The Hypothalamus–Pituitary Axis

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Abstract

The hypothalamic pituitary axis is an intricate pathway with a central role in maintaining homeostasis by integrating complex physiological and endocrine inputs, and neuronal and hormonal output. Disorders of the pathway result in profound disturbance in blood pressure, thirst and electrolyte balance, body temperature, appetite and energy metabolism, reproduction, circadian rhythms and sleep, and the emergency response to stress. Untreated, abnormalities of the axis are incompatible with life.

In this chapter we discuss the embryology, anatomy and physiology of the axis. The function of the hypothalamus as the primary regulator of neuroendocrine system is described, examining the neurological and endocrine responses that maintain physiological set points in response to neurological, chemical, and hormonal inputs. The physiology of the endocrine function of the pituitary is discussed, drawing on examples of developmental abnormalities in man to illustrate the clinical consequences of deficiencies in this pathway.

Keywords

Hypothalamus • Pituitary • Homeostasis • Neuroendocrine

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The neuroendocrine system plays a critical role in homeostatic regulation, which is essential for survival and reproduction. Homeostasis is the process by which a steady state is achieved in physiological functions, primarily, heart rate and blood pressure, thirst and electrolyte balance, body temperature, appetite and energy metabolism, reproduction, circadian rhythms and sleep, and the emergency response to stress.

Hypothalamus

The hypothalamus is the integrator of the neuroendocrine system monitoring neurological, chemical, and hormonal inputs, comparing these to physiological set points (electrolyte and fluid balance, body temperature, blood pressure, and body weight) and responding both neurologically and through hormone secretion to restore homeostasis (Fig. 1). This involves the complex integration of positive and negative feedback loops and synaptic inputs from other brain areas and from the autonomic nervous system. Hypothalamic neuropeptides are also secreted in regions of the brain out with the hypothalamus where they modulate and coordinate behavior to complement their hormonal actions. The hypothalamic hormones include thyrotropin-releasing hormone, gonadotropin-releasing hormone, growth hormone-releasing hormone, somatostatin, corticotrophin-releasing hormone, dopamine, oxytocin, and AVP. The set points remain stable from day to day through homeostasis, the coordinated integration of the classic neuroendocrine pathways with the autonomic and central nervous systems.

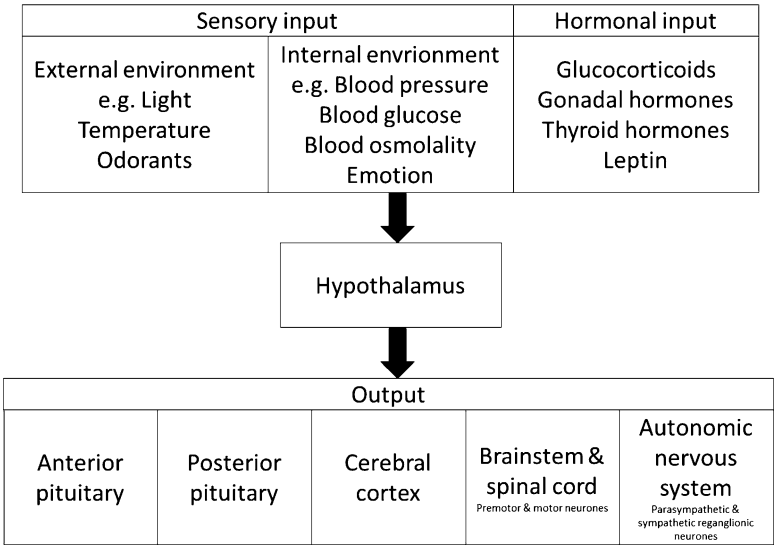

Fig. 1 Simplified overview of hypothalamic integration and coordination

Embryology

Three weeks following conception, the cells of the developing embryo have organized in to three sheets: ectoderm, mesoderm, and endoderm. The ectoderm, the most exterior or distal layer, gives rise to epidermal skin cells and neuroectoderm, which in turn produces the neural tube and neural crest. Vesicles develop at the cranial end of the neural tube. At the end of fourth week, as the vesicles grow, the neural tube undergoes flexion to form three vesicles: the prosencephalon (future forebrain), mesencephalon (future midbrain), and rhombencephalon (future hindbrain).

In the fifth week, the three vesicles become five, with the forebrain and hindbrain both splitting into two, forming the telencephalon and diencephalon from the forebrain and the metencephalon and the myelencephalon from the hindbrain. Historically, the optic cup and stalk, pituitary gland, thalamus, hypothalamus, and pineal body were thought to arise from the diencephalon. The more recently proposed "prosomere model" (Puelles 2009), the segmental structural model based on gene expression in the mouse, suggests that the hypothalamus is derived from the secondary prosencephalon; ventral aspects of the two or three rostral (anterior) segments of the neural tube and the dorsal derivatives of which form the telencephalon (Freeman 2003; Puelles 2001; Alvarez-Bolado 2015) (Fig. 2).

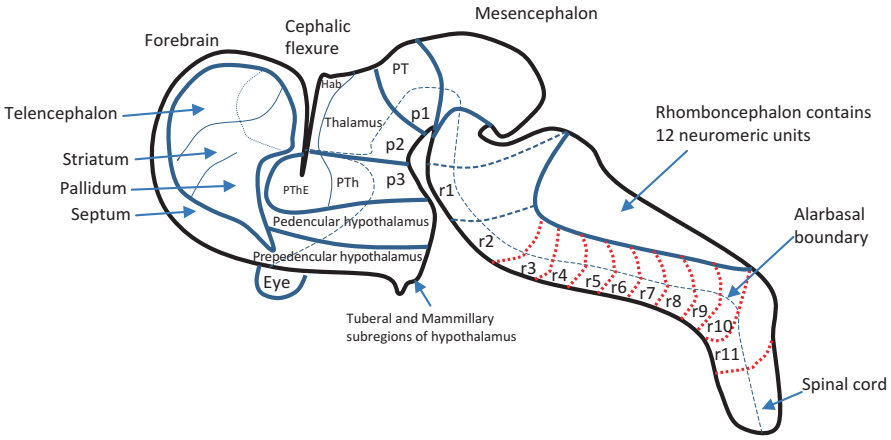

Fig. 2 The scheme shows all longitudinal components, but the floor and roof plates are not represented. The caudal forebrain or diencephalon consists of three prosomeres (p1–p3) whose alar regions include the pretectum (PT), the thalamus and habenula (Th–hab), and the prethalamus and prethalamic eminence (PTh, PThE) (Modified from the prosomeric model of Puelles and Rubenstein (2003))

Anatomy

The hypothalamus constitutes less than 1 % of brain volume and weighs approximately 5 g. It is a highly conserved region of the brain whose destruction is not compatible with life. The hypothalamus is a bilateral structure like the cerebral hemispheres, unlike the pituitary. It extends from the optic chiasm and anterior commissure to the posterior margins of the mammillary bodies and from the thalamus laterally to form the floor and part of the lateral wall of the third ventricle. The regional structures of the hypothalamus are defined by nuclei with distinct functions (Figs. 3, and 4 and Table 1).

The hypothalamic floor projects down to continue as the median eminence, then the infundibulum, and ultimately the posterior pituitary (neurohypophysis). Hormones released from the median eminence reach the anterior pituitary via the hypophysial portal system.

The floor of hypothalamus between the infundibulum and mammillary bodies is known as the tuberal area and contains most of the cell bodies of the small neurons containing hypothalamic-releasing hormones.

Functional Aspects of Hypothalamic Function

Neurosecretory cells are neurons that do not terminate in classical synapses but secrete their neurotransmitters/hormones direct into the bloodstream. In the

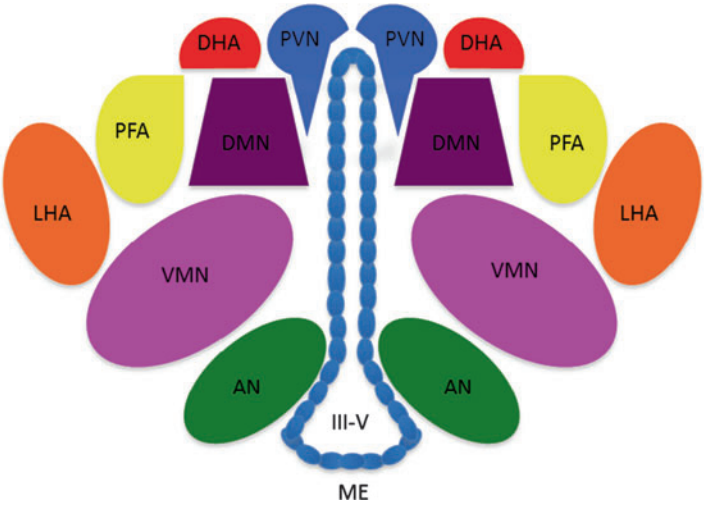

Fig. 3 Schematic coronal view of hypothalamic nuclei location around the third ventricle (III-V). *III-V* third ventricle, *ME* median eminence, *AN* arcuate nucleus, *VMN* ventromedial nucleus, *DMN* dorsomedial nucleus, *PVN* periventricular nucleus, *DHA* dorsal hypothalamic area, *PFA* perifornical area, *LHA* lateral hypothalamic area, *SCN* suprachiasmatic nucleus, *SON* supraoptic nucleus, *POA* preoptic area, *MB* mammillary bodies, *AHN* anterior hypothalamic nuclei, *PHN* posterior hypothalamic nuclei

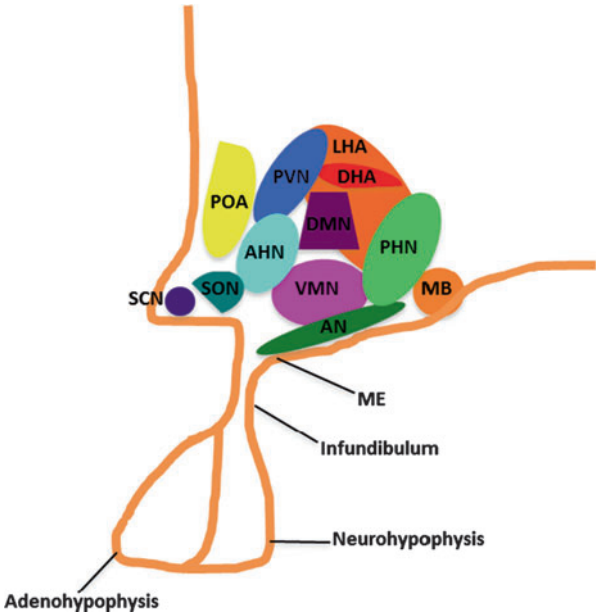

Fig. 4 Schematic sagittal view of the hypothalamic nuclei. *III-V* third ventricle, *ME* median eminence, *AN* arcuate nucleus, *VMN* ventromedial nucleus, *DMN* dorsomedial nucleus, *PVN* periventricular nucleus, *DHA* dorsal hypothalamic area, *PFA* perifornical area, *LHA* lateral hypothalamic area, *SCN* suprachiasmatic nucleus, *SON* supraoptic nucleus, *POA* preoptic area, *MB* mammillary bodies, *AHN* anterior hypothalamic nuclei, *PHN* posterior hypothalamic nuclei

Table 1 A summary of the hypothalamic nuclei and their functions

Nucleus	Output	Functions
Paraventricular	Autonomic system	Fluid balance
	TRH	Milk letdown
	CRH	Parturition
	Oxytocin, vasopressin	Autonomic
	Somatostatin	Ant pit control
Preoptic	LHRH	Lateral anterior thermoregulation
		Sexual behavior
Anterior	Thermoregulation, panting, sweating	Lateral anterior thermoregulation
	Thyrotropin inhibition	Sexual behavior
Suprachiasmatic (SCN)	Projections to hypothalamic nuclei	Major pacemaker
Supraoptic	Vasopressin	Fluid balance
	Oxytocin	Milk letdown
		Parturition
Dorsomedial		Emotion (rage)
		BP, heart rate
		GI stimulation
Ventromedial	Satiety	Appetite
	Neuroendo control	Body weight
		Insulin regulation
Arcuate	ANS, caudal brainstem, parts of cortex, and limbic system	Control of anterior pituitary
	GHRH (neuroendocrine neurons)	Energy balance
	Dopamine	Prolactin inhibition
Posterior	Increase BP	Thermoregulation
	Pupillary dilation	
	Shivering	
	Vasopressin release	
Mammillary	Memory	Emotion, short-term memory
Tuberomammillary		Arousal, feeding, and energy balance
		Learning, memory, sleep
Lateral complex	Orexin	Arousal, appetite
	Melanin-concentrating hormone	Feeding, mood, sleep/wake cycle

hypothalamic region, these have been classified as “magnocellular,” large cells with high synthetic activity located in the supraoptic and paraventricular regions, and “parvocellular,” small neurons in the paraventricular nucleus and rostrally in adjacent parts of the septal region. Magnocellular neurosecretory cells synthesize and secrete oxytocin and AVP. Parvocellular neurosecretory cells release factors at the

median eminence into the hypophysial portal blood system to regulate pituitary function. Their hormones in turn control the secretion, and often synthesis, of hormones from five classic cell types in the anterior pituitary. These cells receive multiple neuronal inputs and integrate these in their subsequent neurosecretory response. While the anterior pituitary releases hormones in response to the stimulatory or inhibitory hypothalamic hormones, these are in turn influenced by neurological input from several regions of the brain.

The hypophysial portal system is a rich complex of blood vessels from the base of the hypothalamus, draining into a mesh of capillaries and ultimately the pituitary sinusoids. They create a great increase in vascular surface area and are also fenestrated, further facilitating the diffusion of hypothalamic factors to the anterior pituitary.

Another major input to neuroendocrine homeostatic regulation through the hypothalamus is the autonomic nervous system. Additionally direct innervation of glands, including the adrenals, pancreas, and pineal and salivary glands, influences the regulation of their exocrine and endocrine functions. The pancreas receives both sympathetic and parasympathetic inputs whose interplay exquisitely influences glucose homeostasis through insulin and glucagon secretion.

The hypothalamus, as part of the brain, is protected from peripheral humoral and chemical signals through the blood–brain barrier. However for homeostatic control, key regions of the brain must receive sensory information from the bloodstream including hormone levels, electrolytes, and glucose as well as potential toxins. The circumventricular organs (CVOs) are regions that allow the passage of peripheral cues into key neuronal cell groups, facilitating homeostasis. The CVOs lie along the third and fourth ventricles in the midline and include the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT), the median eminence, and the neurohypophysis. In these CVO regions, there is a rich blood supply with fenestrated capillaries that allow relatively free diffusion of proteins and peptide hormones. Several of the CVOs have major projections to hypothalamic nuclei that play a role in homeostasis.

Circadian Rhythms

Circadian rhythms refer to the daily fluctuations that occur in hormone secretion, body temperature, and sleep/wake cycle. The main hypothalamic nucleus involved is the suprachiasmatic nucleus (SCN), the body's master clock. SCN neurons have intrinsic rhythmical discharge activity with a 25 h cycle in the absence of light input. Light-stimulated input from the retinohypothalamic tract entrains the SCN neuronal rhythm to a 24 h cycle. The SCN has output projections into multiple hypothalamic nuclei controlling the circadian rhythm of several specific functions including thermoregulation, glucocorticoid secretion, sleep, arousal, and feeding.

Light-stimulated activation of the SCN results in increased input to the paraventricular nucleus which stimulates sympathetic pathways which inhibit the

secretion of melatonin from the pineal gland. Thus darkness and the subsequent loss of sympathetic inhibitory signals allow increased melatonin secretion.

Disorders of circadian rhythm can manifest themselves as sleep disorders, for example, phase shifting or jet lag, delayed sleep phase syndrome often seen in teenagers, or advanced sleep phase syndrome seen in the elderly. Disorders of circadian rhythm often, but not always, affect the blind. The retinohypothalamic tract is not a visual tract and can thus be normal in the blind or defective in those with normal vision.

Sleep allows energy conservation through reduced organic and physical activities and thus influences energy homeostasis. During wakefulness activities lead to hunger which promotes feeding. Chronic circadian rhythm disruption influences sleep, the immune system, appetite, and energy balance (Markwald 2013).

The SCN functionally connects hypothalamic sleeping to feeding centers. The SCN efferent projections target the subparaventricular zone (SPZ) with axons also extending to the dorsomedial nuclei (DMN). Lesions in the ventral SPZ have demonstrated its key regulation of rhythmicity in sleep, feeding, and activity. The DMN sends efferents to the sleep regulation center in the ventrolateral preoptic area, the PVN (corticotrophin-releasing hormone, CRH) neurons and signals to autonomic nervous system, and the lateral hypothalamus (orexin- and melanin-concentrating hormone). The DMN also receive inputs from the arcuate nucleus (appetite and energy expenditure regulation). The ventromedial hypothalamus expresses brain-derived neurotrophic factor (BDNF) under regulation of the melanocortin 4 receptor (MC4R). BDNF regulates sleep onset and hedonic food intake (Faraguna et al. 2008).

In humans a diurnal variation in temperature has been observed depending on the periods of rest and activity, with core temperature lowest between 23 and 3 h during sleep and peaking during the day between 10 and 18 h.

Energy Homeostasis

The obesity epidemic has been the stimulus to much research in energy homeostasis. Imbalance between food intake and energy expenditure causes weight gain and metabolic dysfunction with significant morbidity and mortality in energy excess, whereas in starvation, energy must be conserved for essential organs, e.g., the brain, and diverted from nonessential functions, e.g., reproduction.

The central melanocortin system in the hypothalamus integrates peripheral signals and regulates peripheral organ functions. Arcuate nucleus pro-opiomelanocortin (POMC)-expressing neurons and neuropeptide Y (NPY) and agouti-related peptide (AgRP) co-expressing neurons interact with melanocortin 4 receptor (MC4R)-expressing neurons in the paraventricular nucleus. POMC neurons stimulate MC4R and induce reduced food intake and increased energy expenditure (anorexigenic effect), while NPY–AgRP neurons are orexigenic, antagonizing POMC action and inducing increased food intake and reduced energy expenditure.

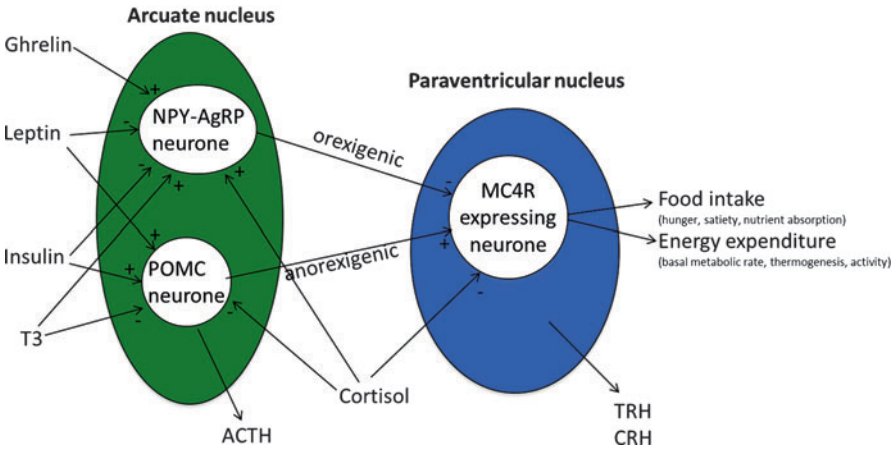

Fig. 5 Schematic overview of hormonal regulation of energy homeostasis

In POMC knockout mice and patients with POMC gene mutations, early-onset obesity is observed (Krude 1998; Yaswen et al. 1999). In contrast NPY and AgRP mutations have no significant effect on food intake or body weight (Qian et al. 2002).

The POMC gene protein precursor generates a number of bioactive peptides (ACTH, α-, β-, and γ-melanocyte-stimulating hormone (MSH), β-endorphin) through posttranslational modifications. Alpha MSH mediates its anorexigenic and AgRP its orexigenic effects through binding and activation of MCRs. The MC3R is expressed in the POMC neurons of the arcuate nucleus, and MC4R are expressed in several regions of the central nervous system (CNS) including the hypothalamic paraventricular nucleus. MC3R and MC4R mice mutations are associated with reduced energy expenditure and MC4R mutations also with hyperphagia. Human MC4R mutations have been reported in nonsyndromic obesity (Vaisse et al. 1998).

The melanocortin system is in turn influenced by many peripheral signals including leptin, ghrelin, insulin, glucocorticoids, and thyroid hormones. These hormones feed information into the melanocortin system regarding the metabolic status of the organism (Fig. 5).

Leptin is anorexigenic and produced by white adipose tissue in amounts proportional to the body fat mass. While leptin has several receptors, only the long form with extracellular and cytoplasmic domains mediates the effect of leptin. Leptin or leptin receptor deficiency is associated with a morbid obese phenotype with hyperphagia, hyperglycemia, hyperlipidemia, and reduced energy expenditure (Montague et al. 1997; Clément et al. 1998). In mice neuron-specific Ob-R deficiency was associated with obesity, while hepatocyte-specific deficiency was not, showing that the direct effect of leptin on the CNS is key to exerting its metabolic effects. Leptin has been shown to activate POMC neurons and suppress activation of NPY–AgRP neurons.

Insulin, secreted from pancreatic β islet cells, stimulates glucose uptake in peripheral organs promoting weight gain. However, in the CNS, insulin receptors

are widely expressed, and insulin's actions are anorexigenic. Brain-specific insulin receptor-deficient mice have a phenotype of obesity with hyperphagia (Brüning et al. 2000). Studies in L1 mice (reduced insulin receptor in the arcuate nucleus) suggest that insulin receptor activation in POMC neurons positively regulates hepatic glucose production and energy expenditure, while insulin signaling in AgRP neurons has the opposite effect. Insulin and leptin appear to have similar effects on glucose homeostasis but opposing effects on body weight (Williams et al. 2010).

Ghrelin is secreted from endocrine stomach cells when the stomach is empty. It exerts its orexigenic effects through activation of the growth hormone secretagogue receptor (GHSR). GHSR is strongly expressed in the hypothalamus, predominantly in the NPY–AgRP neurons of the arcuate nucleus, ghrelin's main site of action in the CNS. Ghrelin's inhibition of POMC action is probably mediated through the activation of NPY–AgRp neurons. Indeed its effect is abolished in NPY–AgRP double knockout mice (Chen et al.). Ghrelin also increases enzymatic degradation of α-MSH to further enhance its orexigenic effects (Kwon Jeong et al. 2013). Ghrelin resistance develops in obese overfed mice but not in ob/ob mice suggesting leptin plays a role in this resistance. CNS administration of leptin to ob/ob mice induced ghrelin resistance confirming this hypothesis (Wang et al. 2013).

Thyroid hormones affect both food intake and energy expenditure. Hyperthyroidism induces hyperphagia by T_3 stimulation of NPY and inhibition of POMC neurons in the arcuate nucleus (Ishii et al. 2003). Starvation leads to increased T_4 to T_3 conversion in the hypothalamus. T_3 regulates uncoupling protein 2 activity which mediates ghrelin action on the NPY–AgRp neurons to increase feeding behavior (Vella et al. 2011).

Glucocorticoid excess in Cushing's syndrome is associated with rapid weight gain, hypertension, hyperglycemia, and insulin resistance, whereas hypocortisolism in Addison's disease or after adrenalectomy is associated with weight loss, reduced appetite, and hypoglycemia. ACTH produced by POMC cells stimulates adrenal glucocorticoid production. However POMC also has direct central effects (Smart et al. 2006). In adrenalectomized mice, there are changes in the synaptic organization of arcuate POMC neurons and enhanced central effects of leptin.

There are many additional influences on appetite – glucose, fatty acid, and amino acids also function as signal molecules of peripheral energy homeostasis. These components have differential effects by altering the activity levels of different components of the system.

Glucose is the primary energy source of the brain, and hypothalamic glucose-sensing neurons are present in several hypothalamic nuclei, suggesting that nutrient status can influence many other systems (Routh et al. 2012). Brain glucose levels are lower than blood glucose levels, and there are distinct diffusion barriers (e.g., circumventricular organs) allowing movement of glucose from the periphery to the CNS and also between brain regions. Controlled by glial cells capable of glucose sensing, this diffusion is regionally differentially regulated and influenced by nutritional status.

Glucose-excited neurons have been found among GnRH neurons of the anterior hypothalamus, the preautonomic neurons in the paraventricular hypothalamus, and the melanin-concentrating hormone neurons in the lateral hypothalamus. Glucose sensing through activation of the KATP channel as in the beta pancreatic cell has been described but not for all regions.

Glucose-inhibited neurons are also found in many hypothalamic regions, e.g., ventromedial nucleus, arcuate nucleus, paraventricular nucleus, dorsolateral nucleus, and the lateral hypothalamus. While nitric oxide signaling is responsible for glucose sensing in some glucose-inhibited neurons, the exact mechanism is not understood in many regions, including the arcuate NPY–AgRP neurons.

There is a sensitive mechanism for providing the brain with a constant supply of glucose, and glucose-sensing neurons detect hypoglycemia and play a role in the initiation of the counter-regulatory response to hypoglycemia. During fasting, reduced leptin and ghrelin levels lead directly and indirectly to activation of NPY–AgRP and orexigenic glucose inhibitory neurons. This is associated with increased food intake, gluconeogenesis, and ketogenesis in order to maintain a supply of energy to the brain. Additionally, glucose-sensing neurons may divert energy away from competing systems or allow such functions, e.g., reproduction, only when glucose levels are adequate.

The hypothalamus is the main integrator of inputs and responses in the control of appetite and energy expenditure. It is a complex process involving the input of several endocrine, chemical, and neurological signals, coordinated predominantly by the melanocortin system into an endocrine and neurological response to maintain body weight. However there is much research still needed to understand the exact details of the control of energy homeostasis.

The homeostatic control of energy intake and expenditure is tightly controlled by the hypothalamus. Signals from the "hedonic" corticolimbic pathways are also integrated but can override the homeostatic system increasing desire to consume palatable foods despite satiety. Environmental changes with increased availability of energy-rich foods, increased portion size, and reduced physical activity due to more sedentary jobs further facilitate the development of obesity through "hedonic" overriding the homeostatic controls (Lenard and Berthoud 2008).

Water and Electrolyte Balance

The balance of water and electrolyte intake must be carefully balanced with water and electrolyte loss in order to maintain a stable total body fluid volume and osmolality. Osmoreceptors in the anterior hypothalamus and circumventricular organs detect changes in plasma osmolality. Projections from these regions then activate both stimulatory and inhibitory neurons connecting with the supraoptic and paraventricular nuclei. So, if osmolality increases, then AVP, which is produced in the supraoptic nucleus and magnocellular neurons in the paraventricular nucleus, is released from the posterior pituitary gland into the circulation. In the nephron, AVP promotes water reabsorption to correct the increased osmolality.

Non-osmotic stimuli from baroreceptors influence the same hypothalamic nuclei via the medulla and nucleus tractus solitarius. In addition to AVP released from the posterior pituitary, there are AVP-secreting neurons stretching from the PVN and SCN to the brainstem and spinal cord where they influence the sympathetic nervous system.

Thirst regulates water intake and involves neural and hormonal input. Activation of the hypothalamic thirst center occurs when the mouth is dry and when osmolality increases. Decreased blood volume results in release of renin from the kidney and subsequent activation of the angiotensin II which directly stimulates the hypothalamic thirst center too.

Renin-stimulated aldosterone production results in increased nephron reabsorption of sodium with secretion of potassium. In addition to AVP action, this makes sure that the volume and osmolality are restored. Activation of the sympathetic nervous system also causes vasoconstriction of the afferent arteriole and reduced nephron perfusion resulting in a fall in urine output.

Blood Pressure and Heart Rate

Blood pressure homeostasis primarily involves the interplay between sympathetic and parasympathetic autonomic nervous systems but is also influenced by the neuroendocrine factors (e.g., CRF, GH, angiotensin II, AVP). Changes in hypothalamic nuclei output can result in a rise or reduction of blood pressure by altering sympathetic nervous activity. These nuclei are closely interconnected and receive afferent input from the midbrain, medulla, and chemo- and baroreceptors in the heart, aorta, carotids, and kidneys with efferent outputs to spinal sympathetic preganglionic neurons which control the sympathetic ganglia and adrenal medulla.

The hypothalamic regions particularly involved in blood pressure homeostasis lie along the third ventricle and also include the circumventricular organs (SFO and OVLT) which allow the input of peripheral chemical signals, including sodium ion concentration. The paraventricular, arcuate, medial preoptic, and supraoptic are primarily involved, but there are many projections to, and input from, other hypothalamic nuclei including the SCN which influences the circadian rhythm of heart rate and blood pressure related to sleep. The dorsomedial nucleus has direct and indirect connections to the autonomic nervous system.

The arterial baroreceptors autonomic reflexes respond rapidly to changes in blood pressure and alter heart rate through changed sympathetic tone. Low-pressure baroreceptors in the large veins and right atrium influence blood volume through autonomic stimulation of the neuroendocrine system. A drop in blood pressure will also stimulate retention of salt and water and increase thirst. A wide range of neurotransmitters and hormones play a role in this process including GABA, natriuretic peptides, angiotensin II, AVP, nitric oxide, serotonin, NPY,

opioids, bradykinins, thyrotropin-releasing hormone (TRH), and corticotropin-releasing hormone (CRH). Their individual roles and complex peripheral and central interactions are out with the scope of the chapter. A few examples are discussed below.

The angiotensin pathways from the lamina terminalis to the PVN, supraoptic nucleus, and rostral ventrolateral medulla are activated by circulating angiotensin II, CSF sodium ion concentration, and possibly aldosterone. Activation leads to increased sympathetic output largely by reducing GABA and raising glutamate release in fast synaptic transmission pathways.

High dietary salt is detected in the circumventricular organs of the brain when CSF sodium ion concentration rises. This in turn promotes endogenous ouabain release from the adrenal gland which leads to a sustained increase in angiotensin II. The latter is a much slower pathway, but these two neuromodulatory paths allow the CNS to shift gears rapidly and cause sustained sympathetic hyperactivity in an efficient manner (Blaustein et al. 2012; Hamlyn et al. 2014).

Temperature

Body temperature is tightly regulated as excursions from this range result in detrimental changes to cellular function, e.g., reduced enzyme efficiency and altered membrane diffusion, which in turn have significant impact on energy availability. While recovery from low temperatures in hibernating mammals is usual, smaller increases in brain temperature are incompatible with life. Small increases in temperature can occur in the febrile response to endogenous pyrogens released during infections. This is supposed to improve host defense and reduce pathogen viability. Thus temperature homeostasis is essential for survival and plays a role in defense against pathogens.

Information on temperature is provided by cutaneous thermal receptors through sensory nerves to the spinal dorsal horn neurons and to the lateral parabrachial nucleus in the pons. Body core structures including the brain, spinal cord, and abdomen transmit temperature information through the splanchnic and vagal nerve afferents. At the level of the hypothalamus, this information is integrated in the preoptic and anterior areas. The preoptic area has been shown to respond to both increases and decreases in temperature and integrates these sensory inputs to generate signals aimed at restoring normal body temperature. Signals from the dorsomedial hypothalamus to the rostral ventromedial medulla complete the pathway to the sympathetic nervous system. The effectors in thermoregulation under sympathetic nerve control include cutaneous circulation (vasoconstriction or vasodilation); thermogenesis from brown adipose tissue, skeletal muscle (shivering), or the heart (increased heart rate); and evaporative loss (e.g., sweating, panting) (Morrison and Nakamura 2011).

Pituitary

The anterior pituitary gland plays a critical role in homeostasis by integrating complex peripheral signals from the hypothalamus and other peripheral organs, intrapituitary signals, and external stimuli to regulate release of anterior pituitary hormones into the peripheral circulation.

The classical feedback mechanisms of the hypothalamic pituitary axis and its target organs were described many years ago. In more recent years, our understanding of the role of intrapituitary regulators of pituitary cell growth, apoptosis, hormone secretion, and hormone release has expanded rapidly, to give finer detail of the complex mechanisms underlying the release of anterior pituitary hormones.

Embryology

The pituitary gland is similar in all vertebrates and has been studied extensively in the mouse (Fig. 2) (Kelberman and Dattani 2007; Alatzoglou et al. 2009). The anterior and intermediate lobes arise from oral ectoderm, while the posterior pituitary is derived from neural ectoderm.

During the third week of gestation, an outpocketing of oral ectoderm, the hypophysial diverticulum, appears in front of the buccopharyngeal membrane, preceded by localized thickening of the ectoderm (pituitary placode). This placode is located ventrally in the midline of the anterior neural ridge and in the continuity with the future hypothalamo–infundibular region, which is located posteriorly in the rostral part of the neural plate (Alatzoglou et al. 2009). The hypophysial diverticulum forms Rathke's pouch which, in time, will become the anterior lobe of the pituitary. During week 5 of gestation, the neuroectoderm from the diencephalon extends to form the infundibulum (neurohypophysial diverticulum) which grows downward developing into the posterior lobe. The hypophysial diverticulum and the infundibulum grow toward one another, and by the second month, the hypophysial diverticulum is isolated from its ectodermal origin in the oral cavity and lies close to the infundibulum.

Hesx1 is the first transcription factor to be expressed in the developing pituitary, and normal function is required for the development of Rathke's pouch and other midline structures. Abnormalities in this gene are reported in children with pituitary hypoplasia, ectopic posterior pituitaries, optic nerve hypoplasia, and loss of pituitary function (Kelberman et al. 2009). These features may present together as septo-optic dysplasia, in which the corpus callosum is also affected.

The expression of Pitx1 and Pitx2 is evident in the early stages of pituitary embryogenesis and persists during pituitary cell differentiation. Mutations of the Pitx2 gene are associated with Axenfeld–Rieger syndrome. Affected patients have abnormalities of the anterior segment of the eye, dental hypoplasia, a protuberant umbilicus, and abnormalities of the brain. Pituitary involvement is suggested by the presence of a small sella turcica in some patients.

The SOXB1 group of transcription factors, Sox2 and Sox3, are expressed throughout the developing brain and in high levels in the infundibulum and developing hypothalamus. Mutations of the SOX2 gene are associated with anophthalmia, optic nerve hypoplasia, and pituitary hypoplasia and with gonadotropin deficiency and genital abnormalities in boys and growth hormone deficiency. Abnormalities of forebrain structures, including hypoplasia of the corpus callosum, hypothalamic hamartoma, and hippocampal malformations, are also reported.

The SOX3 gene is located on the X chromosome, and the phenotype of SOX3 mutations is inherited in an X-linked manner. Affected boys have learning difficulties and variable pituitary failure, in which GH deficiency is constant and other pituitary hormones may be involved. Imaging studies demonstrate pituitary and infundibular hypoplasia, ectopic posterior pituitary, and hypoplasia of the corpus callosum.

Lhx3 and Lhx4 are essential for normal pituitary development, the role of Lhx3 being primarily in the regulation of cell differentiation and maturation and Lhx4, cell proliferation. Abnormalities of the LHX3 and LHX4 genes have been associated with hypopituitarism, pituitary hypoplasia, and abnormalities of the spine (Kelberman et al. 2009).

The differentiation and proliferation of pituitary stem cells into five distinct hormone-producing cell types are regulated by a spatial and temporal distribution of key transcription factors and signaling pathways. The wingless (WNT) and the sonic hedgehog pathways are important for the regulation of cell proliferation, while bone morphogenetic protein (BMP) and fibroblast growth factor (Fgf) are important in regulating cell proliferation and migration.

Within the ventral ectoderm of Rathke's pouch, a ventral-to-dorsal gradient of BMP 2 and, in the opposite direction, a gradient of Fgf 8 are established. In this way, overlapping sets of transcription factors are synthesized in different populations of cells, dependent upon their location along the dorsal–ventral axis. A simplified cartoon illustrating key transcription factors in the regulation of pituitary cell differentiation is given in Fig. 6.

Mutations in pituitary transcription factors have been identified in patients with multiple pituitary hormone deficiencies (MPHD), less commonly, an isolated pituitary hormone deficiency which may be associated with anatomical changes. Pituitary stalk interruption (Fig. 7) has been described in patients with mutations of the HESX1, LHX4, and SOX3 genes (Yang et al. 2013), while the more severe phenotype of septo-optic dysplasia (Fig. 8) has been described in patients with mutations of HESX1.

The clinical phenotype of patients with mutations of pituitary transcription factors is summarized in Table 2.

Anatomy

The pituitary gland, a small pea-sized organ weighing approximately 0.5 g, rests in the sella turcica, a saddle-shaped depression in the body of sphenoid bone. The

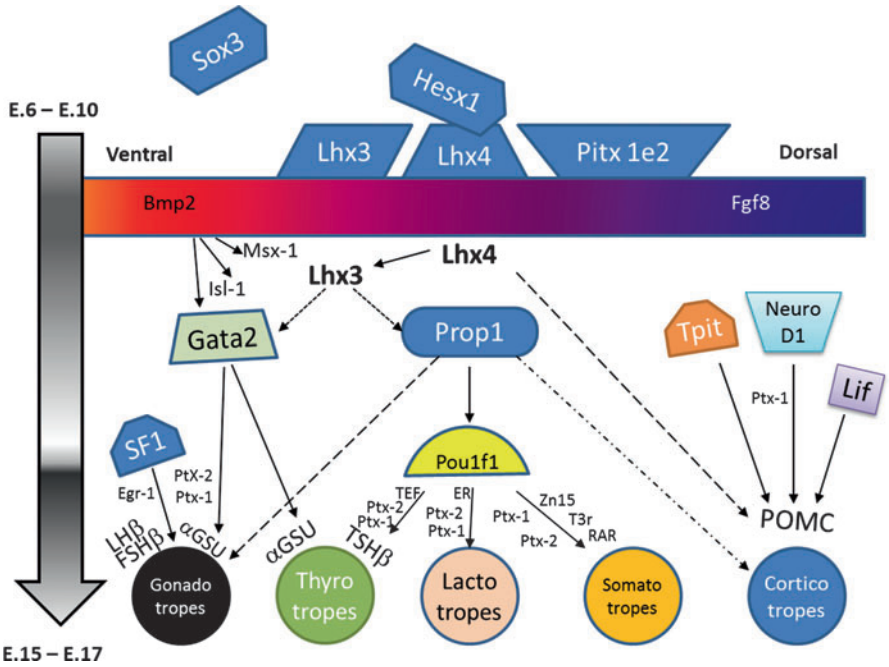

Fig. 6 Activation of pituitary transcription factors. In response to the BMP2–FGF8 ventral–dorsal gradient. *Solid arrows* indicate the activation of expression, *dotted arrows* indicate an unknown role in the activation of expression, *dashed arrows* indicate an undefined role, and *dash–dot arrows* indicate an action of an important factor in the maintenance of long-term cell function. *BMP2* bone morphogenetic protein 2, *EGR1* early growth response 1, *ER* estrogen receptor, *FGF8* fibroblast growth factor 8, *GATA2* GATA-binding protein 2, *HESX1* HESX homeobox 1, *ISL1* ISL LIM homeobox 1, *LHX3* LIM homeobox 3, *LHX4* LIM homeobox 4, *LIF* leukemia inhibitory factor, *MSX1* MSH homeobox 1, *NeuroD1* neurogenic differentiation 1, *PIT1* POU class 1 homeobox 1, *PITX1* paired-like homeodomain 1, *PITX2* paired-like homeodomain 2, *POMC* pro-opiomelanocortin, *PROP1* prophet of Pit-1, *RAR* retinoic acid receptor, *SF1* steroidogenic factor 10, *T3r* thyroid hormone nuclear receptor, *TEF* thyrotroph embryonic factor, *TPIT* T-box19, *Zn15* zinc finger protein Zn15 (Adapted from de Moraes et al (2012)

pituitary lies between optic chiasm, separated by the diaphragma sellae from above and the sphenoid air cells which located below it. The cavernous sinus and its contents are to be found on each side of the pituitary. The pituitary stalk, which connects the median eminence of the hypothalamus to the pituitary gland, passes through an opening in the dura surrounding the brain.

The pituitary comprises of anterior (adenohypophysis) and posterior (neurohypophysis) lobes. The anterior lobe is subdivided into the pars anterior (pars distalis) and the pars intermedia, which may be separated by a cleft that is a remnant of an embryonic pouch. The pars tuberalis is a projection from the pars anterior that extends upward and forward along the anterior and lateral surfaces of the pituitary.

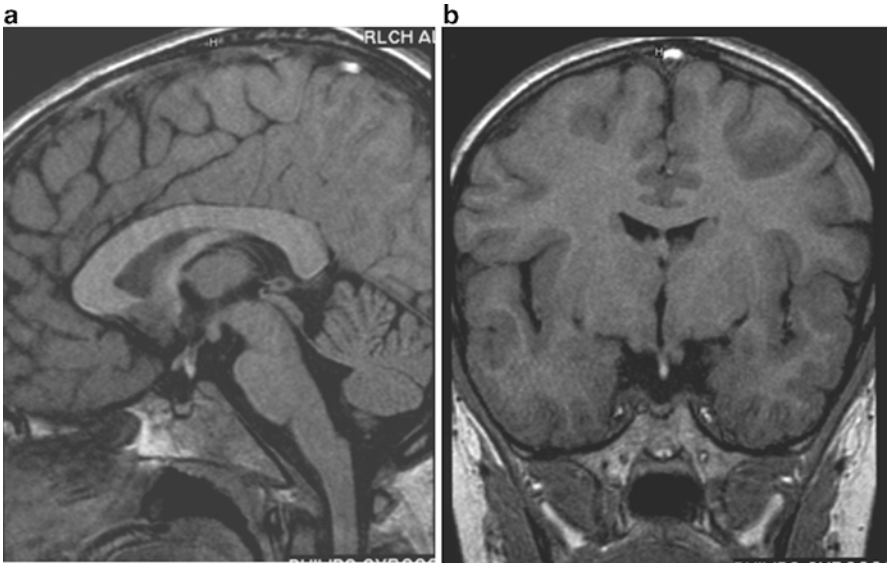

Fig. 7 Pituitary stalk interruption syndrome (PSIS). (**a**) Sagittal and (**b**) coronal T1-weighted MR images show that the posterior lobe of the pituitary is in an ectopic location, the pituitary stalk is absent, and the anterior lobe of the pituitary is hypoplastic (Images courtesy of Dr Laurence Abernethy, Alder Hey Children's NHS Foundation Trust, Liverpool)

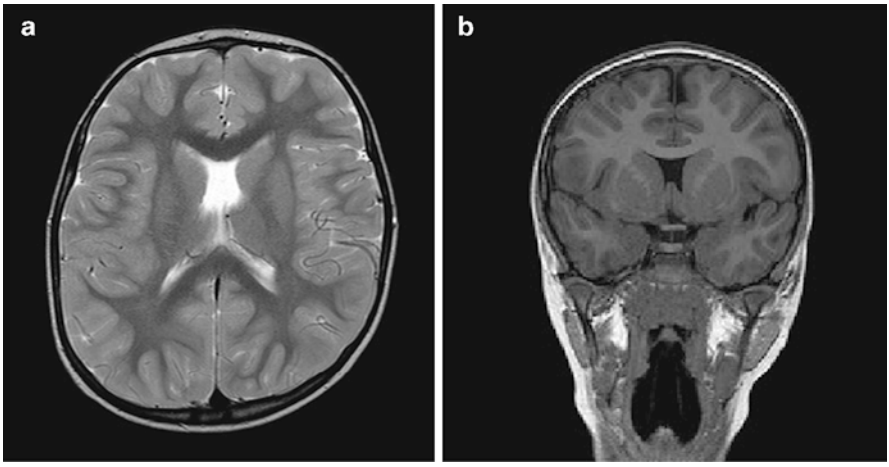

Fig. 8 Septo-optic dysplasia. (**a**) Axial T2-weighted MRI shows the absence of the interventricular septum and an abnormal configuration of the frontal horns of the lateral ventricles. (**b**) Coronal T1-weighted MRI shows absence of the interventricular septum and hypoplasia of the optic chiasm and anterior pituitary (Images courtesy of Dr Laurence Abernethy, Alder Hey Children's NHS Foundation Trust, Liverpool)

Table 2 Mutations in pituitary transcription factors and associated phenotypes

Gene	Key clinical features	Endocrine phenotype
HESX1	Variable, no obvious phenotype–genotype correlation	IGHD or combined with ACTH, TSH, LH, and FSH deficiency
OTX2	Anophthalmia or microphthalmia	CPHD
SOX2	Esophageal atresia, genital abnormalities in males, bilateral anophthalmia, or severe microphthalmia, sensorineural hearing loss, hypothalamic hamartoma	Hypogonadotropic hypogonadism
SOX3	Short male with varying degree of mental retardation, facial anomalies in some patients	IGHD or combined with ACTH, TSH, LH, and FSH deficiency
GLI2	Single nares, single central incisor, postaxial polydactyly, and partial agenesis of the corpus callosum	GH, TSH, PRL, LH, and FSH
LHX3	Short, rigid cervical spine with or without sensorineural deafness	Sparing ACTH in majority, however it has been reported in c.80–32_775 _ 454 del3,088 and p.K50X mutations. Mainly GH, TSH, and gonadotropin deficiency
LHX4	Variable, persistent craniopharyngeal canal and abnormal cerebellar tonsils	IGHD or combined with TSH, ACTH
PROP1	Enlarged pituitary with later involution	GH, TSH, PRL, and gonadotropin deficiency. Evolving ACTH deficiency
POU1F1 (PIT1)	Clinical features of central hypothyroidism at early age	GH, PRL, TSH deficiency
PITX2	Malformation of the anterior segment of the eye, dental hypoplasia, and a protuberant umbilicus	GH deficiency

During childhood the upper border of the anterior pituitary is flat on magnetic resonance imaging, and the height of the pituitary is <6 mm. During normal puberty, physiological pituitary hypertrophy is observed, and the upper border may appear convex. These changes are more evident in girls than in boys, with pituitary height reaching 10 mm in girls (Elster et al. 1990) (Figs. 8 and 9).

Blood Supply of the Pituitary

The principal arterial supply of the pituitary gland is from the superior and inferior hypophysial arteries. The superior hypophysial arteries originate from the internal carotid artery shortly after it enters the cranial cavity and then promptly divide into posterior and anterior branches, each of which anastomoses with the corresponding branch from the opposite side to form an arterial ring around the upper pituitary stalk. Trabecular or loral arteries, from the anterior branches, descend along the upper surface of the anterior lobe toward the pituitary stalk and terminate in long stalk arteries. Short stalk arteries, from both the posterior and anterior branches of the

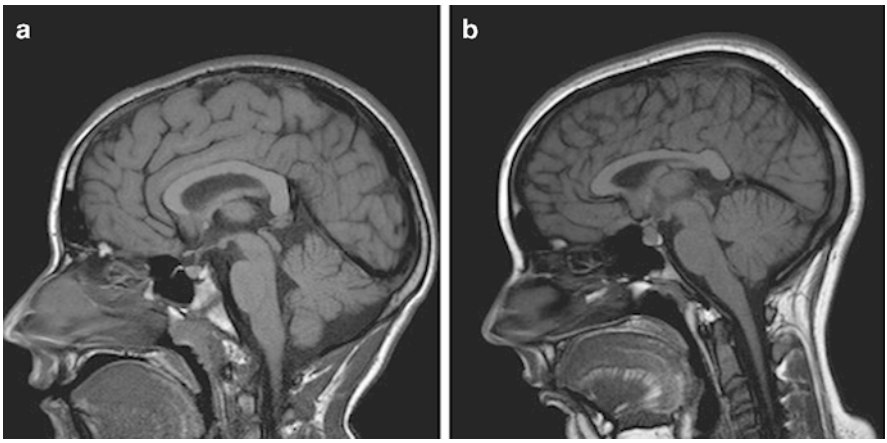

Fig. 9 MRI of pituitary. Sagittal T1-weighted images. (**a**) Normal prepubertal girl. The upper surface of the anterior lobe of the pituitary is flat. (**b**) Normal pubertal girl. The upper surface of the anterior lobe of the pituitary is convex and almost reaches the optic chiasm (Images courtesy of Dr Laurence Abernethy, Alder Hey Children's NHS Foundation Trust, Liverpool)

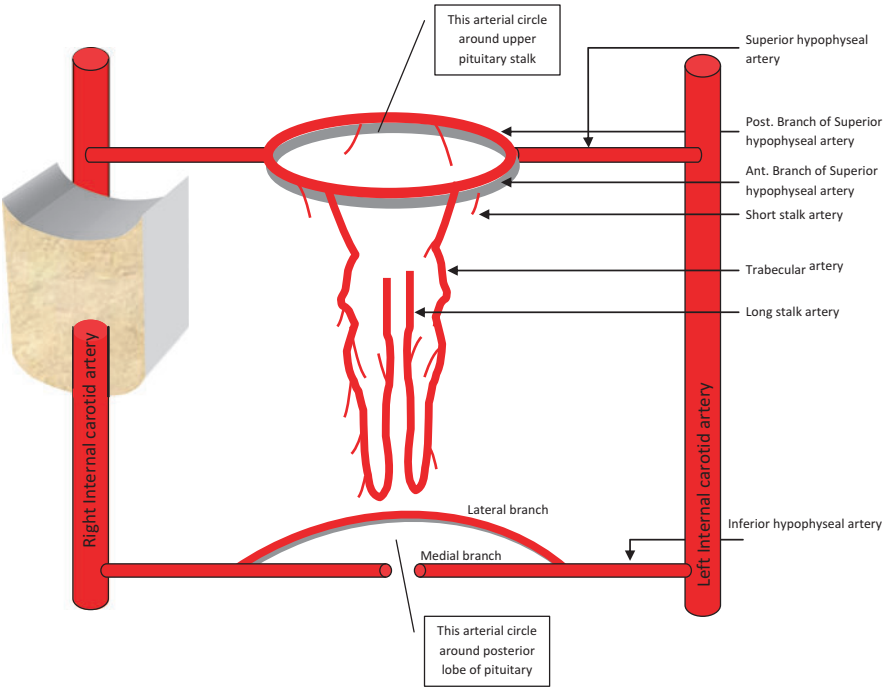

Fig. 10 Blood supply of the pituitary gland

superior hypophysial arteries, penetrate the superior aspect of the pituitary stalk to run superiorly or inferiorly.

The inferior hypophysial arteries originate from the meningohypophysial trunks within the cavernous sinuses. They pass along the inferolateral portions of the gland and bifurcate into medial and lateral branches that anastomose with their opposite counterparts to form an arterial circle about the posterior lobe. Branches of the inferior hypophysial arteries supply the posterior lobe and lower portion of the stalk, with only a minor contribution to the periphery of the anterior lobe (Fig. 10).

Gomitoli, "balls of thread," are unique vascular complexes formed from arterial branches of the pituitary stalk and infundibulum. Blood flow through these vessels is regulated by thick smooth muscle sphincters located in short specialized arterioles at the transition from central arteries to capillaries. The periarteriolar capillaries drain into an extensive pampiniform network, the portal system, which envelopes the stalk. The anterior pituitary receives the majority of its blood supply not from arteries but from the portal system which forms a vital link between the hypothalamus and the pituitary gland.

Venous outflow of the pituitary is via collecting vessels that drain into the subhypophysial sinus, cavernous sinus, and superior circular sinus.

Folliculostellate Cells

Folliculostellate (FS) cells are star-shaped, non-endocrine cells that comprise approximately 5 % of the total pituitary cell mass. They form follicles within the pituitary that increase in number and size during aging. FS cells have phagocytic properties, removing cell debris from pituitary cell apoptosis, and a supportive role for other pituitary cells, surrounding them with long cytoplasmic processes.

FS cells have an additional, critical role in coordinating pituitary hormone release, communicating directly with each other through desmosomes and gap junctions and with endocrine cells by gap junctions. They function within a complex network that coordinates FS cell and endocrine cell function and activity over long distances. The rapid communication of secondary messengers through this network is dependent on the density and size of intercellular gap junctions, which may be influenced by hormones, such as glucocorticoids (GC) and sex hormones, and other factors such as leptin, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β3.

Anterior pituitary cells also communicate in a paracrine manner through soluble factors, including growth factors, cytokines, hormones, and peptides, some of which may be produced primarily or exclusively by FS cells. One important example is vascular endothelial growth factor (VEGF-A), which was first identified in the pituitary FS cells in 1989 and has since been recognized as a key regulator of blood vessel and lymph angiogenesis (Ferrara 1989; Gospodarowicz et al. 1989). Two VEGF receptors (VEGFR-1 and VEGFR-2) are expressed in the pituitary, VEGFR-1 located in endocrine cells and VEGFR-2 primarily in endothelial cells (Onofri et al. 2006). VEGF-A may play an important role in the development of the

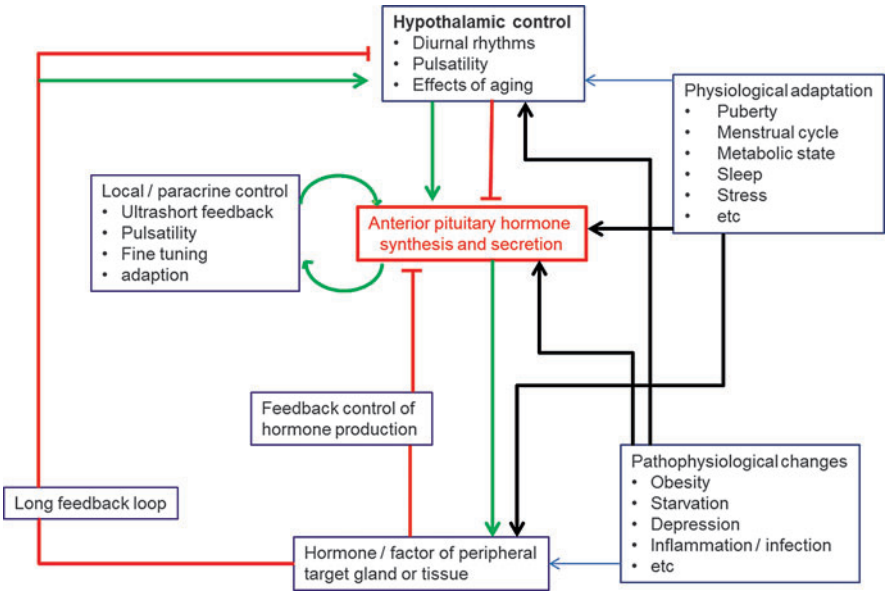

Fig. 11 Principle regulators of anterior pituitary hormone synthesis and release. *Green lines* indicate factors that stimulate hormone secretion, *red lines* factors that inhibit hormone secretion, and *black lines* factors that may either stimulate of inhibit secretion (From Perez-Castro et al. 2012)

intrapituitary vascular network during embryogenesis, maintenance in postnatal life, and in enabling pituitary plasticity during adult life, for example, by promoting angiogenesis to support the increased lactotroph cell mass during pregnancy and lactation (Turner et al. 2000). VEGF also increases vascular permeability by altering fenestration of endothelial cells. In this way, FS cells may regulate the activity of pituitary gland messengers, by increasing the exchange of soluble factors between the bloodstream and endocrine cells.

Anterior Pituitary Hormones

There are six principle hormones synthesized and secreted by specialized cells of the anterior pituitary: prolactin, thyrotrophin (thyroid-stimulating hormone, TSH), adrenocorticotropin (ACTH), growth hormone (GH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Each hormone is regulated by multiple sources of input acting at the level of the pituitary and hypothalamus.

The pituitary hormones regulate their own synthesis and secretion, acting at the level of the pituitary and through log loop feedback, at the level of the pituitary. Within the pituitary, there are multiple ultrashort loop feedback pathways that are thought to be important in fine-tuning pituitary hormone release. The activity of the pituitary is also subject to multiple peripheral influences, including nutritional status,

temperature, illness, mood, sleep, etc. The general principles of anterior pituitary hormone regulation are illustrated in Fig. 11.

Lactotrophs and Prolactin

Prolactin is secreted from lactotrophs, cells derived from the Pit-1-dependent lineage of pituitary cells, of which there are two types: large polyhedral cells, containing large secretory granules that are found throughout the pituitary, and smaller elongated cells, containing smaller secretory granules that are located in the lateral wings. Together they comprise approximately 15–20 % of pituitary functional cell mass. Both cell types hypertrophy during pregnancy and lactation when the pituitary may more than double in size.

Animal studies suggest that lactotrophs are derived from postmitotic somatotrophs (Burrows et al. 1996), and occasional cells (mammosomatotrophs) secrete both prolactin and growth hormone. Lactotrophs have the highest mitotic and apoptotic rate of all pituitary cells.

Prolactin

The prolactin gene is 10 kb in size, comprising five exons and four introns encoding a 199 amino acid polypeptide hormone with three intramolecular disulfide bonds. There are a number of prolactin variants which are the product of alternative splicing of the primary transcript, proteolytic cleavage, and other posttranslational modifications of the amino acid chain (Sinha 1995). The most abundant form of prolactin, monomeric (23 kDa), is also the most potent variant. Other variants include dimeric (48–56 KDa) and polymeric (>100 KDa) prolactin. An abundance of polymeric prolactin ("macroprolactinemia") is rarely associated with the clinical manifestations of prolactin excess.

Prolactin is secreted in a pulsatile manner, with 4–14 pulses in 24 h, each lasts approximately an hour. There is a diurnal pattern of hormone release: Peaks of greatest amplitude are secreted overnight, with a temporal relationship with REM sleep, and those of lowest amplitude are secreted during the morning (Sassin et al. 1972). Prolactin pulses are more frequent and of higher amplitude in females than in males and decline with age in both genders.

Regulation of Prolactin Secretion

Prolactin secretion is stimulated by thyroid hormone-releasing hormone, which preferentially increases the secretion of monomeric prolactin. Other factors that stimulate prolactin secretion include fibroblast and epidermal growth factors, vasoactive intestinal polypeptide (VIP), and hypothalamic prolactin-releasing hormone, which binds to a specific receptor.

The dominant action of estrogen on lactotrophs is to increase prolactin gene transcription and secretion; however it is also recognized that estrogen also promotes both lactotroph proliferation and apoptosis. There is some evidence that

these contrary actions of estrogen are mediated through different receptors, apoptosis being medicated by membrane bound receptors and cell proliferation by intracellular estrogen receptors (Zárate et al. 2009). Estrogen-induced changes in lactotroph cell growth are mediated through growth factors including TGF-α, TGF-β, epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), IGF-I, IGF-II, interleukin-6, and others. Prolactin levels also increase in response to opiates.

Prolactin secretion is inhibited, primarily, by dopamine synthesized and secreted from the tuberoinfundibular cells and the hypothalamic tuberohypophysial dopaminergic system. It reaches the lactotrophs of the pituitary via the hypothalamic pituitary portal circulation, to bind on specific type 2 dopamine receptors on lactotroph cell membranes. Disruption of the hypothalamic pituitary portal circulation is often associated with an increase in peripheral prolactin concentrations.

Prolactin increases dopamine synthesis by promoting tyrosine hydroxylase activity, thus regulating its own secretion through a classical negative feedback loop. Other inhibitors of prolactin release include endothelin 1 and TGT-β1, which act in a paracrine manner, and calcitonin which maybe of hypothalamic origin.

Prolactin Actions

The prolactin receptor, a member of the cytokine receptor superfamily, is expressed in a wide range of tissues, including the breast, pituitary, liver, adrenal cortex, kidney, prostate, ovary, testes, intestine, epidermis, pancreatic islet cells, myocardium, lung, brain, and lymphocytes. Collectively, human and animal studies have identified more than 300 prolactin actions (Freeman et al. 2000), leading some authors to speculate that prolactin is a prohormone that exerts these diverse actions through a number of prolactin derivatives.

The most important role of prolactin in humans is lactation (milk production), and women with mutations of the prolactin gene do not lactate (Falk 1992). Prolactin is not essential for human breast development, which requires growth hormone, epidermal growth factor, estrogen, parathyroid hormone-related protein, and progesterone.

During the third trimester of pregnancy, prolactin acts in a synergistic manner with estrogen, progesterone, and other breast-derived growth factors, to stimulate the production of colostrum. Following birth, suckling stimulates prolactin release which is essential for the maintenance of lactation, and in the absence of suckling, prolactin levels return to nonpregnant levels approximately 7 days. During lactation, prolactin inhibits GnRH and gonadotropin secretion and therefore acts as a natural contraceptive.

Thyrotrophs and Thyrotrophin

Thyrotrophin, or thyroid-stimulating hormone (TSH), is synthesized and secreted by thyrotrophs, irregularly shaped cells with flattened nuclei that are located in the

anterior medial aspects of the pituitary. Thyrotrophs are smaller than the other pituitary cells and comprise approximately 5 % of pituitary cell mass.

TSH Structure

TSH, one of four glycoprotein hormones which comprise an α-subunit, covalently bound to a unique β-subunit which confers biological specificity. Other glycoprotein hormones include TSH, LH, FSH, and placental chorionic gonadotropin. The gene encoding the common α-subunit is located on 6p14.3. The gene encoding the TSH β-subunit is located on 1p13.2 and comprises three exons, of which the first is noncoding. The TSH β-subunit is 112 amino acid long.

Thyrostimulin, a heterodimer of two more recently identified glycoprotein subunits, also stimulates the TSH receptor (Nakabayashi et al. 2002). The role of thyrostimulin is a subject of ongoing research, but it appears to have a number of important peripheral actions (Sun et al. 2010; Bassett et al. 2015).

Regulation of TSH Secretion

Like other pituitary hormones, secretion of TSH is pulsatile and shows a diurnal pattern of secretion, with concentrations of TSH being highest in the late evening.

TSH secretion is stimulated by hypothalamic TRH, secreted from the paraventricular nuclei as pro-TRH which contains five copies of the TRH molecule. Peptidase action, followed by cyclization of the glutamine residue to form a pyroglutamyl residue, results in the release of individual TRH molecules which act on G protein-coupled type 1 TRH receptors and induce the inositol phosphate/calcium/protein kinase C signaling pathway to stimulate TSH release.

The TRH neuron has an important role in setting TSH levels in response to external stimuli. In response to cold, adrenergic input increases the set point for TRH inhibition by T_3, allowing thyroid hormone levels to rise, increasing thermogenesis. In response to fasting, stimulation of the pro-opiomelanocortin (POMC) system, which promotes weight loss, and inhibition of the neuropeptide Y/agouti-related peptide system, which promotes weight gain, result in a reduction of TRH expression.

The major inhibitors of TRH and TSH synthesis and secretion are thyroxine (T_4), synthesized in the thyroid gland, and 3,3′,5′-triiodothyronine (T_3), the product of T_4 deiodination. The effects of T_3 are mediated through thyroid hormone receptors (TR), part of the superfamily of nuclear hormone receptors, of which α and β are the major isoforms. TR-α is the principal mediator of T_3 suppression of hypothalamic TRH synthesis and TRH receptor expression. Levels of T_3 are determined by type 2 and type 3 deiodinase, which increase and inactivate T_3, respectively. Type 2 deiodinase is found in the glial cells of the hypothalamus and tanycytes, which line the third ventricle, while type 3 deiodinase is found in the TRH neuron, indicating complex mechanisms of local regulation of TRH secretion.

TSH secretion is regulated within the pituitary by FS cells which express TSH receptors, type 2 deiodinase, and the specific T_3 transporter, monocarboxylate transporter 8. It is proposed that FS cells act in an ultrashort feedback, releasing an inhibitor of TSH secretion, possibly TGF-β2, upon stimulation of FS cell TSH

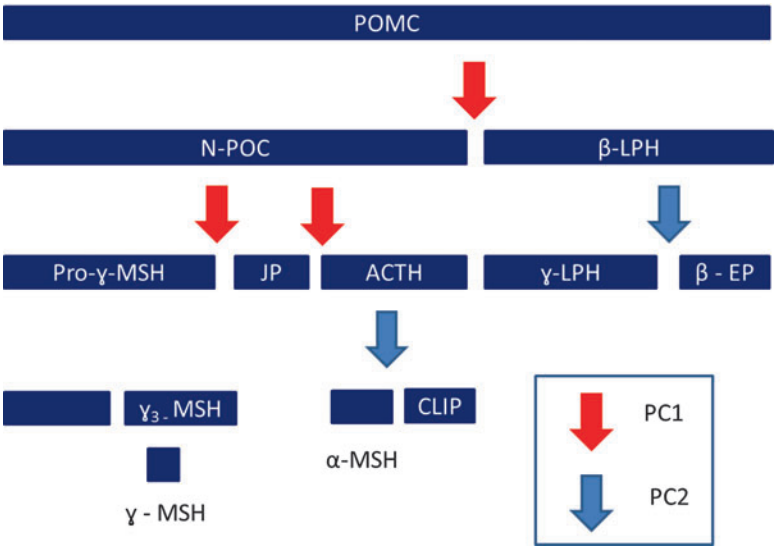

Fig. 12 Processing and cleavage of pro-opiomelanocortin. *ACTH* adrenocorticotropic hormone, *CLIP* corticotropin-like intermediate lobe protein, *EP* endorphin, *JP* joining peptide, *LPH* lipoprotein, *MSH* melanocyte-stimulating hormone, *N-POC* N-terminal POMC fragment (From Clark and Swords 2001)

receptors (Pazos-Mour et al. 2003). Type 3 deiodinase and TR are found in thyrotrophs, again indicating a complex local interplay between promoters and inhibitors of hormones regulating thyroid hormone release.

Transporter proteins play an important role in mediating the actions of T_3 in the brain, of which two, organic anion-transporting polypeptide and MOAT8, are the two most important.

Somatostatin inhibits the nocturnal release of TSH acting at the level of the pituitary and possibly through inhibition of TRH secretion and TRH receptor expression. Dopamine also has the effect of inhibiting the nocturnal rise in TSH secretion. TRH and TSH secretion is also inhibited by glucocorticoids and inflammatory cytokines.

Corticotrophs and Adrenocorticotropic Hormone (ACTH)

Corticotrophs are large, irregular cells with prominent neurosecretory granules located around the median pituitary wedge and posteriorly adjacent to the pars nervosa. They are the first endocrine cells of the pituitary to produce hormones, being active from the eighth week of gestation. They comprise approximately 20 % of functional pituitary cell mass and produce the products of the POMC gene, including adrenocorticotropic hormone (ACTH) and opioid and melanotropic

peptides. These POMC gene products have a high glycoprotein content, making the corticotroph stain strongly positive for periodic acid–Schiff.

The POMC gene is located on the short arm of chromosome2, 2p23, and consists of three exons: The first encodes a leader sequence and the second the signal initiation sequence and N-terminal portion of the POMC peptide, and the third contains most of the sequence for corticotropic, melanotropic, and opioid peptides. Translation of the gene results in a 266 amino acid preprohormone which undergoes extensive modification and processing including removal of the N-terminal sequence, glycosylation of Thr45, N-linkage of Asn65, and serine phosphorylation (Fig. 12). Cleavage of POMC at pairs of basic residues (lys–lys or lys–arg) by prohormone convertase 1 (PC1) releases N-terminal POMC fragment (N-POC) and β-LPH. Further cleavage of N-POC by PC1 releases pro-ɣ-MSH, joining peptide and ACTH, and further cleavage of β-LPH by PC2 results in ɣ-LPH and β-endorphin. ACTH may be further cleaved by PC2 to α-melanocyte-stimulating hormone (α-MSH) and corticotrophin-like intermediate lobe peptide (CLIP).

Products of POMC have a wide range of actions. ACTH binds to the melanocortin receptor type 2 receptor to induce synthesis of adrenal glucocorticoids, androgens, and, to a lesser degree, mineralocorticoids. Stimulation of the melanocortin receptor type 1 on melanocytes by ACTH, β-lipotropin (β-LPH), and ɣ-LPH induces skin pigmentation. The effects of leptin on appetite suppression are mediated by the melanocortin system via α-MSH, acting at the level of the hypothalamus. Deficiency of POMC results in hyperphagia and weight gain in both mice (Yaswen et al. 1999) and humans (Krude et al. 1998), which can be reversed by infusing α-MSH into the ventricles.

α-MSH also has an important role in the inflammatory response, regulating the activity of antigen-presenting cells and T cells and inhibiting macrophage activity and leukocyte migration.

The hypothalamic pituitary adrenal axis plays a central role in the stress response to pain, hemorrhage, hypovolemia, trauma, psychological stress, infection, inflammation, and hypoglycemia. Upregulation of the axis in response to peripheral and central signals of stress, including vasovagal, catecholamine, and cytokine messengers, results in an increase in glucocorticoid synthesis and release, affecting energy supply, metabolism, cardiovascular function, and immunity.

ACTH Secretion

ACTH is secreted in a pulsatile manner, with pulses of ACTH being followed, approximately 15 min later, by pulses of cortisol. A circadian pattern of ACTH secretion is evident, with maximum levels of ACTH being observed between 06.00 and 09.00, falling to a nadir between 23.00 and 02.00 The circadian rhythm is set by the suprachiasmatic nucleus of the hypothalamus.

Regulation of ACTH

Levels of ACTH are regulated by factors from the hypothalamic, including CRH, dopamine and arginine vasopressin (AVP), within the pituitary by cytokines and

growth factors and by glucocorticoids through a negative feedback loop at the level of the hypothalamus and pituitary.

CRH is a 41-amino acid peptide derived from a 196-amino acid prohormone synthesized by neurons in the parvocellular division of the hypothalamic paraventricular nuclei. These neurons also secrete other ACTH secretagogues including AVP, cholecystokinin, and opioid peptides. Hypothalamic CRH secretion is increased by a number of cytokines and neurotransmitters, including acetylcholine, norepinephrine, histamine, serotonin, tumor necrosis factor, oxytocin, vasoactive peptide (VIP), catecholamines, angiotensin II, and interleukins (IL), with the exception of IL2, which appears to act at the level of the pituitary. Secretion is inhibited by gamma-aminobutyric acid.

AVP is synthesized in the supraoptic and periventricular nuclei of the hypothalamus and corticotrophs, where it acts in a paracrine manner. AVP stimulates ACTH release via the V1b receptor. It is a relatively weak stimulant of ACTH but acts synergistically with CRH by increasing the number of corticotrophs responsive to CRH.

In response to CRH binding with the CRH type 1 receptor (CRH-R1), corticotrophs release ACTH stored in secretory vesicles. CRH also activates POMC gene expression, resulting in a second, slower wave of ACTH release. Subpopulations of corticotroph cells may differ in their CRH-R1 expression, with some subpopulations responding quickly with immediate release of stored ACTH, while others respond more slowly, thus ensuring a sustained ACTH rise during periods of prolonged stress (Mason et al. 2002).

CRH and AVP are thought to be the major mediators of stress-related ACTH release, and physical and psychological stress increases transcription of both secretagogues. Cytokines released from immune cells (TNF-α, IL-1, IL-6), FS cells, and corticotrophs of the pituitary (leukemia inhibitory factor (LIF), IL-6) are also potent stimulators of ACTH secretion during periods of stress (Arzt et al. 1999).

Glucocorticoids inhibit ACTH release at three levels: at the level of the hypothalamus by inhibiting CRH and AVP synthesis, at the level of the pituitary by inhibiting POMC transcription, and by modifying corticotroph response to CRH-R1 and V1b receptor stimulation.

Growth Hormone and Somatotrophs

Somatotrophs

Growth hormone (GH) is synthesized in somatotrophs, cells that comprise approximately 50 % of pituitary cell mass and are located in the lateral wings of the pituitary. They are polyhedral in appearance and a small subpopulation (mammosomatotrophs) stain for both GH and prolactin.

The human growth hormone gene is located on the long arm of chromosome 17q22-24. GH is a 191 amino acid single-chain polypeptide hormone consisting of four α-helixes with two disulfide bonds. There are two major isoforms, full length

(22 kDa) which accounts for approximately 70 % of circulating GH. An alternatively spliced GH (20 kDa), which lacks residues 32–46 and has a slower clearance rate than 22 kDa GH, accounts for a further 15 % of pituitary-derived GH. An acetylated 22KDA GH isoform can also be detected, and other isoforms are present in low concentrations (Bauman 2009).

Patterns of Growth Hormone Secretion

From early infancy, growth hormone is secreted in pulses of the greatest frequency and amplitude during sleep with the onset of slow-wave sleep being the trigger for the peaks of the greatest amplitude and frequency (Van Cauter et al. 1998). Between pulses, growth hormone concentrations return to levels below the limits of detection of most laboratory assays.

Growth hormone levels are higher during the neonatal period than in later childhood, and over the first 4 days of life, the magnitude and frequency of growth hormone pulses fall by 50 % (Vigneri and Agata 1971). In the first few months of life, there is no relationship between sleep and growth hormone secretion.

Production of GH during childhood ranges from 200 to 600 μg/L per day. During adolescence GH production rises sharply in concert with the increase in sex hormones, to 1,000–1,800 μg/L per day, falling to 200–600 μg/L once again during young adult life and falling progressively during middle and old age (Giustina and Veldhuis 1998).

Regulators of Growth Hormone Secretion

Growth hormone peaks are regulated primarily, by the balance between growth hormone-releasing hormone (GHRH), the principle GH secretagogue which stimulates GH gene transcription and GH release, and somatostatin which is the primary inhibitor of GH secretion. The secretion of these two hormones is under complex and multilayered control by neurotransmitters, neuropeptides, and opiates.

GHRH, of which there are two principal forms, GHRH (1–40) and GHRH (1–44), is derived from a 108 amino acid preprohormone. The C-terminal residues 30–44 may be redundant as full biological activity is retained in their absence. GHRH acts through a seven-transmembrane domain G protein-coupled receptor to stimulate GH synthesis and release and somatotroph proliferation.

Ghrelin, a peptide released primarily from the gastric mucosal cells, is a potent GH secretagogue, acting directly at the level of the pituitary and via hypothalamic GHRH where it binds with the GH secretagogue receptor (Kojima et al. 1999). Other sources of ghrelin include the hypothalamus, and somatotrophs, thyrotrophs, and lactotrophs, where it acts in a paracrine manner. The actions of ghrelin are mediated, at least in part, by GHRH, as transection of the pituitary stalk results in loss of ghrelin-mediated GH suppression.

Clonidine, arginine, exercise, and L-dopa all augment GH secretion via α-adrenergic pathways. In contrast, β-adrenergic pathways inhibit GH secretion. Enkephalins and endorphins increase GH release, as do galanin, neurotensin, VIP, motilin, cholecystokinin, and glucagon.

Sex steroids promote GH secretion, increasing the amplitude of GH pulses. Estrogen promotes GH secretion through the estrogen receptor α, expressed on both GHRH neurons and somatotrophs, but also reduces GH sensitivity, resulting in a fall in IGF-I levels. Testosterone promotes GH secretion, with no loss of GH sensitivity, increasing levels of both GH and IGF-I.

The primary action of leptin, a hormone released from white adipose tissue, is the maintenance of a healthy body fat mass by inhibiting the appetite centers of the brain. Short-term exposure to leptin increases GH release, probably by enhancing GHRH release and inhibiting somatostatin, but prolonged exposure results in a reduction in GHRH sensitivity and lower GH levels. During periods of fasting, GH levels rise. In contrast, GH levels are low in obese subjects.

GH secretion is stimulated for up to 3 h following glucocorticoid exposure, followed by suppression within 12 h of sustained exposure. Thyroid hormones are essential for the maintenance of normal GH levels. In hypothyroid patients, the GH response to stimulation is impaired and recovers after restoration of normal thyroid hormone levels. Sex steroids increase GH levels. In men, testosterone effects are mediated via aromatization to estrogen

Somatostatin is the primary inhibitor of GH secretion. It is also the product of a preprohormone and circulates in two forms: somatostatin-28 and somatostatin-14. Somatostatin has diverse effects within the pituitary and in other organs including the gut, pancreas, and liver. Pituitary actions of somatostatin include inhibition of GH secretion directly and also through inhibition of GHRH release from the hypothalamus. Somatostatin levels rise in response to increases in GHRH, growth hormone, and IGF-I.

Gonadotropins and Gonadotrophs

The gonadotropins LH and FSH are synthesized and released by gonadotrophs, which contribute approximately 10 % of the pituitary cell mass and are located throughout the pars distalis and pars tuberalis. They are in intimate contact with lactotrophs, with which they interact in a paracrine manner.

LH and FSH are members of the glycoprotein hormone family, which also includes TSH and placental chorionic gonadotropin. They comprise a common 92 amino acid α-subunit covalently bound to a hormone-specific β-subunit, which varies in size from 110 to 145 amino acids. The gene encoding the common α-subunit is located on chromosome 6 and comprises four exons, of which the first is noncoding. The gene encoding the LH-β-subunit is located on 19q.13.3 and comprises three exons. The FSH β-subunit gene also comprises three exons and is located on 11p.14.1.

Regulators of Gonadotropin Secretion

The major regulators of LH and FSH concentrations are hypothalamic GnRH, which stimulates release, and gonadal factors, including testosterone, estradiol,

progesterone, and inhibin, which inhibit release. Auto and paracrine pathways within the pituitary also regulate gonadotropin release and are of particular importance in determining the differential regulation of LH and FSH from the same cell.

During embryogenesis, the migration of GnRH neurons from the medial olfactory placode along the olfactory bulb to the infundibulum, medial basal and the periventricular regions of the hypothalamus, is dependent on a number of factors including anosmin-1 (the product of KAL gene), leukemia inhibitory factor, and fibroblast growth factor receptor 1. Kallmann syndrome, characterized by anosmia and hypogonadotropic hypogonadism, results from defective GnRH neuron migration in patients with mutations of the KAL1 gene (Bick et al. 1992).

GnRH is encoded by two genes. $GNRH_1$ is found in hypothalamic neurons. It encodes a 92 amino acid precursor protein which regulates pituitary release of gonadotropins. The second GnRH gene, $GNRH_2$, is found in the midbrain and encodes a decapeptide that serves as a neurotransmitter rather than a pituitary-releasing factor.

Like other hypothalamic hormones, GnRH is released in a pulsatile manner. This pulsatility is essential for normal activity of the hypothalamic pituitary axis, as continuous exposure of to GnRH results in downregulation of GnRH receptors and desensitization of gonadotrophs.

GnRH binding to its membrane receptor on gonadotrophs stimulates the release of both LH and FSH, and differential regulation of LH and FSH is achieved, in part through changes in GnRH pulse frequency (Dalkin et al. 1989). LH, FSH, and TSH share a common α-subunit, and hormone specificity is conferred from the β-subunit. High-frequency GnRH pulses increase transcription of α- and LH-β-subunits, whereas low-frequency GnRH pulses increase FSH-β gene transcription. Furthermore, animal studies report that GnRH pulses released once an hour favor LH secretion over FSH secretion, while pulses of lower frequency favor FSH secretion.

The frequency of GnRH pulses also influences the half-life and biological activity of gonadotropins. Prior to secretion, terminal sugars are attached to gonadotropin molecules, influencing gonadotropin activity. These sugars include sialic acid, the most important, galactose, n-acetylglucosamine, and mannose. Gonadotropins with sialic acid are protected from degradation and have a longer half-life, while gonadotropins with less sialic acid are able to bind the gonadotropin receptor with greater affinity. Glycosylation is influenced by the frequency of GnRH pulses. In the follicular phase, the frequency of GnRH pulses is slow, favoring glycosylation of FSH and sustained FSH support of developing follicles. Just before the midcycle gonadotropin surge, GnRH pulses are released with higher frequency. Glycosylation is less, favoring the release of more potent gonadotropins with a shorter half-life at the time of ovulation.

GnRH release is regulated, in part, by Kisspeptin, which acts directly on the GnRH neuron to stimulate GnRH release into the portal circulation. Kisspeptin binding with its receptor on gonadotropins has been reported to upregulate LHβ and FSHβ gene expression and to increase LH and FSH secretion. Animal models with inactivating mutations of Kiss1 and the Kiss1 receptor have delayed puberty

(Chan et al. 2009), while an activating mutation of the receptor has been reported in a girl with precocious puberty (Teles et al. 2008).

Inhibins are members of the transforming growth factor β family which inhibit FSH secretion. They comprise a common α-subunit and two β-subunits, which confer specificity: βA and βB. Inhibins are produced in gonadal tissue and gonadotrophs and to a lesser degree somatotrophs, thyrotrophs, and FS cells. In males, inhibin B is released in response to FSH stimulation. In females inhibin A is released from dominant ovarian follicles and corpora lutea in the late follicular and luteal phase of the menstrual cycle, whereas inhibin B levels rise during the late luteal and early follicular phase.

Activins comprise two β-subunits, of which two have been most extensively studied: activin A (βA, βA) and activin B (βB, βB). In contrast to the action of inhibin, activins stimulate FSH release. Inhibins compete with activins for type II activin receptors, thereby modulating activin effects on FSH secretion. The relative production of inhibins and activins may depend on the relative availability of intracellular α- and β-subunits: In the presence of a surplus of α-subunit, the production of inhibin may be favored over activin, whereas the contrary would be true in the presence of a surplus of β-subunits. This raises the possibility that the regulation of FSH release is mediated, in part, by the relative production of α- and β-subunits.

Follistatin is a monomeric peptide that is synthesized and released from gonadal cells and intrapituitary endocrine and FS cells. Follistatin binds activin with high affinity, preventing it from binding to its receptor and thereby blocking the effect of activin on FSH secretion.

Sex steroids (testosterone, estradiol, and progesterone) act at the level of the hypothalamus to slow the pulsatile release of GnRH into the portal circulation. The GnRH neuron lacks steroid hormone receptors, so these actions of sex steroids on GnRH release must be mediated through another pathway or messenger. Sex steroids also inhibit gonadotropin release, acting directly at the level of the pituitary to reduce LH and FSH release and to reduce the sensitivity of gonadotrophs to GnRH stimulation.

In the female, during the follicular phase of the menstrual cycle, estrogen switches from a negative to a positive feedback effect, resulting in the gonadotropin surge. This switch is dependent on the maintenance of critical estrogen concentration for a critical period of time, which is associated with an increase in GnRH receptors and increased GnRH responsiveness.

Menstrual Cycle

The menstrual cycle starts with the onset of menstrual bleeding, when ovaries contain multiple small follicles and estrogen concentrations are low. Pulses of LH are relatively fast, and FSH levels are higher than at other times of the cycle, stimulating the development of ovarian follicles. As follicles develop, estrogen levels rise, increasing the negative feedback effect on GnRH and gonadotropin release.

In response to the rise in estrogen, the frequency of LH pulses falls, until estrogen levels are maintained at an adequate level to induce the switch from a negative to a positive feedback effect. As gonadotropin levels rise, the follicular wall dissolves, and the matured ovum is released into the fallopian tube. Progesterone is released in high concentrations, slowing LH pulses. If fertilization does not occur, progesterone levels fall after 14 days, and LH and FSH levels rise once again. The fall in progesterone also results in the shedding of the endometrium and the start of a new menstrual cycle.

Conclusion

The activity of the hypothalamic pituitary axis is exquisitely regulated, integrating messages from within the pituitary, the hypothalamus, peripheral tissues and organs, and the external environment, to ensure hormone levels that support physiological and homeostatic processes, critical to health and well-being. It is an awe-inspiring example of the complexity, elegance, and sophistication of the endocrine system, and no doubt, there is still much for us to learn.

Cross-References

- ▶ Ovarian Physiology
- ▶ Physiology of the Thyroid
- ▶ The Endocrine Pancreas
- ▶ The Endocrine Regulation of Blood Pressure
- ▶ The Endocrine Regulation of Energy and Body Weight
- ▶ The Endocrinology of Puberty
- ▶ The Physiology of Adrenal Glands
- ▶ The Physiology of the Testis

References

Alatzoglou KS, Kelberman D, Dattani MT. The role of SOX proteins in normal pituitary development. J Endocrinol. 2009;200(3):245–58. 1479-6805.

Alvarez-Bolado G, Grinevich V, Puelles L. Editorial: development of the hypothalamus. Front Neuroanat. 2015;9:83. doi:10.3389/fnana.2015.00083.

Arzt E, Pereda MP, Castro CP, Pagotto U, Renner U, Stalla GK. Pathophysiological role of the cytokine network in the anterior pituitary gland. Front Neuroendocrinol. 1999;20(1):71–95.

Bassett JH, van der Spek A, Logan JG, Gogakos A, Bagchi-Chakraborty J, Murphy E, van Zeijl C, Down J, Croucher PI, Boyde A, Boelen A, Williams GR. Thyrostimulin regulates osteoblastic bone formation during early skeletal development. Endocrinology. 2015;156(9):3098–113.

Baumann GP. Growth hormone isoforms. Growth Horm IGF Res. 2009;19(4):333–40.

Bick D, Franco B, Sherins RJ, Heye B, Pike L, Crawford J, Maddalena A, Incerti B, Pragliola A, Meitinger T, Ballabio A. Brief report: intragenic deletion of the KALIG-1 gene in Kallmann's syndrome. N Engl J Med. 1992;326:1752–5.

Blaustein MP, Leenen FH, Chen L, Golovina VA, Hamlyn JM, Pallone TL, Van Huysse JW, Zhang J, Wier WG. How NaCl raises blood pressure: a new paradigm for the pathogenesis of salt-dependent hypertension. Am J Physiol Heart Circ Physiol. 2012;302(5):H1031–49.

Brüning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Müller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and reproduction. Science. 2000;289(5487):2122–5.

Burrows HL, Birkmeier TS, Seasholtz AF, Camper SA. Targeted ablation of cells in the pituitary primordia of transgenic mice. Mol Endocrinol. 1996;10(11):1467–77.

Chan YM, Broder-Fingert S, et al. Kisspeptin/Gpr54-independent gonadotrophin-releasing hormone activity in Kiss1 and Gpr54 mutant mice. J Neuroendocrinol. 2009;21 (12):1015–23.

Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EG, Shen Z, Marsh DJ, Feighner SD, Guan XM, Ye Z, Nargund RP, Smith RG, Van der Ploeg LH, Howard AD, MacNeil DJ, Qian S. Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein. Endocrinology. 2004;145(6):2607–12.

Clark AJL, Swords FM. Molecular biology of corticoroph function. In: Rappaport R, Anselm S, editors. Hypothalamic-pituitary development. Basel: Karger; 2001.

Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougnères P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392(6674):398–401.

Dalkin AC, Haisenlender DJ, et al. The frequency of gonadotropin-releasing-hormone stimulation differentially regulates gonadotropin subunit messenger ribonucleic acid expression. Endocrinology. 1989;125(2):917–23.

de Moraes DC, Vaisman M, Conceição FL, Ortiga-Carvalho TM. Pituitary development: a complex, temporal regulated process dependent on specific transcriptional factors. J Endocrinol. 2012;215(2):239–45. doi:10.1530/JOE-12-0229. Epub 2012 Aug 7.

Elster AD, Chen MY, Williams 3rd DW, Key LL. Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. Radiology. 1990;174(3 Pt 1):681–5.

Falk RJ. Isolated prolactin deficiency: a case report. Fertil Steril. 1992;58(5):1060–2.

Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C. A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci. 2008;28(15):4088–95.

Ferran, et al. Molecular codes defining rostrocaudal domains in the embryonic mouse hypothalamus. Front Neuroanat. 2015;9:46.

Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. 1989. Biochem Biophys Res Commun. 2012;425 (3):540–7.

Freeman J. The anatomy and embryology of the hypothalamus in relation to hypothalamic hamartomas. Epileptic Disord. 2003;5:177–86.

Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000;80(4):1523–631.

Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19(6):717–97.

Gospodarowicz D, Abraham JA, Schilling J. Isolation and characterization of a vascular endothelial cell mitogen produced by pituitary-derived folliculo stellate cells. Proc Natl Acad Sci U S A. 1989;86(19):7311–5.

Hamlyn JM, Linde CI, Gao J, Huang BS, Golovina VA, Blaustein MP, Leenen FH. Neuroendocrine humoral and vascular components in the pressor pathway for brain angiotensin II: a new axis in long term blood pressure control. PLoS One. 2014;9(9):e108916.

Ishii S, Kamegai J, Tamura H, Shimizu T, Sugihara H, Oikawa S. Hypothalamic neuropeptide Y/Y1 receptor pathway activated by a reduction in circulating leptin, but not by an increase in circulating ghrelin, contributes to hyperphagia associated with triiodothyronine-induced thyrotoxicosis. Neuroendocrinology. 2003;78(6):321–30.

Kelberman D, Dattani MT. Hypothalamic and pituitary development: novel insights into the aetiology. Eur J Endocrinol/Eur Fed Endocr Soc. 2007;157 Suppl 1:S3. 0804-4643 (August 2007).

Kelberman D, Rizzoti K, Lovell-Badge R, Robinson IC, Dattani M. Genetic regulation of pituitary gland development in human and mouse. Endocr Rev. 2009;30(7):790–829.

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402(6762):656–60.

Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet. 1998;19(2):155–7.

Kwon Jeong J, Dae Kim J, Diano S. Ghrelin regulates hypothalamic prolyl carboxypeptidase expression in mice. Mol Metab. 2013;2(1):23–30.

Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: pathways and genes. Obesity (Silver Spring). 2008;16 Suppl 3:S11–22.

Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright Jr KP. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc Natl Acad Sci U S A. 2013;110(14):5695–700.

Mason D, Hassan A, Chacko S, Thompson P. Acute and chronic regulation of pituitary receptors for vasopressin and corticotropin releasing hormone. Arch Physiol Biochem. 2002;110 (1–2):74–89.

Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387(6636):903–8.

Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci (Landmark Ed). 2011;16:74–104.

Nakabayashi K, Matsumi H, Bhalla A, Bae J, Mosselman S, Hsu SY, Hsueh AJ. Thyrostimulin, a heterodimer of two new human glycoprotein hormone subunits, activates the thyroid-stimulating hormone receptor. J Clin Invest. 2002;109(11):1445–52.

Onofri C, Theodoropoulou M, Losa M, Uhl E, Lange M, Arzt E, Stalla GK, Renner U. Localization of vascular endothelial growth factor (VEGF) receptors in normal and adenomatous pituitaries: detection of a non-endothelial function of VEGF in pituitary tumours. J Endocrinol. 2006;191 (1):249–61.

Pazos-Mour, Otiga-Carvalho TM, Gasper de Moura E. The autocrine/paracrine regulation of thyrotropin secretion. Thyroid. 2003;13:167–75.

Perez-Castro C, Renner U, Haedo MR, Stalla GK, Arzt E. Cellular and molecular specificity of pituitary gland physiology. Physiol Rev. 2012;92(1):1–38.

Puelles L. Brain segmentation and forebrain development in amniotes. Brain Res Bull. 2001;55 (6):695–710.

Puelles L. Forebrain development: prosomere model. Murcia: University of Murcia; 2009. Elsevier Ltd.

Puelles L, Rubenstein JL. Forebrain gene expression domains and the evolving prosomeric model. Trends Neurosci. 2003;26(9):469–76.

Qian S, Chen H, Weingarth D, Trumbauer ME, Novi DE, Guan X, Yu H, Shen Z, Feng Y, Frazier E, Chen A, Camacho RE, Shearman LP, Gopal-Truter S, MacNeil DJ, Van der Ploeg LH, Marsh DJ. Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice. Mol Cell Biol. 2002;22(14):5027–35.

Routh VH, Donovan CM, Ritter S. 2. Hypoglycemia detection. Transl Endocrinol Metab. 2012;3 (4):47–87.

Sassin JF, Frantz AG, Weitzman ED, Kapen S. Human prolactin: 24-hour pattern with increased release during sleep. Science. 1972;177(4055):1205–7.

Sinha YN. Structural variants of prolactin: occurrence and physiological significance. Endocr Rev. 1995;16(3):354–69.

Smart JL, Tolle V, Low MJ. Glucocorticoids exacerbate obesity and insulin resistance in neuron-specific proopiomelanocortin-deficient mice. J Clin Invest. 2006;116(2):495–505.
Sun SC, Hsu PJ, Wu FJ, Li SH, Lu CH, Luo CW. Thyrostimulin, but not thyroid-stimulating hormone (TSH), acts as a paracrine regulator to activate the TSH receptor in mammalian ovary. J Biol Chem. 2010;285(6):3758–65.
Teles MG, Bianco SD, et al. A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med. 2008;7:709–15.
Turner HE, Nagy Z, Gatter KC, Esiri MM, Harris AL, Wass JA. Angiogenesis in pituitary adenomas and the normal pituitary gland. J Clin Endocrinol Metab. 2000;85(3):1159–62.
Vaisse C, Clement K, Guy-Grand B, Froguel P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. Nat Genet. 1998;20(2):113–4.
Van Cauter E, Plat L, Copinschi G. Interrelations between sleep and the somatotropic axis. Sleep. 1998;21(6):553–66.
Vella KR, Ramadoss P, Lam FS, Harris JC, Ye FD, Same PD, O'Neill NF, Maratos-Flier E, Hollenberg AN. NPY and MC4R signaling regulate thyroid hormone levels during fasting through both central and peripheral pathways. Cell Metab. 2011;14(6):780–90.
Vigneri R, D'Agata R. Growth hormone release during the first year of life in relation to sleep-wake periods. J Clin Endocrinol Metab. 1971;33(3):561–3.
Wang Q, Liu C, Uchida A, Chuang JC, Walker A, Liu T, Osborne-Lawrence S, Mason BL, Mosher C, Berglund ED, Elmquist JK, Zigman JM. Arcuate AgRP neurons mediate orexigenic and glucoregulatory actions of ghrelin. Mol Metab. 2013;3(1):64–72.
Williams KW, Margatho LO, Lee CE, Choi M, Lee S, Scott MM, Elias CF, Elmquist JK. Segregation of acute leptin and insulin effects in distinct populations of arcuate pro-opiomelanocortin neurons. J Neurosci. 2010;30(7):2472–9.
Yang Y, Guo QH, Wang BA, Dou JT, Lv ZH, Ba JM, Lu JM, Pan CY, Mu YM. Pituitary stalk interruption syndrome in 58 Chinese patients: clinical features and genetic analysis. Clin Endocrinol (Oxf). 2013;79(1):86–92.
Yaswen L, Diehl N, Brennan MB, Hochgeschwender U. Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. Nat Med. 1999;5(9):1066–70.
Zárate S, Jaita G, Zaldivar V, Radl DB, Eijo G, Ferraris J, Pisera D, Seilicovich A. Estrogens exert a rapid apoptotic action in anterior pituitary cells. Am J Physiol Endocrinol Metab. 2009;296(4): E664–71.