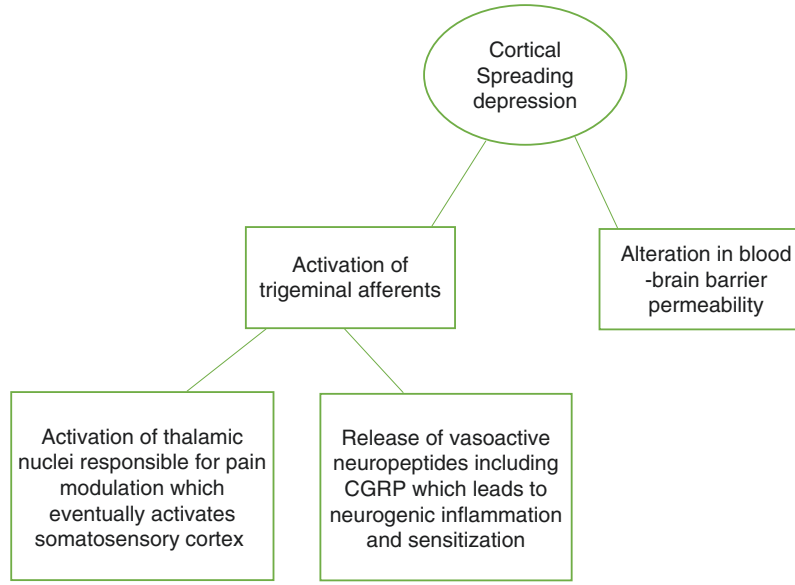

Fig. 7.3 Current understanding of the pathophysiologic mechanisms involved in migraine. Cortical spreading depression is a phenomenon theorized in migraine etiology, which is described as an extending electrophysiological hyperexcitability of nerves and glial cells that propagates alterations in the blood-brain barrier permeability and activation of trigeminal afferent sensory fibers

processes such as appetite regulation, pain, and circadian rhythms. The authors of this study administered neuropeptide Y systemically and noted inhibition of the trigeminocervical complex. Additionally, this study proposed the possible hypothalamic role in the association of migraine with impaired appetite and serum glucose levels [16]. Other studies suggest migrainous hypothalamic roles in sleep/mood disturbances and emotionality [17, 18]. Furthermore, there has been some evidence supporting that stimulation of the A11 nucleus of the hypothalamus lessened nociception by diminishing trigeminocervical complex signals [19]. As previously mentioned, one of the most common reported premonitory phase symptoms is yawning. Yawning is thought to be partly dopamine-mediated as it can be triggered by dopamine-agonists and countered by hypophysectomy. Somatostatin, another hypothalamic hormone, may also play a significant role in primary headache disorders [20].

Hypothalamic involvement in migraines has also been noted radiographically. Maniyar, FH., et al. demonstrated early hypothalamic activation on positron emission tomography (PET) scan during the premonitory phase of nitroglycerin-triggered migraine attacks [21]. Other brain structures included the dorsolateral pons and multiple cortical areas as well. These findings may explain some of the migraine premonitory phase symptomatology and alterations in homeostasis. Functional MRI (fMRI) studies have shown some evidence of hypothalamic involvement in migraines. In one study [22] an individual with a history of migraines was followed by daily fMRIs for a month. The authors found that hypothalamic activity was altered in the 24 hours preceding the headache onset as well as alterations in the functional signaling between the hypothalamus, spinal trigeminal nuclei, and dorsal rostral pons during the headache phase of migraine. These results are also consistent with hypothalamic involvement of the headache phase in migraines.

Trigeminal Autonomic Cephalgias and Cluster Headache

Trigeminal autonomic cephalgias (TACs) are a group of primary headache disorders that are typically unilateral and are associated with ipsilateral autonomic features such as lacrimation, conjunctival injection, and nasal congestion. This group of primary headache disorders includes (1) cluster headache, (2) short-lasting unilateral neuralgiform headache with conjunctival injection

Table 7.5 Trigeminal autonomic cephalgias

Diagnosis	Features	Duration	Common trigger	Treatment
CH	Periorbital, excruciating pain with autonomic and migrainous features	30 to 90 minutes	Alcohol	Sumatriptan, oxygen
SUNCT	Orbital sharp pain with autonomic features	5 seconds to 6 minutes	Touch	IV lidocaine
SUNA	Orbital sharp pain with autonomic features	15 seconds to 3 minutes	Touch	IV lidocaine
PH	Orbital stabbing pain with autonomic and migrainous features	2 to 30 minutes	Touch	Indomethacin
HC	Mild to severe throbbing pain which is continuous and has exacerbations; can be periorbital, temporal, and/or frontal	>3 months	Food/stress	Indomethacin

TACs trigeminal autonomic cephalgias, *CH* cluster headache, *SUNCT* short-lasting unilateral neuralgiform headache with conjunctival injection and tearing, *SUNA* short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, *PH* paroxysmal hemicrania, *HC* hemicrania continua

and tearing (SUNCT), (3) short-lasting unilateral neuralgiform headache with cranial autonomic symptoms (SUNA), (4) paroxysmal hemicrania, and (5) hemicrania continua (Table 7.5 shows major TACs and their characteristic features). While the symptoms of these cephalgias are similar in headache with autonomic features, they differ vastly in duration and treatment [23].

Cluster headaches are more specifically characterized as a unilateral headache disorder with ipsilateral autonomic features and/or restlessness. Cluster headaches are more common than other trigeminal autonomic cephalgias, and interestingly, they are often more severe. There is a higher incidence of attacks in men when compared to women. The usual age of onset is between 20 and 40 years old. Cluster headaches can be episodic in nature (90% of affected individuals), which is defined as having headache-free periods for greater than 3 months, or chronic, that is, having attacks frequently within a 3-month timeframe. Interestingly, one distinguishing feature of cluster headaches compared to other TACs is a clocklike pattern and circannual periodicity of attacks. For example, an affected individual may report having daily headaches for the month of May at a specific time of day and then experience years of resolution until he/she experiences another bout of headaches during May at the same time of day. It is noted that this clocklike pattern is present in 82% of individuals affected by cluster headaches but not classically seen in other TACs [23].

It is important to consider cluster headache therapies in understanding the hypothalamic role in TACs. Preventative therapy for cluster headaches and other trigeminal autonomic cephalgia headaches includes verapamil and lithium. Verapamil, a calcium-channel blocker, should be considered for treatment of cluster headache prevention. Verapamil modulates muscarinic, serotoninergic, and dopaminergic receptor activity of central neurons and increases noradrenaline release by inhibiting presynaptic adrenergic receptors [24]. The inhibition of presynaptic adrenergic receptors is most critical in the hypothalamus. While the mechanism of action of lithium is largely unknown, lithium has been found to accumulate in the hypothalamus, which may provide some insight to its use in cluster headaches. There is evidence to suggest that lithium also modulates serotonin pathways and inhibits the spontaneous release of serotonin in the hypothalamus and other areas of the brain. Additionally, lithium inhibits the encephalin system and circadian sleep cycles [24].

The exact pathophysiology of trigeminal autonomic cephalgias is partially unclear; however, some data suggest the inclusion of the trigeminovascular system, the cranial autonomic system, and the hypothalamus [25]. The trigeminovascular system is largely responsible for the pain experienced in TACs. This system receives signals from the trigeminal nerves (CN V1–3) and projects nociceptive signals to the brainstem and upper cer-

vical spinal cord, then to the thalamus, and lastly to the pain neuromatrix (multiple areas of the brain that alter and register many types of pain). The autonomic symptoms of TACs are a result of sympathetic inactivation or parasympathetic overactivation via the transmissions between the superior salivatory nucleus and the sphenopalatine ganglion [25]. The hypothalamus, conversely, may serve as a large component in TACs. Considering that the hypothalamus is responsible for circadian rhythms and partly responsible for aggressive emotions, the restlessness reported in TACs and the clocklike patterns of cluster headaches may be attributed to the hypothalamus. One study used PET scans to assess cerebral blood flow during nitroglycerin-induced cluster headaches and found repeated dysfunction in the posterior hypothalamus [21]. Reduced melatonin has also been noted in cluster headaches [26]. Additionally, stimulation of the posterior hypothalamus has been shown successful in treating TAC attacks [27]. Based on these outcomes, it is appropriate to assume significant hypothalamic role in the pathophysiology of cluster headaches.

Wernicke-Korsakoff Syndrome

Wernicke's encephalopathy (WE) is a preventable and treatable neurological syndrome in which vitamin B1, or thiamine, has been depleted in the central nervous system. Within the body, thiamine is converted to thiamine pyrophosphate synthetase to the metabolically active form of thiamine, thiamine pyrophosphate. Thiamine pyrophosphate is a crucial cofactor in glucose metabolism throughout the body, including the central nervous system. A reduction of thiamine pyrophosphate activates the pyruvate dehydrogenase kinase (PDK) in the brain, which triggers neuronal phosphorylation of pyruvate dehydrogenase E1α (p-PDE1α). Phosphorylated p-PDE1α consequently causes reduced mitochondrial aerobic metabolism that can lead to neurodegeneration [28].

Thiamine deficiency syndromes like Wernicke's encephalopathy are almost exclusively seen in alcoholics in the United States [29]. Ethanol (EtOH) inhibits the conversion of thiamine to thiamine pyrophosphate and impairs absorption of thiamine in the duodenum. Additionally, severe hepatic impairment, as commonly seen in chronic alcoholics, leads to decreased conversion of thiamine to thiamine pyrophosphate and reduced thiamine stores in the liver as the liver becomes infiltrated with fatty acids or cirrhotic [28].

Other causes of thiamine deficiency include malnutrition, malabsorptive syndromes (i.e., inflammatory bowel disease), and eating disorders (i.e., anorexia). The classical presentation of Wernicke's encephalopathy is characterized by the triad of confusion, ataxia, and ophthalmoplegia. However, realistically only ~10–16% of affected patients have all three of the triad symptoms together [30]. Other symptoms include hypotension, tachycardia, hearing loss, daytime somnolence, dysphagia, seizures, memory impairment, psychosis, hypothermia, hyperhidrosis, and peripheral neuropathy [1]. Many structures of the central nervous system that can be affected by Wernicke's encephalopathy are visible on MR sequences including the mammillary bodies, periaqueductal and periventricular gray matter, superior and inferior colliculus, and thalamus. CNS alterations seen on MRI in WE are typically symmetrical [31]. One of the most well-known structural sequelae of chronic Wernicke's encephalopathy is mammillary body hemorrhage and necrosis. Early recognition of Wernicke's encephalopathy is important as it is associated with significant morbidity and mortality and can be reversed with thiamine supplementation. Without diagnosis and/or intervention, Korsakoff syndrome can develop.

Wernicke-Korsakoff syndrome (WKS) is an irreversible neurological condition characterized by cognitive/memory impairment, confabulation, and personality changes [1]. The mortality rate of WKS is near 17% in severe cases; however, given the difficulty in diagnosis with nonspecific and variable signs/symptoms, the true mortality rate is difficult to determine [32]. The treatment of choice is parenteral thiamine (considering gastrointestinal malabsorption of thiamine is a key factor in the disease process) in addition to oral thiamine supplementation as early a diagnosis is suspected.

Neurodegenerative Disorders

Neurodegenerative diseases are a group of progressive disorders characterized by deterioration of brain structures and functions. This group of disorders include age-related Alzheimer's disease, early-onset Alzheimer's disease, frontotemporal dementia, Parkinson's disease, Parkinson-plus syndromes (multiple systems atrophy, progressive supranuclear palsy, corticobasal degeneration), spinocerebellar ataxias, Huntington disease, amyotrophic lateral sclerosis (ALS), and prion diseases (Table 7.6 shows major neurodegenerative conditions and their characteristic features). Patients with neurodegenerative disorders often present with complaints of cognitive/memory impairments, ataxia, and motor dysfunction, lack of energy, endocrine abnormalities, changes in behavior/mood, and changes in patterns of food intake.

Alzheimer's disease (AD) is one of the most common types of neurodegenerative disorder/dementia that typically slowly progresses and causes difficulties in memory, cognition, and behavior [33]. The name "Alzheimer's disease" can be referenced to two subtypes: early-onset or late-onset (Table 7.7 shows differences between early-onset AD and late-onset AD). Early-onset Alzheimer's disease is much less common than its variant and has been associated with familial causes – mutations of amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes [34]. However, some forms of early-onset AD are also sporadic like the classically known late-onset AD. Both variants are characterized by the presence of neurofibrillary

Table 7.6 Neurodegenerative diseases and characteristic features

Neurodegenerative disease	Characteristic features
Alzheimer's disease	Progressive memory and cognitive impairment with loss of ability to carry out simple tasks
Frontotemporal dementia	Personality changes, impulsivity/disinhibition, loss of language skills
Parkinson's disease	Resting tremor, bradykinesia, rigidity, postural instability
Parkinson-plus syndromes	*Multiple system atrophy* – autonomic features (postural hypotension, urinary/bowel dysfunction, sweating abnormalities) *Progressive supranuclear palsy* – early falls, vertical gaze palsy *Corticobasal degeneration* – gradual loss of motor skills, apraxia along with cognitive and behavioral deficits
Spinocerebellar ataxia	Progressive loss of coordination of gait, arm movement, eye movement, and speech
Huntington disease	Chorea, dementia
Amyotrophic lateral sclerosis	UMN and LMN signs
Prion diseases	Quickly progressive infectious disease with psychiatric features and abnormal movements

Table 7.7 Feature variations between early-onset Alzheimer's disease and late-onset Alzheimer's disease [34]

	Early-onset Alzheimer's disease	Late-onset Alzheimer's disease
Age of onset	<65 years old	>65 years old
Genetic predisposition	Significant predisposition	Complex
Progression	Typically accelerated clinical progression; increased mortality after onset	Relatively more gradual in clinical progression
Presenting symptoms	Language, visuospatial, cognitive deficits	Memory loss
MRI	Widespread cortical atrophy with parietal cortical predominance	Bilateral temporal atrophy
PET scan	Increased parietal hypometabolism	Bilateral temporal hypometabolism
CSF analysis	Low amyloid-β, increased total and phosphorylated tau	Low amyloid-β, increased total and phosphorylated tau

tangles, which are hyperphosphorylated tau protein aggregates intracellularly and accumulated amyloid plaques of Aβ peptides extracellularly. These histopathological findings can lead to parenchymal inflammation, glial dysfunction, microtubule hindrance, and inhibition of neuronal cell signaling [34].

Many studies have noted hypothalamic involvement and atrophy in patients affected by Alzheimer's disease [35–37]. Expectedly, the volume of the hypothalamus was reduced (by an average of about 11%), and many hypothalamic nuclei exhibited amyloid plaques and neurofibrillary tangles [37]. Additionally in AD, orexin levels are slightly reduced in CSF studies, and suprachiasmatic nuclei degeneration has been noted – which may account for sleep disturbances seen in AD [37]. Altered food-intake behaviors are seen in roughly 50–60% of AD cases, declined nutritional status is seen in 14–80%, and weight loss is seed in 20–45% [37]. One theory suggests that the hypothalamus is largely to blame for these weakening sequelae of AD; although, a definitive cause is currently unknown. It is important to mention, however, that obesity and diabetes mellitus are significant risk factors for developing Alzheimer's disease. Paradoxically, patients with Alzheimer's disease are also at risk for developing diabetes, which may augment evidence that suggests metabolic derangements are a consequence of AD. Weight loss and tight glycemic control are imperative for patients already at high risk for AD development.

Frontotemporal dementia (FTD), previously known as Pick's disease, is another subtype of neurodegenerative disease which, as its name implies, affects the frontal and temporal lobes. FTD is the second most prevalent type of neurodegenerative disease, manifesting most commonly between the ages of 45 and 65 [38]. The typical signs and symptoms include personality/behavioral changes, abulia (an absence of willpower or drive), and expressive/receptive aphasias. Interestingly, eating habit changes frequently occur in patients with frontotemporal dementia as well; however, inversely to Alzheimer's disease, hyperphagia is more prevalent as well as weight gain [39].

It is presumed that FTD affects majorly the posterior hypothalamus, specifically the mammillary bodies, paraventricular nucleus, and dorsomedial nuclei via atrophy [37]. Volume loss of the hypothalamus on average was slightly more than that of Alzheimer's disease (~15–20%). Those seen with more atrophy of the hypothalamus had more significant eating behavioral changes further suggesting the role of the hypothalamus in nutritional intake [37].

Amyotrophic lateral sclerosis (ALS) is also a progressive neurodegenerative disease that affects primarily motor neurons. ALS is a process with no known cure nor definitive causal etiology to date. A large current theory is that there are minimal hereditary factors and variants but a larger unclear environmental component [40]. The hallmark of this disease is the conjunction of both upper motor neuron disease (i.e., hyperreflexia, spasticity) and lower motor neuron disease (i.e., hypotonia, lack of or loss of reflexes, fasciculations) patterns (Table 7.8 demonstrates characteristics of upper and lower motor neuron lesions). While the extent of the disease is not typically confined either to the spinal cord or to neurons within the cranium, the disease process can affect the hypothalamus [41].

One study found pathological amounts of transactive response DNA-binding protein 43 (TDP-43) seen in the hypothalamus in roughly one third of the ALS patient sample population [42]. The amount of these inclusions had no correlation to the severity of the disease state. Additionally, as seen in AD and FTD, atrophy can also be noted; however, in ALS, there was no discrimination in hypothalamic areas – involving the anterior and posterior aspects.

Based on this discussion of few neurodegenerative disease processes, it is important to recognize the importance of eating habit changes in patients affected. While practitioners may commonly focus on the cognitive impairments, motor/sensory abnormalities, and affective medications, it is important to screen for nutritional status changes as both weight loss and weight

Table 7.8 Upper motor neuron vs. lower motor neuron disease

	Upper motor neuron (UMN) lesion	Lower motor neuron (LMN) lesion
Muscle strength	Weakness/paralysis	Weakness/paralysis
Type of weakness	Spastic paresis	Flaccid paralysis
Muscle tone	Spasticity, rigidity	Reduced; hypotonia
Deep tendon reflexes (DTRs)	Increased; hyperreflexia	Reduced; hyporeflexia
Atrophy	Disuse atrophy (slight)	Severe atrophy
Plantar response	Extensor	Normal; flexor
Fasciculation	Absent	Present
Electromyography	Normal; reduced interference pattern and firing rate	Fasciculations and fibrillations

gain can have significant worsening of prognosis. Diabetes and hyperlipidemia should be routinely screened for in all patients and particularly in those with hyperphagic symptoms. Malnutrition and depressive symptoms should also be considered in all patients affected by neurodegenerative diseases and particularly in those with a reduced appetite.

Narcolepsy

Narcolepsy is a neurological syndrome affecting the ability to self-regulate sleep-wake cycles characterized by excessive daytime somnolence, intermittent loss of consciousness, cataplexy (sudden loss of muscle tone), sleep paralysis, and hypnogogic hallucinations (Table 7.9 ICSD-3 Narcolepsy Diagnostic Criteria) [43]. The prevalence of this disorder is roughly 47 individuals per 100,000 in the general population [44]. Age of onset varies but typically peaks in adolescence and the fourth decade of life. Two subtypes of narcolepsy exist: Type 1 and Type 2 narcolepsy. Type 1 narcolepsy is diagnosed when an affected individual has associated cataplexy or low orexin, or hypocretin, hormone in the CSF. Type 2 narcolepsy is diagnosed when a patient experiences excessive daytime somnolence without cataplexy or reduced CSF orexin levels [45]. While the exact cause for narcolepsy remains poorly understood, many theories exist. An important and consistent finding is reduced level of CSF orexin, which is a neuropeptide released by the dorsolateral hypothalamus that plays an important role in sleep regulation and wakefulness [46]. While it may be understood that individuals living with narcolepsy have these findings, the presumed causal factors include autoimmunity, post-infectious, genetics, or trauma [46, 47].

Diagnosis can be made with a polysomnogram, which may reveal reduced REM latency, or a multiple sleep latency test (MSLT), which may also show a quickness to REM sleep. Treatment typically involves lifestyle modifications, avoidance of triggers, and sometimes stimulant medications, like Modafinil or amphetamine-like medications [46]. It is important to note that in the brain, hypocretin is solely produced by the hypothalamus, which projects mainly to the locus coeruleus, dorsal raphe nuclei, amygdala, suprachiasmatic nucleus, cholinergic nuclei in the brainstem, and spinal cord [48]. The neuropeptide acts mostly as an excitatory neurotransmitter to the aforementioned structures, in turn, increasing serotonin, dopamine, norepinephrine, epinephrine, histamine, and acetylcholine [48]. Secondarily, orexins are believed to have some role in other functioning such as energy regulation, eating habits, metabolism, sexual desire, and gut motility/acid production and have some role in increasing mean arterial blood pressure and pulse rate [46]. One postmortem study comparing hypothalami of individuals with narcolepsy versus controls showed remarkable reductions (85–95%) in the density of hypocretin-producing neurons [49]. An increased amount of gliosis and astrocytes were found suggesting degeneration of these neurons [49]. Other conditions in which hypocretin is believed to be

Table 7.9 ICSD-3 Narcolepsy Diagnostic Criteria

Narcolepsy type 1
Alternate names: Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy
Diagnostic criteria: Criteria A & B must be met
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months[a]
B. The presence of one or both of the following:
1. Cataplexy (as defined under Essential Features) and a mean sleep latency of ≤8 minutes and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT[b]
2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same standardized assay

Notes:
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CSF cerebrospinal fluid, *MSLT* multiple sleep latency test, *REM* rapid eye movement
[a]In young children, narcolepsy may sometimes present as excessively long night sleep or as resumption of previously discontinued daytime napping
[b]If narcolepsy type 1 is strongly suspected clinically but the MSLT criteria of B1 are not met, a possible strategy is to repeat the MSLT

Narcolepsy type 2
Alternate names: Narcolepsy without cataplexy
Diagnostic criteria: Criteria A–E must be met:
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months
B. A mean sleep latency ≤8 minutes and ≥ 2 sleep-onset REM periods (SOREMPs) are found on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT
C. Cataplexy is absent[a]
D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg/mL or > 1/3 of mean values obtained in normal subjects with the same standardized assay[b]
E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal

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CSF cerebrospinal fluid, *MSLT* multiple sleep latency test, *REM* rapid eye movement
[a]If cataplexy develops later, then the disorder should be reclassified as narcolepsy type 1
[b]If the CSF hypocretin-1 concentration is tested at a later stage and found to be either ≤110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same assay, then the disorder should be reclassified as narcolepsy type 1

involved with is Kleine-Levin syndrome, age-related reduction in REM sleep, and other primary sleep disorders (hypersomnolence and insomnia-related).

Kleine-Levin Syndrome

Kleine-Levin syndrome (KLS) is a peculiar and rare neurological disorder affecting typically teenaged boys that is characterized by episodic hypersomnolence, hypersexualism, impulsive eating, and cognitive impairment. These episodes of hypersomnolence can vary from days to months at a time, and patients affected with KLS are often unable to perform their activities of daily living (i.e., going to school). Given the rarity of KLS, limited information is currently understood about this disease. Based on the symptomatology of KLS, it has long been postulated that the hypothalamus is the culprit. One case report in 1987 [50] showed slightly elevated

prolactin levels and abnormalities in LH and 11-OHCS. Another more recent study of five KLS patients noted normal hormonal patterns in sleep except hGH, suggesting no underlying circadian disorder [51].

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8 Neuropsychiatric and Neurobehavioral Syndromes of the Human Hypothalamus

John Wagner III, Noeen Sarfraz, Kunal Maini, and Amber N. Edinoff

Introduction

The role that the human hypothalamus plays in behavior, as well as psychiatric disorders, has been known for quite some time. As early as the 1930s, Selye studied the physiological response to stress [1]. His work led to our understanding of the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic activity influences human behavior [2, 3] and plays a role in a wide range of mental disorders. These include anxiety disorders, affective disorders such as major depression and bipolar, and substance use disorders.

The Hypothalamus and Basic Behavior

The hypothalamus mediates a variety of basic human behaviors, including sexual, food and water intake, fear, and aggressiveness. These are considered as evoked behaviors or "survival needs," and they are the result of neuronal stimuli upon discrete hypothalamic regions [3]. The posterior nucleus of the posterior hypothalamus has been linked to the drive for drugs and sex, the mammillary bodies to episodic memory. Pascual et al. describe the result of damage by craniopharyngiomas to various hypothalamic structures and resulting psychiatric disorders. In their systemic review and meta-analysis of work investigating the damage caused by craniopharyngiomas to hypothalamic structures and resulting psychiatric disorders, Pascual et al. describe a loss of episodic memory resulting from damage to the mammillary bodies. In particular, there was a significantly higher proportion of atrophic or absent mammillary bodies in subjects with a psychiatric disorder than in those without, and tumor distortion of the mammillary bodies was noted to the key anatomic distortion associated with episodic memory loss. Memory loss was observed in up to 86% of subjects with atrophic mammillary bodies [4].

Interestingly, some of these behaviors have been observed during neurosurgical procedures. In 1933, Foerster and Gagel published their observations made during the removal of a cyst from the third ventricle. Whenever the ventricle floor was contacted, the patient laughed, whistled, and made obscene remarks. These behaviors ceased when contact with the ventricular floor was removed [2]. The periventricular zone (PVZ) was implicated in mood regulation by Angelergues et al. in a case reported of persistent euphoria after a bilateral infarct [5].

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Multiple regions of the hypothalamus affect sexual drive and behavior. Small lesions in the medial preoptic area/anterior hypothalamus (MPOA/AH) temporarily affected male rat sexual drive [6]. The dorsomedial and ventromedial nuclei of the hypothalamus (DMH and VMN) affect penile erection through projections to the dorsolateral funiculus in the spinal cord [7]. The ventromedial hypothalamus was a frequent target for stereotactic brain lesion surgery to treat paraphilia and exhibitionism in the 1960s and 1970s in Germany. These procedures drastically reduced sexual drive [8]. The paraventricular nucleus is active during sexual activity, including orgasm, most likely through the production of oxytocin, vasopressin, and dopamine [7]. A recent quantitative meta-analysis of visual cues shows consistent activation of the hypothalamus [8].

The hypothalamus has also been a target for neurosurgical intervention to treat refractory aggressive behaviors. From 1962 to 1977, Sano conducted stereotactic hypothalamotomy surgeries focusing on the posterior hypothalamus on 60 patients with severe aggressive behaviors. He later published the long-term outcomes, which showed a 78% positive result, with no violent or aggressive behaviors exhibited postoperatively [9]. Schvarcz reported on 11 cases of stereotactic posterior hypothalamotomy to treat severe aggressiveness with associated violent behavior. In each case, psychiatric treatment had failed. At follow-up, up to 4 years postop, 10 of the 11 patients had marked improvement with or without psychotropic medication. One was deemed a failure [10].

Although psychosurgery has fallen out of favor due to public outcry, the advent of deep brain stimulation (DBS), which is both less destructive and reversible, is a viable alternative. DBS, along with the development of more advanced stereotactic neurosurgical techniques and improved neuroimaging, provides neurosurgeons with an intervention to address psychopathological symptoms. Thus, the hypothalamus is once again a target for treatment. Several case reports and a cohort of seven patients have been published documenting DBS application to the posterior hypothalamus to treat aggressive behavior, with positive results [11].

The Hypothalamus and Anxiety

The DSM-5 describes a variety of anxiety disorders. These include (with their 12-month prevalence rates) separation anxiety disorder (0.9–1.9%), social anxiety disorder (7%), panic disorder (2–3%), agoraphobia (1.7%), specific phobia (7–9%), and generalized anxiety disorder (2.9%). The DSM-5 classifies post-traumatic stress disorder (PTSD) separately as a trauma-related disorder. Its lifetime prevalence rate is 8.7%. Anxiety disorders occur more frequently in females with a ratio of 2:1. Excessive fear and anxiety as well as behavioral disturbances are common to all anxiety disorders. Fear is the response to a real or perceived threat often with autonomic arousal. Anxiety is associated with internalizing symptoms including muscle tension, hyper-vigilance, and avoidance behaviors [12].

HPA axis dysfunction can lead to the development of anxiety disorders [13]. The HPA axis has been shown to demonstrate dramatic reactivity to psychological and/or physiological stressors, as evidenced by increased production of hormones like adrenocorticotropic hormone (ACTH), corticotropin-releasing factor (CRF), and cortisol (aptly termed a "stress hormone"). In addition to dysregulation to the HPA axis, insults to the hypothalamic-pituitary-thyroid (HPT) axis have also been shown to play a role in the development of anxiety disorders vis-à-vis an increase in the triiodothyronine (T3)/thyroxine (T4) ratio [14]. In a systematic review, Fischer and Cleare synthesize the literature on the relationship between cortisol levels and response to psychotherapy in individuals with anxiety disorders [15]. They conclude that current evidence is equivocal in terms of the predictive value of basal cortisol levels in response to psychotherapy for the treatment of anxiety disorder. In another systematic review on the role the HPT plays in anxiety disorders, Fischer and Ehlert found that nearly all 20 studies included in the review revealed a significant degree of comorbidity between thyroid disorder and symptoms of anxiety [16]. The findings of the systematic review support current clinical guidelines to test for thyroid disorders in patients

presenting with symptoms of anxiety, including, but not limited to, palpitations and diaphoresis.

While the role of the HPA axis in disorders such as generalized anxiety disorder is well understood, such is not the case for PTSD [14, 17]. Similar to other anxiety disorders, plasma levels of CRH are abnormally elevated in PTSD, but in cases of PTSD, the response of ACTH to CRH is blunted. These findings have implications for treatment modalities for PTSD and represent an area of continued research.

The Hypothalamus and Mood Disorders

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been implicated in mood disorders, including major depressive disorder, postpartum depression, and bipolar disorder.

Major depressive disorder (MDD) is the most prevalent psychiatric disorder worldwide. The annual incidence rate in developed countries is 10%, while 20% of individuals are depressed during their lifetime [18]. According to the DSM-5, five or more of the following symptoms must be present during the same 2-week period: (1) depressed mood most of the day nearly every day, (2) diminished interest or pleasure in activities, (3) significant weight loss or weight gain, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue, (7) feelings of worthlessness or guilt, (8) decreased concentration or indecisiveness, and (9) recurrent thoughts of death or suicidal ideation (with or without a specific plan) [12]. Once diagnosed, current pharmacologic treatment with antidepressants is effective in up to 70% of patients. Unfortunately, a substantial number of patients (19–34%) fail to respond fully, and up to 34% are treatment-resistant [19].

Psychosocial stressors play a significant role in the development of depression. Childhood exposure to stressors, such as the death of a parent or caregiver, maternal deprivation, paternal abandonment, parental separation, or divorce, increases the risk of adult depressive episodes. The likely mechanism for this relationship between acute stress and depression lies in the abnormal activation of the HPA axis.

HPA axis dysfunction can result in hypersecretion of cortisol, enlargement of the pituitary and adrenal glands, and elevated corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone. Depressed patients have shown to have elevated 24-hour urinary free cortisol, elevated serum cortisol, and elevated CSF cortisol. Other abnormalities in depressed patients include non-suppression of cortisol, beta-endorphin, and ACTH after dexamethasone challenge. Postmortem examination has shown evidence of increased CRF mRNA and protein in the PVN of the hypothalamus [20].

There are several theories as to the cause of HPA axis dysfunction in depression. One suggests of increased central drive in the hypothalamus, resulting in hypersecretion of CRF and/or arginine vasopressin (AVP). Interestingly, animal studies have shown that elevated CRF itself is tied to alterations in activity, appetite, and sleep, which are also observed in depressed patients [21]. Chronic stress with associated increased cortisol levels may decrease the hypothalamus' ability to downregulate CRF released by the paraventricular nucleus (PVN) by altering negative feedback of glucocorticoid receptors [4, 22]. Normally, glucocorticoids serve as potent inhibitors of CRF release by the PVN, as well as ACTH by the pituitary, as evidenced by the increased volume of the pituitary in depressed patients [23].

Two types of corticosteroid receptors have been identified, mineralocorticoid receptor (MR) and glucocorticoid receptor (GR), which help regulate the HPA axis. Mineralocorticoid receptors, found mainly in the hippocampus, have a high affinity for endogenous glucocorticoids. Glucocorticoid receptors are found in multiple areas of the brain, including the hippocampus, the amygdala, the brain stem, and the hypothalamus. MR is thought to regulate basal levels of cortisol, and GR regulates at higher or "stressed" levels of cortisol. Thus GR receptors are believed to play a larger role in response to stress. However, the balance of MR and GR activity may affect the set point of the HPA axis. Several studies have shown a decrease in GR response in

depressed patients. It is unknown if this decrease in GR activity is due to the lack of efficacy of the receptor type and a decrease in the number of receptors in the brain. Pariante proposes that the elevated cortisol levels observed in depressed patients are a compensatory mechanism to overcome glucocorticoid resistance [23].

Hypocretins (Hcrts) are neuropeptides produced by the lateral hypothalamus (LH) with projections throughout the brain to include the locus coeruleus, basal forebrain, ventral tegmental area, raphe nuclei, and tuberomammillary nucleus. Animal studies link hypocretins to the HPA axis, showing that stress increases the expression of one type of hypocretin, Hcrt-1 mRNA in Hcrt neurons located in the LH [24]. Hyperfunction of the Hcrt system may be linked to depression, in both unipolar and bipolar depressive episodes. One study showed higher mean levels of CSF Hcrt-1 levels in these patients. Furthermore, treatment with antidepressants restored Hcrt-1 to normal levels [25].

Melancholic and Atypical Depressions Types

There are two subtypes of major depressive disorder, the melancholic type and the atypical type. Depression with melancholic features is defined as having either loss of pleasure in all or most activities or lack of emotional reactivity to pleasurable stimuli along with at least three of the following: (1) profound despondency or despair, (2) worse depression in the morning, (3) early-morning awakening, (4) psychomotor agitation or retardation, (5) significant anorexia or weight loss, and (6) excessive guilt. Atypical depression has the following characteristics: mood reactivity and at least two of the following: (1) significant weight gain or increased appetite, (2) hypersomnia, (3) leaden paralysis, and (4) heightened sensitivity to interpersonal rejection [12].

Juruena and colleagues published an extensive review of 48 studies examining the role of HPA functioning in melancholic and atypical depression. They concluded that HPA axis activity differed in these two subtypes of major depression. Specifically, patients with melancholic depression were shown to have increased cortisol levels, both at baseline and post-challenge. Atypical depressed patients exhibited lower levels of HPA axis activity, suggesting the possibility of enhanced negative feedback [26].

Postpartum Depression

Postpartum depression (PPD) is defined as major depressive disorder with peripartum onset [12]. Criteria for PPD are very similar to that of major depressive disorder, with the additional temporal requirement of onset within 4 weeks of delivery. Risk factors for PPD include ongoing psychosocial stressors such as the lake of social support, marital discord, and socioeconomic status. Other risk factors include a history of childhood trauma and sexual abuse. The severity of symptoms of PPD is related to chronic and acute stress [27].

Bipolar Disorder

Bipolar disorder, historically known as manic depression, is characterized by both episodes of depression and mania. The DSM-5 identifies multiple variations of bipolar disorder due to its heterogeneity in symptom severity and duration. Broadly defined criteria for a bipolar I diagnosis include a manic episode lasting a minimum of 1 week, with a persistently elevated or irritable mood, increased activity or energy, as well as associated symptoms including grandiosity, decreased need for sleep, pressured speech, racing thoughts, and impulsive behavior. Bipolar II can be viewed as a milder form, with no history of a fully manic episode. These individuals have exhibited an episode of hypomania, which may last less than 1 week and is less severe [12].

The hypothalamus may play a role in bipolar disorder through the activity of the neuropeptide oxytocin. Oxytocin, produced predominately by magnocellular cells in the supraoptic and paraventricular nuclei of the hypothalamus, plays a variety of roles including placentation, viviparity, lactation, and smooth muscle contraction of the

uterus during labor. Oxytocin also regulates social interactions, including those between the mother and her offspring, as well as more broad pro-social behaviors such as empathy and trust [28]. Although oxytocin is commonly viewed for its positive impact on psychological functioning, elevated levels of oxytocin may result in increased emotionality and anxiety. Some studies have tied elevated levels of oxytocin to several mental illnesses, including depression, schizophrenia, and bipolar disorder [29]. Yueh-Ju et al. examined oxytocin levels in patients with MDD and bipolar II disorder in a depressed state and found that plasma oxytocin levels were significantly higher in the bipolar II group than either the MDD group or healthy controls. The MDD group's oxytocin levels were elevated compared to controls but were not statistically significant [30].

GABA and Neurosteroids

CRF neuronal activity in the PVN is tightly regulated by GABAergic signaling. Up to one-third of CRF, neuron inputs are GABAergic. GABAergic neurons project to the PVN from multiple hypothalamic sources, including the anterior and lateral areas, the dorsomedial nucleus, the medial preoptic area, as well as the stria terminalis [27]. Culliana et al. showed evidence of the role GABA plays in corticosterone release in rats by microinjection of muscimol into the PVN, which reduces the stress-related elevation of corticosterone with the opposite effect with microinjection of bicuculline [31].

GABA receptors are themselves regulated by allosteric modulators, both positive (PAM) and negative (NAM) types. Neuroactive steroids and neurosteroids can act as both PAMs and NAMs. Several of these have been identified and have been shown to have antidepressant and anxiolytic effects, including allotetrahydrodeoxycorticosterone (THDOC) and allopregnanolone. Both of these are decreased following chronic stress, suggesting that at low levels, the inhibiting effects of GABA on the PVN's release of CRF are decreased [27]. The 5α-reductase inhibitor finasteride, which blocks neurosteroidogenesis, is known to cause both anxiety and depression, supporting the model that reduced neurosteroid levels may lead to these disorders. In fact, one possible treatment of anxiety and depression is medications which stimulate neurosteroidogenesis [32].

Schizophrenia

Schizophrenia is a chronic mental health disorder that affects approximately 3.3 million people in the United States. Its symptoms, which must be present for greater than 6 months, comprise disorganized behavior and speech, a diminished capacity to comprehend reality, hearing voices unheard by others, seeing things unseen by others, delusions, and decreased social commitment and motivation. Some individuals may also have magical thinking, such as the belief that others can read their minds, as well as debilitating paranoia with notions that others can read and, thus, control their minds. More severely, certain people can develop catatonic behavior and therefore require help with daily activities [33].

Multiple studies have correlated specific areas of the brain that can be affected in schizophrenia. Evidence not only shows abnormalities in the gray matter but white matter as well. The most evidence-based anatomical brain aberrations found in multiple meta-analysis studies include reduction in total brain volume; hypertrophy of the cavum septum pellucidum and lateral ventricles; atrophy of the midsagittal callosum as well as the thalamus, anterior cingulate cortex, bilateral hippocampus, and amygdala; and, finally, a reduction in size of frontal, parietal, and temporal lobes [34]. Larger basal ganglia and hypothalami were also noted.

Any or all of these abnormalities can be related to glutamate deficiency due to functional deficits in particular neuronal circuits present in these atrophied regions of the brain. Due to these structural abnormalities, patients with schizophrenia can have both hypo- and hyperfunctioning of the hypothalamic-pituitary-adrenal axis, leading to a multitude of complex correlations due to increased or decreased production of

hypothalamic neuropeptides from functionally compromised neuroendocrine neurons.

Studies have shown that the hippocampal changes may be a consequence of the disease process rather than the cause. One theory suggests that the physiological stress induced by the negative symptoms of schizophrenia could lead to altering the structure of the hippocampus, interrupting neurogenesis, decreasing dendritic density, and leading to cell destruction [34].

Schizophrenia typically presents in early adulthood. Females have a later onset of symptoms in comparison to males, due to protective estrogenic effects. Greater exposure to 17 beta-estradiol (E2) at age onset of menarche in females correlates to a later onset of schizophrenia. There was no correlation between the onset of puberty and disease presentation in males. Females typically have less severe symptoms when compared to their male counterparts, including decreased disability in activities of daily living and requiring lower dosing of antipsychotic medication. Furthermore, females admitted for inpatient treatment and stabilization of psychotic symptoms due to schizophrenia also had lower E2 concentrations [35].

Many studies have shown that a continued state of stress can cause HPA axis dysfunction, partly due to decreased feedback of glucocorticoid secretion in the hippocampus or hypothalamus. A study conducted in patients diagnosed with chronic schizophrenia showed much higher basal cortisol levels in comparison to control groups and a larger cortisol surge after dexamethasone pretreatment. Abnormal haloperidol metabolism and a decreased response to antipsychotic treatment were seen due to nonspecific chronic stress combined with cerebral atrophy and ventricular enlargement. Even when these patients have increased basal cortisol levels, they have a reduced response to environmental stressors suggesting a disturbance in HPA axis [36].

These feedback mechanisms that regulate cortisol secretion may also be due to altered or dysfunction of glucocorticoid receptors in the hippocampus. Structural changes, including atrophy, may attribute to NMDA (N-methyl-D-aspartate) glutamate receptor malfunction and may be the cause of negative symptoms and cognitive impairment. Structural changes in the hippocampus are also worsened by hypercortisolism, thus creating an inverse relationship and a worsening cycle of symptoms [36].

As discussed above, Hcrt neuronal hyperfunction has been linked to affective disorders. Individuals with schizophrenia have significantly higher plasma Hcrt-1 levels versus healthy controls [37]. Antipsychotic medications reduce CSF levels of Hcrt-1 [38].

Schizophrenia may be an NMDA receptor hypofunctioning disorder. NMDA receptors are not able to respond to peptides appropriately. This dysfunction is similar to that seen with ketamine and phencyclidine (PCP) use, which can lead to acute psychosis in otherwise healthy individuals. The atypical antipsychotic clozapine, used for treatment-resistant schizophrenia and other structurally similar atypical antipsychotics, can prevent this NMDA antagonist-induced neurotoxicity making it more effective. Clozapine's effectiveness, particularly concerning addressing negative symptoms, more so than the typical D2 receptor antagonist antipsychotics, is attributed to its effect of decreasing plasma cortisol levels [36]. There is a positive relationship with CNS infections occurring during childhood- and adult-onset schizophrenia and other varying psychosis disorders. Plasma IL-6 and its receptor, TNF-alpha, and IL-2 receptor were shown to be higher in patients with schizophrenia.

Many of the negative symptoms of schizophrenia, which can affect activities of daily living, are correlated to both plasma cortisol levels and multiple cytokines. This data can further be utilized to understand the different causes of negative symptoms better and be used to determine the modalities of the most effective treatment better. Schizophrenia is a multifaceted, complex psychotic disorder, and the correlation of treating with medications that not only affect plasma cortisol levels but glutaminergic receptors as well can lead to a better understanding and higher level of efficacy when considering treatment options.

The majority of these symptoms can be managed with the proper antipsychotic medication with therapy being an adjunctive treatment modality showing an increased improvement in developing insight and awareness of one's condition.

Drugs, Alcohol, and the Hypothalamus

Stress, drugs, and alcohol have been intricately connected in preclinical models using rodents. Stress and its relationship to the HPA axis can lead to both the acquisition and the reinforcement using the reward pathway in both illicit drug and alcohol use.

Substance use, in terms of alcohol or other illicit drugs, can be a life-controlling condition. According to the centers for disease control, the prevalence of illicit drug use in people aged 12 and over is 10.6%. The prevalence of adults who have had at least one heavy drinking day, as defined by five or more drinks for males and four or more drinks for females, is 25.1%. What makes some individuals more prone to drug and alcohol use and/or dependency? Preclinical data suggest that chronic exposure to stress and the resulting release of glucocorticoids via the HPA axis sensitizes dopaminergic response to some drugs. There could be an interplay of stress and drug-induced activation of this axis that allows glucocorticoids to sensitize the reward pathways [39, 40]. When first exposed to drugs, an individual experiences pleasurable feelings. As this progresses to the addicted state, the HPA axis is activated, and high levels of glucocorticoids and stress peptides, which are associated with addiction, create an internal form of stress, which is seen as anxiety-like behaviors.

The pleasurable state of drug intoxication is a positive reenforcer for future use. These reinforcing effects act through signal transduction systems involving the mesocorticolimbic dopaminergic neurons [41]. This leads to increased dopamine expression in the nucleus accumbens. There is evidence that the HPA axis interacts with the mesocorticolimbic dopaminergic system. Preclinical studies have shown that glucocorticoids alter the dopamine signaling in the mesolimbic system and can thereby amplify the positive reinforcing effects of alcohol and illicit drugs [42]. This is known as sensitization of the reward system, which could lead to the user being more responsive to drugs or alcohol and therefore be more vulnerable to the development of addiction [42]. Studies have shown that corticotropin-releasing factor (CRF), released from the paraventricular nucleus of the hypothalamus, as well as the HPA axis end product of glucocorticoids, has led to the increased glutamatergic activity in the ventral tegmental area (VTA). VTA axons extend to the nucleus accumbens resulting in an increase in dopamine release. CRF administration alone can produce the same results [43]. Several studies have shown that stress and corticosterone, as well as substances such as cocaine, methamphetamine, morphine, nicotine, and alcohol, can sensitize VTA dopamine neurons to increase their glutamatergic input [44, 45].

Animal models show that during the acquisition phase of drug-taking behavior, the animal will come into contact with the drug and its rewarding properties for the first time [46]. Stressors applied to rats increase the serum glucocorticoid levels by activation of the HPA axis, ultimately altering the drug self-administration. Tail pinch [39], neonatal isolation [47], and foot shock [48] are examples of stressors that can increase the drug acquisition of stimulants like cocaine and amphetamine and self-administration of opiates. Shaham and Stewart also showed that electric foot shock increases the reinforcing effect of heroin. Researchers further investigated this process by administering the final product of the HPA axis, corticosterone (analogous to cortisol in humans). Increased low-dose cocaine self-administration was observed in foot shock-induced rats with increases in the corticosterone levels [46]. Even more interesting is the fact that self-administration did not occur unless the plasma levels reached a certain threshold of corticosterone [46]. A study also showed that corticosterone administration had been shown to facilitate the psychomotor stimulant effects of both cocaine and morphine [49]. In a related study,

Goeders and Guerin showed that adrenalectomized rats, which eliminated the final step in the HPA axis, actually did not self-administer cocaine at any dose they tested [50]. Pretreatment with corticosterone facilitates the cocaine self-administration in rats [51]. This could be reversed in a dose-dependent manner with the administration of corticosterone [52].

Using an escalation model for cocaine self-administration associated with an increase in reward thresholds, Koob and Kreck reported a positive correlation between presession corticosterone levels and the amount of cocaine that was self-administered [53]. In a related experiment, the blockage of corticosterone synthesis with ketoconazole reduced low-dose self-administration of cocaine during acquisition [54]. Plasma corticosterone levels prior to self-administration predicted cocaine self-administration, but this was only observed at low doses of cocaine (0.25 mg/kg) [55]. This indicates that individual differences in cocaine self-administration that occur during the acquisition period are only relevant at low doses of cocaine. Also, during acquisition, cocaine administration induces the activation of the HPA axis, which leads to increased levels of corticosterone in rats. This cocaine-induced increase in corticosterone in the plasma may result from the effects of the drug on CFR secretion in the hypothalamus [56]. With this in mind, it seems reasonable to deduce that low-dose psychostimulant effects may be related to the initial vulnerability to drug use, and the activation of the HPA axis may contribute to this vulnerability. Cocaine use not only stimulates the HPA axis but also may act as a positive feedback loop to its continued use.

Alcohol Consumption and the Hypothalamus

Neuropeptides play a role in both the consumption of alcohol and to encourage increased intake of alcohol. Galatin, enkephalin, and orexin work to enhance alcohol consumption in various ways and to act in a positive feedback loop in terms of consumption [57].

Galatin (GAL) is found in the paraventricular nucleus, arcuate nucleus, lateral hypothalamus, dorsomedial nucleus, and periventricular area in rats. GAL interacts with three different G-protein receptors. In the paraventricular nucleus, GAL promotes alcohol consumption. Injection of GAL into this area in rats has shown to increase moderate alcohol drinking [58]. This is analogous to the way that GAL seems to trigger increased food intake when interacting in the paraventricular nucleus, which this study also noted. There is also evidence that endogenous GAL has a role in promoting alcohol drinking as well. Barson showed that rats with elevated mRNA expression of GAL were correctly predicted to drink higher levels of alcohol [59]. Furthermore, mice overexpressing the GAL gene were shown to drink more alcohol and show a higher preference for alcohol than their wild-type peers [60]. Alternatively, those who were lacking the GAL gene drank less alcohol and showed a lower preference for it [61]. GAL also has a role in the reward pathway. Increased levels of GAL in the paraventricular nucleus have been found to increase extracellular levels of dopamine in the nucleus accumbens [62]. There is also evidence that supports that GAL has a positive feedback relationship with alcohol. Leibowitz et al. showed that alcohol at moderate and excessive levels led to increased gene expression and peptide levels of GAL in multiple areas of the hypothalamus [63].

Enkephalin (ENK), an endogenous opioid, is another neuropeptide widely disturbed throughout the brain. ENK is active in the paraventricular nucleus, arcuate nucleus, lateral hypothalamus, dorsomedial nucleus, and perifornical area. ENK can promote moderate alcohol drinking through its actions on the paraventricular nucleus. It has been shown to have similar actions as GAL in terms of promoting alcohol drinking when active in the paraventricular nucleus; however, it differs from GAL in also increasing the duration of those drinking episodes [58]. This study suggests that not only do rats drink more with elevated endogenous ENK but that they also drink for a longer period of time. Unlike mice lacking GAL, mice lacking the ENK gene showed no difference from their wild-type controls in either their alco-

hol preference or intake [64] and no increase in alcohol drinking in all individuals under any condition. However, ENK does have a role in the reward pathway, which could promote increased drinking behaviors. It does this by its actions on the delta-opioid receptor (DOR), which increases dopamine in the nucleus accumbens and thereby has a role in the positive reinforcement of drinking. A DOR agonist injected into the paraventricular nucleus was shown to increase extracellular levels of dopamine in the nucleus accumbens [65].

Orexin (OX) is found in cell bodies that lie exclusively within the hypothalamus allowing the effects of OX to be traced back to the actions of neurons within the hypothalamus. Projections of these cell bodies lie in various parts of the brain such as the thalamus, locus coeruleus, nucleus accumbens, ventral tegmental area, amygdala, and various nuclei of the hypothalamus which shows that OX has effects throughout the brain. Generally, OX is thought to promote alcohol consumption, but this does not happen in all brain areas. Injection of OX-A into the paraventricular or lateral hypothalamus of rates stimulates moderate alcohol consumption [58]. Outside of the hypothalamus, OX promotes excessive alcohol consumption in the nucleus accumbens core but not the shell [66], the ventral tegmental area but not the substantia nigra, and the anterior but not posterior paraventricular thalamus [67]. OX is different from ENK and GAL, where the latter stimulates alcohol drinking by increasing the amount and duration of alcohol drinking episodes and the former in the hypothalamus stimulates alcohol drinking by increasing the number of drinking episodes [58]. This suggests that rats with elevated OX initiate more drinking responses. Additionally, scenarios that induce reinstatement of alcohol-seeking have been found to stimulate c-Fos activity within OX neurons [68]. Also, rats predicted to drink higher levels of alcohol based on their novelty-induced locomotor activity showed elevated OX mRNA levels in the perifornical LH [59]. However, there is some evidence that shows that OX levels are the same in alcohol-preferring rats compared to non-preferring rats [69]. Evidence that offers a possible explanation shows that while OX on its own is not necessary for the renewal of alcohol-seeking behaviors, it may work in concert with other neuropeptides to induce this behavior [70]. In terms of the reward system, OX is responsive to conditions associated with rewards. Within the hypothalamus, OX neurons show c-Fos activation in response to condition contextual cues associated with sexual behavior, which is a natural reward [71]. This study also showed that lesions of OX neurons reduced the conditioned place preference for a sexual paired behavior chamber. These effects of OX are attributed to the actions at the OX2R receptor rather than the OX1R since a peripheral injection of an OX2R antagonist reduced the acquisition, expression, and reinstatement of alcohol-conditioned place preference [72], whereas an injection of an OX1R antagonist does not affect the acquisition and only weakly reduces the expression of alcohol-conditioned place preference. There is also a role in positive reinforcement of OX. Studies report that alcohol increases gene expression of OX within the lateral hypothalamus [67, 69]. Chronic alcohol injection in mice also leads to a small increase in c-fos activity in OX neurons [73]. Overall, this indicates that OX can help promote alcohol consumption, while alcohol consumption itself, in turn, increases levels of OX in a positive feedback loop.

There are three other neuropeptides that are associated with the hypothalamus that have a negative effect on alcohol consumption. These are dynorphin (DYN), corticotropin-releasing factor (CRF), and melanocortins (MCs). These neuropeptides have a negative effect on drinking by causing dysphoria, suppress drinking overall, or cause disruptions in the reward pathway.

Dynorphin (DYN) is found through the brain but is most densely expressed within the hypothalamus itself with cell bodies located within the paraventricular nucleus, arcuate nucleus, dorsomedial nucleus, lateral hypothalamus, and ventromedial hypothalamus. DYN in the lateral hypothalamus is highly co-expressed with OX, and the two are found packaged within the same synaptic vesicles in the hypothalamus. DYN exhibits kappa opioid receptor (KOR) activity

resulting in inhibiting alcohol consumption. This was proved when a KOR agonist injected to the lateral hypothalamus or paraventricular nucleus suppressed moderate alcohol drinking [74]. One theory is that KOR activity in the lateral hypothalamus induces a conditioned place aversion and subsequent dysphoria [75]. Alcohol consumption itself also stimulates DYN production. It has been shown that alcohol drinking at moderate levels can lead to elevated DYN gene expression in the paraventricular nucleus and that increase can be observed with just a single alcohol injection [76]. This release is thought to curb the subsequent alcohol consumption and counter the drive for further intake that is induced by the simultaneously released OX peptide.

Corticotropin-releasing factor (CRF) is found densely in the extending amygdala and also in the hypothalamus predominantly in the paraventricular nucleus and the lateral hypothalamus. CRF shows a negative feedback relationship with alcohol. Injection into the lateral ventricles has found to reduce moderate and excessive drinking in rats [77] though when injected into the paraventricular nucleus, it has no effect on excessive alcohol drinking [78]. Additionally, levels of CFR are deceased in the hypothalamus of alcohol-dependent rats at the onset of withdrawal [79]. This is when animals are presumed to crave alcohol, which further supports the theory that CFR helps reduce the drive for alcohol consumption. CFR and DYN are similar in that the reduced alcohol consumption could be due to their ability to induce aversion. Ventricular injection of a CRF agonist will elevate the intracranial self-stimulation threshold, which indicates that it reduces brain stimulation in terms of reward [80]. This, therefore, indicates that CRF can mediate some of the aversive aspects of alcohol consumption and can serve to inhibit subsequent alcohol drinking.

Melanocortin (MC) peptides are derived from proopiomelanocortin (POMC), which includes other components including alpha-melanocyte-stimulating hormone, ß-MSH, gamma-MSH, and adrenocorticotropic hormone. Cell bodies containing MC are located primarily in the hypothalamus, especially in the arcuate nucleus [81]. Projections of the cell bodies terminate in all areas of the hypothalamus as well as in a variety of other brain areas such as the amygdala, periaqueductal gray, and septum. MC shows a double-negative feedback loop in relation to alcohol, which generally is noted in decreasing alcohol consumption and also being endogenously reduced by alcohol. Injection of an MC receptor agonist in the nucleus accumbens, ventral tegmental area, or amygdala showed a reduction in moderate and excessive alcohol consumption [82]. Other studies have shown that this also occurs in the nuclei of the medial hypothalamus, such as the paraventricular nucleus and the dorsomedial nucleus. The ability of MC to inhibit alcohol consumption may be due to the suppression of reward or reinforcement from this behavior. Ventricular injection of alpha-MSH reduces the anxiolytic effect of excessive alcohol consumption, as demonstrated with an experiment using an elevated plus maze [83]. This study also showed that an MC4R antagonist enhanced the anxiolytic effect and reduced the anxiety associated with alcohol withdrawal. Furthermore, an MC4R agonist in the nucleus accumbens reduced the hedonic reactions to alcohol while increasing aversive ones [84]. Therefore, MCs, like CFR, may enhance the aversive aspects of alcohol consumption while also reducing the rewarding effects. Unlike other neuropeptides previously listed, endogenous MC is generally inhibited by alcohol. Peptide levels of POMC in the arcuate nucleus are decreased after long-term exposure to high levels of alcohol via a vapor chamber or alcohol-containing diet [85, 86]. Peptide levels of alpha-MSH after long-term consumption of alcohol-containing diet are also decreased in the arcuate nucleus and possibly in the lateral hypothalamus and in certain limbic regions, including the amygdala and substantia nigra [85]. With this double-negative feedback loop, the reduction of MC levels with alcohol consumption may, in fact, be permissive to further alcohol consumption by reducing the aversive aspects of its intake.

The hypothalamus plays a central role in terms of substance abuse. Its involvement in the HPA axis in stress reactions can prime the use of a sub-

stance. The hypothalamus can also potentiate substance use since it is involved in the reward pathway. This priming of the use and positive feedback loop can have negative consequences for individuals who have been exposed to life stressors such as abuse, neglect, or early trauma. Practitioners must be aware of early stressors and address them with appropriate treatment if substance use treatment is to be successful. Simply removing a person from the substance may not be enough to stop their use in the long term. Treatment must address their behaviors, thoughts, and emotions.

Conclusion

The hypothalamus plays an integral role in the body's response to physiological as well as emotional stress. Chronic exposure to such stressors can have lasting effects on these individuals, including predisposing them for risk of various psychiatric disorders. Pharmacological treatment interventions may be effective by altering either hypothalamic function or the consequence of its dysfunction [32, 87].

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Neurosurgical Aspects of Hypothalamic Disease

9

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Anatomy of the Hypothalamus

The hypothalamus,anatomically, poses many difficulties for a neurosurgeon. The hypothalamus is situated beneath the thalamus, separated by the hypothalamic sulcus of Monro – formed by the lateral wall of the third ventricle, extending anteroposteriorly from the foramina of Monro to the cerebral aqueduct. Anteriorly, the hypothalamus is bordered by the lamina terminalis. Superiorly, the inferolateral wall of the third ventricle and the fornix form the upper limits to the hypothalamus. Posteriorly, the hypothalamus extends to the tegmentum of the midbrain. The lateral wall of the hypothalamus extends to the optic tract(s) [19].

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The hypothalamus itself is divided into eight nuclei, each with their own specific function. The supraoptic, dorsomedial, and paraventricular nuclei sit in the anterior aspect of the hypothalamus, dubbed the "supraoptic area," as this portion of the hypothalamus sits above the optic chiasm and the pituitary gland. The central hypothalamus consists of the paraventricular, dorsomedial, arcuate, and ventromedial nuclei. The posterior aspect of the pituitary contains the mammillary bodies/nuclei, along with the posterior hypothalamic nuclei [19].

Clearly, the hypothalamus sits in an incredibly dense area of the brain, surrounded on all sides by eloquent structures. Surgical approach to these lesions can be incredibly difficult and requires advanced surgical techniques and approaches. We will discuss common diseases of the hypothalamus requiring surgical intervention, as well as the well-reported surgical approaches to treat these lesions.

Hypothalamic Diseases Requiring Surgical Management

Hypothalamic Hamartoma

A hamartoma is a benign noncancerous mass that consists of disorganized growth of native tissue. Although considered a tumor, this lesion rarely exhibits neoplastic characteristics and/or tendencies (i.e., no accelerated growth, no local invasion

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of surrounding area(s), nor do hamartomas spread). These lesions consist of a mix of hyperactive neuronal cells and glial cells within the hypothalamus, usually arising from the floor of the third ventricle [25, 31]. Morphologically, there are two main subtypes: pedunculated and sessile hypothalamic hamartomas – the chief difference being the normal location of the lesion. Pedunculated lesions stem from a common stalk and extend into the third ventricle, whereas the sessile form grows entirely within the hypothalamus [25].

These are associated with a number of endocrine abnormalities as well as gelastic epilepsy. Additionally, these people may suffer from behavioral, psychiatric, and cognitive impairments causing developmental delay in childhood and can complicate therapeutic approach to these patients [16].

The diagnosis is made through clinical symptoms of endocrine abnormalities, precocious puberty, or epileptic symptoms. Appropriate workup includes relevant endocrine labs (electrolytes, pituitary hormones, etc.), EEG, and MR imaging studies. It is important to note that EEG studies can often fail to show ictal/interictal abnormalities (gelastic seizures can present without these findings).

Surgical intervention has limited evidence-based management data due to the novelty of the disease. Common practice and relevant case-report literature indicate that surgical intervention is considered in patients with uncontrollable, medication-refractory seizures in the setting of a known hypothalamic hamartoma. Case reports identify the standard pterional approach, transcallosal approach, and subfrontal translaminar terminalis approach as common surgical approaches to these lesions [21, 31]. Intraoperative guidelines and reports suggest aggressive resection is not advised due to the delicate nature of resection within the region, as injury to the subfrontal region, anterior cerebral artery (and associated perforating arteries), and chiasmatic structures [26].

Pilocytic Astrocytoma

Pilocytic astrocytomas are widely known for being very common ventricular tumors, typically arising within the posterior fossa (cerebellum), extending into the fourth ventricle. These tumors also can originate from the midbrain, thalamus, and hypothalamus – these tumors often extend into the third ventricle. These tumors have good prognosis (5-year survival 80–90%), likely attributable to the slow growth of the mass, which allows for complete surgical resection. Surgery is a staple for effective management of these tumors [23].

Although the majority of pilocytic astrocytomas are found along the fourth ventricle, these tumors can also be found along the third ventricle. The hypothalamus can both complicate an appropriate surgical approach and be involved via direct extension of the tumor. Surgical approach to a third ventricular pilocytic astrocytoma remains relatively consistent regardless of the specific origin of the tumor. Commonly used surgical approaches include suprasellar transventricular approaches as well as a subfrontal translaminar approach or transcallosal approach [22]. The location of the astrocytoma within the third ventricle can affect which approach is chosen. It is essential to identify the hypothalamus when resecting these third ventricular-based lesions, as any that extend anteriorly or laterally to the ventricle risks involving the hypothalamus. Careless resection in these areas risks damaging the nearby, or potentially involved, hypothalamus. An important surgical note in these resections is that traditional practices include draining the cystic portion of the tumor prior to microsurgical resection/dissection, thereby opening additional room to resect and relieving pressure on nearby structures [22, 28].

Expansive Craniopharyngioma

Craniopharyngiomas exist as metaplastic adenohypophyseal cells, remnants of the hypophysiopharyngeal duct (Rathke's pouch). Embryologically, Rathke's pouch is a derivative of the ectoderm, exists as an invagination of the developing mouth, and eventually becomes the anterior pituitary gland and the pars distalis/tuberalis [11, 33]. During this process, cysts can develop during embryologic transformation within Rathke's pouch. In some people, these

cells persist and can proliferate/cause mass effect symptoms in the parasellar region.

The vast majority of craniopharyngiomas sit within the parasellar chiasmatic cisterns, with a minority (less than 5%) existing solely intraventricularly. These tumors are often caught once they grow to be very large, as the bulk of their growth extends into the chiasmatic cisterns and surrounding cisterns. This growth pattern causes large and expansive growth prior to affecting the surrounding parenchyma [24].

Histologically, craniopharyngiomas have two main subtypes: adamantinomatous and papillary subtypes. Adamantinomatous tumors are seen in young children and are cystic, classically known to contain cholesterol and dark cystic fluid. This variant is known to encase/surround numerous deep hemispheric structures, including the pituitary gland, optic chiasm, third ventricle, and hypothalamus. Papillary tumors, on the other hand, can be seen in both child and adult populations and are more solid and well-circumscribed [11, 17].

In patients with craniopharyngioma, evidence of neurocognitive changes best indicates involvement of the hypothalamus, as symptoms like endocrine dysfunction do not help physicians and surgeons differentiate between hypothalamic and pituitary function [17]. Common surgical approaches are transnasal or transcallosal, the decision between the two typically made by the location/size of the lesion. Should the tumor sit too far laterally, an endonasal approach could potentially not provide a wide-enough window to the full extent of the tumor, making maximum resection unlikely. Hypothalamic involvement of these tumors also complicates a surgical approach and can even call into question the need for an operation [33].

Typically, craniopharyngiomas respond extremely well to full resection; however involvement of the hypothalamus limits the surgeon's ability to be aggressive with surgical excision. In these patients, safe, yet incomplete, resection is more valued than gross total resection due to the efficacy of radiotherapy. Radiotherapy and radiosurgery have been found to protect vital structures while still adequately treating the tumor and decreasing morbidity and mortality [29].

Hypothalamic Optic Glioma/ Astrocytoma

Optic pathway and hypothalamic gliomas are rare astrocytic tumors, more commonly seen in children than adults. They comprise 3–5% of pediatric tumors (2% of brain tumors in all ages) and are commonly deemed unresectable. Common presenting symptoms are attributable to local interruption of visual/hypothalamic pathways – visual disturbances, endocrinopathies, hydrocephalus, and hypothalamic dysfunction [10].

To date, surgical resection of these lesions results in middle-term survival, tumor control, and functional outcome equivalent to that of chemotherapy – although the current fold standard treatment includes chemotherapy and as-needed debulking surgery.

Surgical treatment of these gliomas is controversial, likely because the rates of cure and successful treatment are wholly dependent on chemotherapy. Surgery is currently used when the tumor has exhibited growth following chemotherapy, or the size/location of the tumor permits surgical removal – unilaterality of the mass and involvement of only one optic pathway. Tumors localized on the optic chiasm or tumors extending into both optic pathways are deemed inoperable [34].

Common surgical approaches include an interhemispheric transcallosal, translaminar terminalis approach, transcortical, pterional, and, occasionally, an endonasal transsphenoidal approach. Maximal resection is critical, as these lesions commonly regrow and recur [3].

Deep Subcortical Arteriovenous Malformations

Arteriovenous malformations are aberrant connections between arterial and venous blood vessels and can cause numerous issues, such as headaches, seizures, stroke, and, potentially, hemorrhage. Deep subcortical AVMs can be a large headache for surgeons, due to the highly eloquent and functional parenchymal location and surgically difficult-to-reach areas [4].

Blood vessels to the hypothalamus have been implicated as spots for AVMs, both arising from the anterior and posterior circulation. Anterior circulation AVMs affecting the hypothalamus include the median lenticulostriate vessels (branching from the A1 anterior cerebral artery segment *or* the proximal M1 middle cerebral artery segment), which perfuse the suprachiasmatic hypothalamus, and the anterior thalamoperforators, arising from the M1 MCA segment. Posterior circulation AVMs affecting the hypothalamus are from the posterior thalamoperforators. Posterior thalamoperforating arteries are a set of small arteries arising from the proximal P1 segment of the posterior cerebral artery, affecting the posterior hypothalamus, thalamus, and medial midbrain [15].

These lesions are very difficult to approach, and guidelines suggest that resection should only be attempted if the lesion is small enough and the nidus of the AVM is both compact and lies along the ependymal surface [9]. Patients with these lesions who have no experienced hemorrhage nor preexisting neurologic deficits should not be operated on – the risk of the operation outweighs the risk of bleeding/deficits of such benign AVMs. Overaggressive surgical approach leaves the surgeon at risk for entering/rupturing the nidus, leaving the surgeon in a dangerous situation to stop torrential, life-threatening bleeding in a narrow operative window [27].

Should it be the best treatment option, surgical intervention and management of these lesions can best be approached via the transcortical approach or via a transcallosal transforaminal transvenous transchoroidal route. Following the medial wall of the third ventricle, the thalamoperforators, both anterior and posterior, can be identified at the inferior margins [15].

Supratentorial Cavernous Malformation

Cavernous malformations are clusters of small, abnormal blood vessels that can displace neurologic tissue, filled with slow-moving/stagnant blood that are very fragile. These malformations predominantly arise (80%) above the tentorium. The majority of these reside in the cortical and/or subcortical space, with a small percentage of these (5–10%) originating in the thalamic/hypothalamic region. The cavernous malformations in this area are commonly associated with endocrine and thalamic abnormalities and rarely cause changes in cognition [18].

Supratentorial CMs are typically incidental findings but can also present with seizures or progressive neurologic deficits (secondary to hemorrhage). This constellation of symptoms due to SCMs is especially seen in younger patients – those in their 20s and 30s [14].

The approach to treatment about these malformations is heavily debated [14, 20]. Studies have advocated for early/immediate operative intervention, citing better surgical outcomes for those who underwent surgery closer to the initial onset of any seizure activity. On the flip side, studies have also showed that the risk of hemorrhage per year is as low as 0.25% per person per year in patients with no prior history of hemorrhage, calling into question the risk/benefit ratio of an operation to remove these lesions, especially those deep in the hypothalamus.

Several pre-op evaluations are critical: these malformations need to be assessed for an A-V fistula via arteriogram, and a functional MRI may be necessary to assess for functionality within the malformation [18]. Intraoperative image guidance improvements have allowed for more effective excision of deep cavernous malformations, such as those within the hypothalamus. Gross total resection of these CMs is essential, as this effectively removes chance for future hemorrhage and recurrent/continuing seizures.

Histoplasmoma

Histoplasmosis capsulatum is a dimorphic fungus commonly found in the midwestern United States. In immunocompromised states this fungus can disseminate to the brain and form histoplasmomas – small, expansile lesions within the hypothalamus, thalamus, or chiasmatic region [8]. These present on imaging as ring-enhancing

lesions and can cause local destruction and affect the function of these deep structures, resulting in hypothalamic dysfunction. These are very rare, as there are only ten reported cases of thalamic or hypothalamic involvement.

Surgical intervention in these patients has been documented, yet there are too few cases to come to consensus on whether surgical intervention is an effective treatment strategy [30]. For those who have underwent surgery for the fungal masses related to histoplasmosis, the literature suggests that most the cases that went to surgery were done via transcallosal or transocortical approach with great success [8, 30].

Surgical Approaches

Standard Pterional/Trans-sylvian Approach

A pterional approach, also known as a frontotemporal craniotomy, is a very commonly used approach for supratentorial lesions. It allows surgeons a wide range of variability and flexibility in the surgical approach to reach the anterior and middle skull base. From this opening, the surgeon has many options for surgical approach, most commonly trans-sylvian. The key steps of the pterional approach are positioning, skin incision, interfascial dissection, craniotomy, drilling of the sphenoid wing, and the dural opening. After the bone removal, the pterional approach proceeds with the opening of the sylvian fissure and the basal cisterns [32]. The trans-sylvian approach involves a small corticotomy with minimal extension to reach the hypothalamic region. Large landmarks with this approach include the internal carotid artery, the optic nerve/chiasm, and the infundibulum inferiorly. This lateral approach can be a large advantage for surgeons approaching lateral lesions [7].

This approach, however, has its limitations. First and foremost, this approach provides a somewhat narrow surgical window between the ICA, the optic nerve, and the infundibulum, limiting visualization and access of the third ventricle and medially placed surgical targets. Additionally, this exposure increases the risk for additional morbidity – literature has reported increased rates transient third nerve palsy, post-op central diabetes insipidus, and hyperphagia with this approach [34]. Furthermore, Palmini et al. reported that 3 of their 13 patients achieved seizure freedom, and a > 90% reduction in seizure frequency was noted in the remaining 10 children [34].

When approaching hypothalamic lesions requiring surgical intervention that lie too far lateral for an endonasal or transventricular approach, a pterional approach with trans-sylvian approach to the lateral hypothalamus should be considered [1].

Supraorbital Craniotomy

In the mid-2000s, surgeons at the neurosurgery center in Helsinki Finland, most notably professor Juha Hernesniemi, were developing an alternative way to approach craniopharyngiomas, seeking to improve upon the standard pterional approach [1, 2]. Their efforts helped create and establish the lateral supraorbital approach to the parasellar, para-chiasmatic, and intra-sylvian regions. The lateral supraorbital approach involves an eyebrow incision with a minimally invasive keyhole approach to the frontal and frontal temporal region. The trajectory from this angle gives the surgeon a longer operative distance; however it simultaneously requires less brain manipulation and retraction. The benefit to this is that you have a window with many possible working angles to reach interior circulation aneurysms, school-based tumors, as well as parasellar, suprachiasmatic, and third ventricular lesions [1, 2]. Within this window lies the hypothalamus.

This approach is, naturally, not without its limitations. Approaching these deep structures from this angle requires corticectomy of the frontal lobe, which can lead to disinhibition and worsening cognitive processing and decision-making. Additionally, mediobasal injury can lead to amnesia, both anterograde and retrograde. Cosmetically, the incision around the eyebrow can lead to scarring. Similarly, should the incision run too far beyond the zygomatic process,

there is increased risk of injuring the frontal branch of the facial nerve and causing forehead weakness unilaterally (either temporarily or permanently) [7].

When compared directly with a pterional approach, the lateral supraorbital approach offers similar exposure while reducing surgical trauma and manipulation of the brain cortex and simplifying the surgical procedure [33].

Transcallosal Approach

A transcallosal approach involves approaching the hypothalamus/structures between the cerebral hemispheres, retracting each hemisphere laterally, and approaching the corpus callosum from above. The callosum is then split and the third ventricle, hypothalamus, thalamus, etc. all come into view. The patient is positioned with the dominant/affected hemisphere up, with the patient positioned such that the falx runs parallel to the floor. This positioning aids visualization and allows for avoidance of large frontal bridging veins and excellent visualization of the third ventricle, hypothalamus, mammillary bodies, and pituitary stalk beneath. This technique offers reduced rates of injury to the mammillary bodies, pituitary stalk, and optic chiasm. Furthermore, the minimal manipulation of the cerebral hemispheres and neurovascular structures within the suprasellar cisterns decrease the likelihood of cerebral infarction and oculomotor nerve palsy [7].

The inherent risks of the surgery involve the path to the hypothalamus – the septal and forniceal injury can result in postsurgical memory deficits [12]. A 2003 study done by the Melbourne group analyzing complications following hypothalamic hamartoma resection using the transcallosal approach showed common complications, including thalamic infarction, increased appetite, and short-term memory deficits. Subsequent studies show an increased correlation between extent of resection and postoperative seizures [21]. Although these complications have been well-reported, their likelihood is low [21, 31].

Additional limitations toothless approach include a restricted access and visualization to laterally reaching tumors due to the presence of the pericallosal arteries. For medially sitting tumors, however, the transcallosal approach offers fantastic surgical access to this region with limited and infrequent long-term complications.

Subfrontal Translaminar Terminalis Approach

The lamina terminalis is a thin layer of gray matter extending backward from the corpus callosum (above the optic chiasm) and forms the median border of the third ventricle. Perhaps best known for its utility in third ventricle surgery, a subfrontal approach to the hypothalamus extending through this layer of the cortex involves superior retraction of the frontal lobe to expose the hypothalamus and third ventricle. The subfrontal translaminar terminalis approach offers excellent views and visualization of the lamina terminalis, optic nerves, optic chiasm, bilateral carotids, ACA segments, the hypothalamus, and the pituitary stalk [6, 7]. For anteriorly lying hypothalamic lesions, the lamina terminalis approach offers the surgeon great exposure within the surgical corridor. The largest advantage for this approach is the minimal manipulation of the cortex necessary to expose structures within the region of the hypothalamus. Additionally, virtually no manipulation of visual nerves is necessary, thereby reducing the risk of harm to these structures during surgery [6, 31].

The same reasons that make this approach great are also the reasons that make it problematic. The clean surgical window that provides great visualization of midline structures is also long, restricted, and non-flexible. The length of the approach limits lability of the surgeon to extend laterally. The critical anatomy that sits just on the periphery of this approach makes extension beyond the surgical window very dangerous.

When compared to other approaches, the subfrontal terminalis approach is an excellent choice for a small subset of hyper-fire lesions, namely, those that sit close to the midline, whereas lesions that lay nearly anywhere else or

those that extend laterally are best operated on using a different approach.

Endoscopic Endonasal Approach

An endoscopic endonasal approach is a commonly used surgical approach to reach the sellar and suprasellar regions of the brain. This approach involves approaching the sellar and parasellar regions via drilling through the ethmoid sinus via nasal approach. This view has inline access and superior visualization of the pituitary stalk and hypothalamus. This visualization, traditionally used in removal of sellar/suprasellar craniopharyngiomas, offers excellent surgical access to midline lesions [13, 34].

The caveat with the endonasal approach, however, is that masses that extend laterally or posteriorly complicate resection. The laterality of the mass forces the surgeon to have to traverse the cavernous sinus and the cavernous portion of the carotid artery. This anatomy provides a dangerous road and can cause significant increases in morbidity. When these tumors remain midline and the whole capsule can be accessed readily, the endoscopic endonasal approach is preferred. For lesions that do not sit midline, other approaches will give better visualization.

Literature surrounding the capabilities of the endoscopic endonasal approach to lesions is growing. There are case reports and studies focused on the use of the endoscopic endonasal approach to not only pituitary lesions but also craniopharyngiomas (sellar, parasellar, hypothalamic, etc.), hypothalamic hamartomas, optic or hypothalamic gliomas, and meningiomas [31, 34]. Many of these lesions are traditionally operated on via a pterional subfrontal, supraorbital, or transcortical approach. This literature emphasizes that the endoscopic endonasal approach minimizes the manipulation of brain parenchyma or retraction; however it increases the likelihood of a postoperative CSF leak (into the sinus). Although many papers pointed to the increased risk of endocrinologic morbidity of this approach, no study had data or analysis to completely support this claim [31].

Additional Considerations to Surgery

When managing hypothalamic lesions, specifically operative lesions, there must be good discussion and preparation of the possible long-term effects of the operation. Injury to surrounding structures, loss of function of the hypothalamus, and morbidities surrounding intracranial surgery are all worth considering when weighing the risks and benefits of surgery on the hypothalamus. Limitations to surgery or surgical management, however, are not necessarily due to the risks of the surgery, but the circumstances surrounding an operation.

A solid foundational knowledge of the anatomy of the hypothalamus and surrounding structures is imperative for understanding the risks of surgery to this region. The visual pathways, including the optic chiasm, are structures that must be identified and avoided during surgery. Injury to the structures, naturally, will cause visual impairment and possible blindness. The classic presentation of this would be a bitemporal hemianopsia secondary to injury at the chiasm itself. Furthermore, injury to the seller region can cause pituitary dysfunction, as severe as panhypopituitarism due to destruction of the pituitary infundibulum. The close proximity of the hypothalamus to basal ganglia structures can lead to seizures, choreiform movements, involuntary tics, and spasticity, which have all been documented in the literature [5]. Vascular injury can cause several different, yet equally dangerous, outcomes. First and foremost, intraoperative damage to blood vessels can cause bleeding and related ischemic deficits. Additionally, hemorrhage can occur in the postoperative period, both epidural and subdural, dependent on the approach. Postoperative imaging should be completed both to record the extent of resection and also to assess for this undesired outcome [28].

The hypothalamus itself plays roles in numerous bodily functions, namely, multiple endocrine axes, appetite, sleep-wake cycle, behavior, memory, and emotion. The hypothalamus' close relationship with the pituitary gland via endocrine signaling is the source of many side effects and

morbidity surrounding hypothalamic surgery. Many of these complications arise with or are already complications of the lesion itself, as the hypothalamic process disrupts normal hypothalamic function. Manifestations of this include thyroid abnormalities, Cushing syndrome, diabetes insipidus, sexual dysfunction, growth abnormalities, and amenorrhea [5, 7, 19]. Additionally, the hypothalamus is the hub for energy homeostasis and food regulation. Disruption of this network can lead to hyperphagia and morbid obesity, best documented in craniopharyngioma literature, but also noted elsewhere. Regulation of blood pressure, thirst, and body temperature have also been seen and well-reported. Daytime sleepiness and disruption of circadian rhythm is a known warning sign for hypothalamic dysfunction, and the rates of this following surgical treatment spike – one study notes an increase by up to 65–80% [7, 31]. Many of these hypothalamic injury-induced sequelae persist even beyond hormone replacement treatment.

Finally, it is worth noting that the individual risks associated with any particular approach to this region must not be ignored and should be compared on a case-by-case basis to determine the best surgical approach to the lesion. Many of these approach-specific sequelae are detailed above.

Regarding the nonoperative considerations to surgery in many of these patients, there are numerous factors that can influence the decision to operate or not to operate. A proper assessment of comorbid diseases and operative risk is essential to a neurosurgical worker. Although surgery may be the best option to manage the specific lesion, the patient must be considered as a whole, and the decision whether to undergo surgery should be done under such pretense. Additionally, workup of these lesions should include a discussion with the patient on or ability and mortality of their disease both before and after a possible surgery. Neurosurgery can be incredibly taxing to the body, and proper understanding of this will help the patient make the most appropriate decision regarding their care. If at any point it becomes clear that the patient will not be able to tolerate the operation or postoperative therapy, open discussion with the patient is warranted, including a discussion on long-term goals of care.

Conclusion

As neurosurgical technology grows and expands, the ability to surgically manage patients with hypothalamic diseases and lesions becomes more and more possible and prevalent. Common diseases that affect the hypothalamus include tumors (gliomas, hamartomas, astrocytomas, expansive craniopharyngiomas) and vascular abnormalities (SCMs, AVMs) and can be approached by either endonasal techniques or cranial approaches (pterional, supraorbital, subfrontal, etc.).

The decision regarding the appropriate approach to a lesion depends heavily on the location of the tumor. Lateral hypothalamic lesions are best approached via pterional approach, whereas medial lesions can be approached via endonasal or translaminar approaches. Superior lesions and lesions affecting the third ventricle can be approached via the transcallosal approach or the pterional/modified pterional approaches. The ultimate decision made by the surgeon should consider major side effects or possible complications, as well.

The most common postoperative sequelae are due to the loss of hypothalamic function secondary to removal of tissue within the region. Other complications – namely, damage to surrounding structures – can be minimized and mitigated by good surgical technique and good surgical approach. The hypothalamus' location makes clear operations and wide surgical windows difficult to obtain.

New prospects to possibly improve these operations include increased image guidance capabilities. Improvement to intraoperative image guidance will help maximize excision of unwanted tissue while minimizing the loss of extraneous tissue or damage to other structures. Similarly, advanced and innovative operative approaches can provide better surgical windows than we know now.

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10 Hormone Excess Syndromes of the Hypothalamic-Pituitary Axis

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Prolactinomas

Hyperprolactinemia is a condition of excess prolactin, which could be physiologic, pathologic, or idiopathic. Prolactinomas are the most frequent cause of chronic hyperprolactinemia [1]. They are also the most common type of pituitary adenomas and account for approximately half of pituitary tumors requiring medical attention [2]. Based on the size of the tumors, prolactinomas can be classified as microadenomas if less than 10 mm in size, macroadenomas if greater than 10 mm in size, or giant adenomas if larger than 4 cm in size [3].

Clinical Manifestations

The clinical presentation of prolactinomas differs based on the size of the adenoma and the sex of the patient. Most clinically diagnosed prolactinomas are found in premenopausal women and are microadenomas. In men, prolactinomas typically present as macroadenomas or giant adenomas [4]. Patients with macroprolactinomas or giant prolactinomas typically present with neurologic symptoms caused by mass effect. These include headaches, vision changes, cranial neuropathies, hypopituitarism, seizures, and cerebrospinal fluid rhinorrhea [1, 2, 5]. Prolactinomas predominantly affect women between the ages of 20 and 50 years [6]. In premenopausal women, classic symptoms include oligomenorrhea or amenorrhea, galactorrhea, infertility, decreased libido, and decreased bone mass [1, 2]. Postmenopausal women typically do not present with typical hyperprolactinemia-related symptoms as these are dependent on intact ovarian function. These patients therefore usually present with mass effect symptoms when their adenomas become large enough [7]. In men, hyperprolactinemia causes hypogonadotropic hypogonadism. This can manifest as decreased libido, impotence and erectile dysfunction, infertility, gynecomastia, and rarely galactorrhea [3, 8, 9]. Males sometimes present with small testes and prostate [9]. They can also present with decreased bone mass and over time can have diminished energy, reduced muscle mass, and increased risk of osteopenia [1]. In children, prolactinomas typically occur during the start of puberty. The most common presenting symptoms are headaches and

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Table 10.1 Clinical characteristics of prolactinomas

Type of patient	Clinical manifestations
Premenopausal women	Menstrual irregularities such as amenorrhea and oligomenorrhea, galactorrhea, infertility, decreased libido, decreased bone mass, anxiety, depression, fatigue, and emotional instability
Postmenopausal women	Mass effect symptoms including headaches, vision changes, cranial neuropathies, seizures
Males	Hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia, galactorrhea (rare), anxiety, depression, fatigue, and emotional instability
Children	Girls: menstrual irregularities, galactorrhea Boys: delayed pubertal development, hypogonadism
Patients with macroadenomas and giant prolactinomas	Mass effect symptoms including headaches, vision changes, cranial neuropathies, seizures

Modified with information from Majumdar et al. [1], Chanson et al. [2], Yatavelli et al. [3], Luciano, AA [5], Shimon et al. [7], Carter et al. [8], Segal et al. [9], Hoffman et al. [10], Melmed et al. [11]

visual impairment from mass effect [10]. In girls, menstrual irregularities and galactorrhea can be seen, while boys present with delayed pubertal development and hypogonadism [11]. Girls are more often affected than boys; however, prolactinomas in boys are typically larger and more aggressive [10]. Other clinical manifestations in males and females include anxiety, depression, fatigue, and emotional instability. Approximately 10% of prolactinomas also co-secrete growth hormone so gigantism and symptoms of acromegaly can also be seen in patients [3]. The clinical manifestations of prolactinomas are summarized in Table 10.1 [1–3, 5, 7–11].

Diagnosis

When clinical manifestations of prolactin excess are suspected, laboratory evaluation begins with measurement of prolactin levels. The normal prolactin range is approximately 5–20 mcg/L. Prolactin levels are typically elevated and generally correlate with the prolactinoma size [2]. Prolactin levels greater than 250 mcg/L typically indicate the presence of a prolactinoma over other causes, and levels greater than 500 mcg/L are usually diagnostic of a macroprolactinoma. However, select medications such as risperidone and metoclopramide can cause prolactin levels greater than 200 mcg/L [11].

In some cases, there may be an artificially low prolactin level when a prolactinoma is present, caused by the "hook effect." Prolactin levels are measured using an assay based on a sandwich principle in which a prolactin molecule reacts with a capture antibody and then binds to a detection antibody. Each antibody is specific for a particular epitope on the prolactin molecule. The "hook effect" is caused by an assay artifact when there are extremely high levels of prolactin that saturate both the capture and detection antibodies used in the assay, preventing the antibody-prolactin-antibody sandwich formation, resulting in a falsely low reported value (Fig. 10.1) [12–14]. In order to determine whether the low prolactin is accurate or as a result of the hook effect, serial dilution of the prolactin serum sample should be obtained, which will result in an elevated prolactin if the patient has a prolactinoma [3, 14]. There are also cases in which there is an elevated measured prolactin level; however, the true prolactin level is actually low. This occurs when patients have a higher molecular weight prolactin called macroprolactin. Macroprolactin forms by condensation of prolactin molecules or complex formation between prolactin and plasma proteins. Therefore, in patients with asymptomatic hyperprolactinemia, macroprolactin levels should be obtained to assess for this. The lab can precipitate the macroprolactin by pretreating the serum with polyethylene glycol before obtaining the immunoassay for prolactin [3, 15].

In patients suspected of having a hypothalamic-pituitary cause of their hyperprolactinemia, pituitary MRI with gadolinium enhancement should be obtained as it provides the best visualization of the sellar area [1].

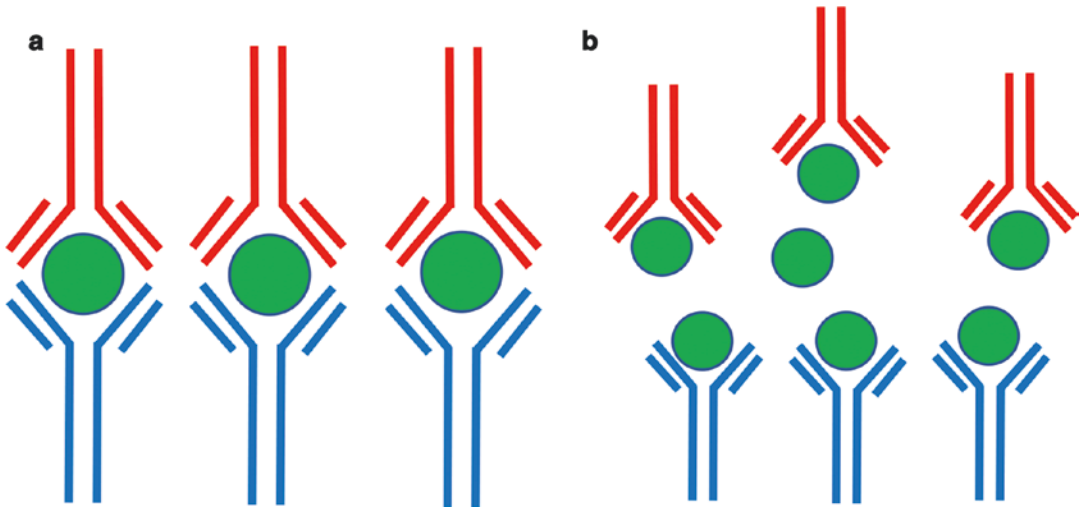

Fig. 10.1 Hook effect sandwich assay. (**a**) shows the normal sandwich assay with the capture antibody in blue, the detection antibody in red, and the prolactin molecule in green. (**b**) shows the hook effect where there is excessive prolactin antigen (in green) which then binds up sites on both the capturing antibody (in blue) and detection antibody (in red), thereby reducing detection levels. (Modified from Binart et al. [12], Romijn [13], and Vilar et al. [14])

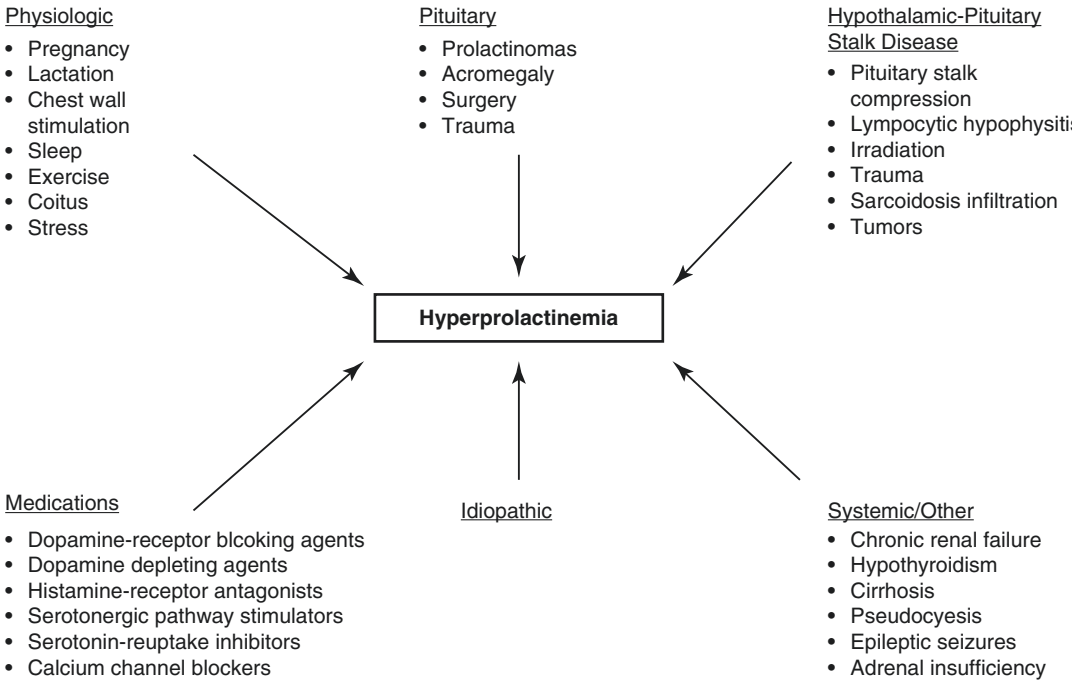

Fig. 10.2 Causes of hyperprolactinemia. (Modified with information from Majumdar et al. [1], Syro et al. [4], Melmed et al. [11], Molitch ME [16])

Differential Diagnosis

There is a wide differential for hyperprolactinemia and many etiologies need to be considered (Fig. 10.2) [1, 4, 11, 16]. Physiologic causes of elevated prolactin levels include pregnancy, lactation, chest wall stimulation, sleep, exercise, coitus, and stress. Hyperprolactinemia in these

cases is usually mild to moderate [1, 11]. While prolactin is synthesized in and secreted by the anterior pituitary, it is also regulated by the hypothalamus via inhibition by dopamine. Therefore, any factors that cause loss of dopamine inhibition via the effects of medications or destruction of the hypothalamus or hypothalamic-hypophyseal tract will result in prolactin excess [3, 17]. Thus, there are a broad range of pathologic etiologies including pituitary causes, hypothalamic-pituitary stalk diseases, medication-induced, and systemic or other causes.

Pituitary causes include prolactinomas, acromegaly due to co-secretion with growth hormone, surgery, and trauma. Hypothalamic-pituitary stalk disease etiologies include pituitary stalk compression, lymphocytic hypophysitis, irradiation, trauma, sarcoidosis infiltration, and tumors such as craniopharyngiomas, meningiomas, dysgerminomas, dermoid cysts, and pineal gland tumors. Medication-induced causes include dopamine receptor blocking agents (such as phenothiazines, haloperidol, metoclopramide, and atypical antipsychotics), dopamine-depleting agents (such as reserpine, methyldopa, and opiates), histamine receptor antagonists (such as ranitidine), stimulators of the serotonergic pathway (such as amphetamine and hallucinogens), estrogens and antiandrogens, serotonin reuptake inhibitors (such as fluoxetine), and calcium channel blockers (such as verapamil). Systemic or other causes include chronic renal failure, hypothyroidism, cirrhosis, pseudocyesis, epileptic seizures, polycystic ovarian disease (PCOS), and adrenal insufficiency [1, 4, 11, 16]. Idiopathic hyperprolactinemia accounts for approximately 40% of cases [1].

Management

The preferred initial treatment for prolactinomas is dopamine agonists. Dopamine agonists bind to the dopamine D2 receptors and inhibit the synthesis and secretion of prolactin from the anterior pituitary gland [18]. These have been shown to lower prolactin levels, decrease tumor size, and restore gonadal function for symptomatic patients [11]. Cabergoline and bromocriptine are the most commonly used dopamine agonists. Others include pergolide, quinagolide, terguride, and metergoline. All are ergot alkaloids except quinagolide, which is a nonergot dopamine agonist [1]. Cabergoline has a long half-life ranging from 63 to 69 hours and the initial dose is usually 0.25 mg twice weekly. The dose can be increased slowly by 0.25 mg twice weekly at a minimum of every 4 weeks [18]. Bromocriptine treatment is usually started at a dose of 1.25–2.5 mg per day and can be titrated up by 2.5 mg per day every 2–7 days. The maintenance dose ranges from 2.5 to 15 mg per day [18]. Side effects of dopamine agonists include nausea, vomiting, headaches, constipation, dizziness, orthostatic hypotension, depression, digital vasospasm, and nasal stuffiness [1]. Regarding efficacy of treatment, bromocriptine treatment has been shown to cause normoprolactinemia and restoration of normal menses in 80–90% of patients [19]. Cabergoline is used more often as it has been shown to achieve higher rates of normalizing prolactin levels and higher frequency of shrinking tumors [11]. Normal prolactin levels are achieved in 80–100% of patients with microprolactinomas and 75–95% of patients with macroprolactinomas. Cabergoline can also normalize prolactin levels in patients with resistance to other dopamine agonists [20]. Treatment with dopamine agonists should be tapered and stopped if prolactin levels normalize, if the tumor is not visible on MRI after at least 2 years of treatment, or if the tumor shrinks by 50% with a mass at least 5 mm from the optic chiasm and no evidence of cavernous sinus or other critical area invasion [3, 11, 21].

In pregnant patients, dopamine agonists should be avoided if possible as they can cross the placenta. However, treatment is indicated during pregnancy if the patient has a large adenoma or symptomatic growth during pregnancy [3, 20]. There do not appear to be any adverse pregnancy outcomes of risks for fetal malformations with either bromocriptine or cabergoline [22].

Resistant prolactinomas are those in which there is failure to achieve normal prolactin levels, reduce prolactin levels by greater than 50%, induce ovulation in women, or reduce symptoms

or normalize prolactin despite high cabergoline doses [20]. Symptomatic patients with prolactinomas resistant to medical therapy may benefit from transsphenoidal surgery [11, 23]. Other indications for surgical therapy include patients with psychiatric conditions with contraindications to dopamine agonist treatment, women with adenomas impinging on the optic chiasm seeking fertility, and patients presenting with CSF leak or pituitary apoplexy [20]. Radiation therapy is typically only used in patients with prolactinomas resistant to cabergoline therapy and who have undergone surgery and have residual tumor present. There is a risk of causing hypopituitarism with radiation therapy [1, 3].

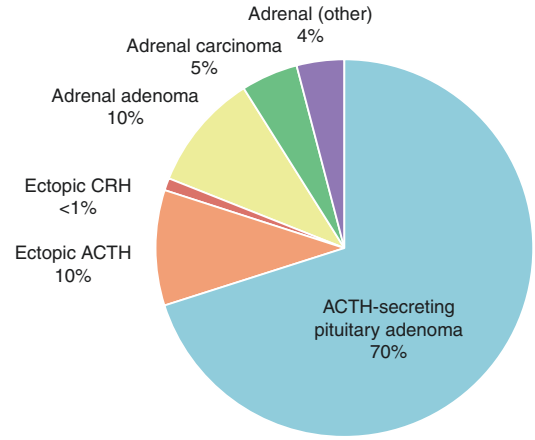

Fig. 10.3 Causes of endogenous Cushing's syndrome. (With permission from Tritos et al. [30])

Cushing's Syndrome

Cushing's syndrome results from prolonged glucocorticoid (GC) excess, from either exogenous GCs or endogenous sources of cortisol. Exogenous Cushing's syndrome is the most frequent cause of hypercortisolism. Most cases are iatrogenic, as high-dose or chronic use of GCs is common in the management of a number of inflammatory, autoimmune, and neoplastic diseases. All modes of exogenous GC delivery (oral, inhaled, topical, subcutaneous) have been implicated in the development of Cushing's syndrome and thus must be ruled out initially [24, 25]. Conversely, endogenous Cushing's syndrome is rare, with an estimated incidence of 0.7–2.4 million per year [26, 27]. More frequently affecting women (female/male ratio 3:1) [28], endogenous Cushing's syndrome results from excessive adrenal cortisol secretion that can be either adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent. A majority are ACTH-dependent, making up about 80–85% of cases [29]. The causes of ACTH-dependent Cushing's syndrome include ACTH-secreting pituitary adenomas, ectopic ACTH secretion, and ectopic corticotropin-releasing hormone (CRH) secretion (Fig. 10.3) [30]. ACTH-secreting pituitary adenomas account for most cases of endogenous hypercortisolism and are referred to as "pituitary-dependent Cushing's syndrome" or "Cushing's disease," in which hypersecretion of ACTH by the adenoma results in pathologic adrenal cortisol secretion [31]. ACTH-independent Cushing's syndrome is even rarer and is characterized by hypersecretion of cortisol by adrenal pathologies such as adrenal adenomas and adrenal carcinomas [30].

Clinical Manifestations

The clinical presentation of Cushing's syndrome is variable and in part is dependent on the extent and duration of cortisol excess. The characteristic features of Cushing's syndrome are depicted in Fig. 10.4 [26, 32–35]. In adults, the signs that best discriminate Cushing's syndrome include easy bruising, facial plethora, proximal myopathy, and purple striae [34]. Other features are less discriminatory but common, such as weight gain, fatigue, depression, facial fullness, acne, decreased libido, and menstrual changes. Central obesity or weight gain is the most common finding in Cushing's syndrome and is seen in approximately 95% of adults [26].

Furthermore, the initial presentation may be characterized by the presence of comorbidities [36–39]. Cushing's syndrome is often complicated by metabolic syndrome (consisting of systemic arterial hypertension, visceral obesity, impaired glucose metabolism, and dyslipidemia),