04 - 390 Physiology of Anterior Pituitary Hormones

390 Physiology of Anterior Pituitary Hormones

Positive feedback control also occurs but is not well understood. The primary example is estrogen-mediated stimulation of the midcycle LH surge. Although chronic low levels of estrogen are inhibitory, gradu ally rising estrogen levels stimulate LH secretion. This effect, which is illustrative of an endocrine rhythm (see below), involves activation of the hypothalamic GnRH pulse generator. In addition, estrogen-primed gonadotropes are extraordinarily sensitive to GnRH, leading to ampli fication of LH release. ■ ■PARACRINE AND AUTOCRINE CONTROL The previously mentioned examples of feedback control involve classic endocrine pathways in which hormones are released by one gland and act on a distant target gland. However, local regulatory systems, often involving growth factors, are increasingly recognized. Paracrine regu lation refers to factors released by one cell that act on an adjacent cell in the same tissue. For example, somatostatin secretion by pancreatic islet δ cells inhibits insulin secretion from nearby β cells. Autocrine regulation describes the action of a factor on the same cell from which it is produced. IGF1 acts on many cells that produce it, including chondrocytes, breast epithelium, and gonadal cells. Unlike endocrine actions, paracrine and autocrine control are difficult to document because local growth factor concentrations cannot be measured readily. Anatomic relationships of glandular systems also greatly influence hormonal exposure: the physical organization of islet cells enhances their intercellular communication; the portal vasculature of the hypo thalamic-pituitary system exposes the pituitary to high concentrations of hypothalamic releasing factors; testicular seminiferous tubules gain exposure to high testosterone levels produced by the interdigitated Leydig cells; the pancreas receives nutrient information and local expo sure to peptide hormones (incretins) from the gastrointestinal tract; and the liver is the proximal target of insulin action because of portal drainage from the pancreas. ■ ■HORMONAL RHYTHMS The feedback regulatory systems described above are superimposed on hormonal rhythms that are used for adaptation to the environment. Seasonal changes, the daily occurrence of the light-dark cycle, sleep, meals, and stress are examples of the many environmental events that affect hormonal rhythms. The menstrual cycle is repeated on average every 28 days, reflecting the time required to follicular maturation, ovulation, and potential implantation (Chap. 390). Essentially all pitu itary hormone rhythms are entrained to sleep and to the circadian cycle, generating reproducible patterns that are repeated approximately every 24 h. The HPA axis, for example, exhibits characteristic peaks of ACTH and cortisol production in the early morning, with a nadir during the night. Recognition of these rhythms is

important for endocrine testing and treatment. Patients with Cushing's syndrome characteristically exhibit increased midnight cortisol levels compared with normal indi viduals (Chap. 398). In contrast, morning cortisol levels are similar in these groups, as cortisol is normally high at this time of day in normal individuals. The HPA axis is more susceptible to suppression by glu cocorticoids administered at night as they blunt the early-morning rise of ACTH. Understanding these rhythms allows glucocorticoid replace ment that mimics diurnal production by administering larger doses in the morning than in the afternoon. Disrupted sleep rhythms can alter hormonal regulation. For example, sleep deprivation causes mild insulin resistance, food craving, and hypertension, which are revers ible, at least in the short term. Emerging evidence indicates that circa dian clock pathways not only regulate sleep-wake cycles but also play important roles in virtually every cell type. For example, tissue-specific deletion of clock genes alters rhythms and levels of gene expression, as well as metabolic responses in liver, adipose, and other tissues. Other endocrine rhythms occur on a more rapid time scale. Many peptide hormones are secreted in discrete bursts every few hours. LH and FSH secretion are exquisitely sensitive to GnRH pulse frequency. Intermittent pulses of GnRH are required to maintain pituitary sensitivity, whereas continuous exposure to GnRH causes pituitary gonadotrope desensitization. This feature of the hypothalamic-pitu itary-gonadotrope axis forms the basis for using long-acting GnRH

agonists to treat central precocious puberty or to decrease testosterone levels in the management of prostate cancer. It is important to be aware of the pulsatile nature of hormone secretion and the rhythmic patterns of hormone production in relating serum hormone measurements to normal values. For some hormones, integrated markers have been developed to circumvent hormonal fluctuations. Examples include 24-h urine collections for cortisol, the measurement of IGF1 as a bio logic marker of GH action, and HbA1c as an index of long-term (weeks to months) blood glucose control.

Often, one must interpret endocrine data only in the context of other hormones. For example, PTH levels typically are assessed in combina tion with serum calcium concentrations. A high serum calcium level in association with elevated PTH is suggestive of hyperparathyroidism, whereas a suppressed PTH in the setting of hypercalcemia is more likely to be caused by hypercalcemia of malignancy, or other causes of hypercalcemia. Similarly, when T4 and T3 concentrations are low, TSH should be elevated, reflecting reduced feedback inhibition. When this is not the case, it is important to consider secondary hypothyroidism, which is caused by a defect at the level of the pituitary. Physiology of Anterior Pituitary Hormones CHAPTER 390 ■ ■FURTHER READING Fukami M et al: Gain-of-function mutations in G-protein-coupled receptor genes associated with human endocrine disorders. Clin Endocrinol 88:351, 2018. Herbison AE: A simple model of estrous cycle negative and positive feedback regulation of GnRH secretion. Frontiers Neuroendocrinol 57:100837, 2020. Kim YH, Lazar MA: Transcriptional control of circadian rhythms and metabolism: A matter of time and space. Endocr Rev 41:707, 2020. Robertson RP (ed): DeGroot's Endocrinology: Adult and Pediatric, 8th ed. Philadelphia, Elsevier, 2023. Scholtes C, Giguère V: Transcriptional control of energy metabo lism by nuclear receptors. Nature Rev Mol Cell Biol 23:750, 2022. Shlomo Melmed, J. Larry Jameson

Physiology of Anterior

Pituitary Hormones The anterior pituitary often is referred to as the “master gland” because, together with the hypothalamus, it orchestrates the complex regula tory functions of many other endocrine glands. The anterior pituitary gland produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropic hormone (ACTH), (4) lutein izing hormone (LH), (5) follicle-stimulating hormone (FSH), and

(6) thyroid-stimulating hormone (TSH) (Table 390-1). Pituitary

hormones are secreted in a pulsatile manner, reflecting regulation by an array of specific hypothalamic releasing factors. Each of these pitu itary hormones elicits specific trophic responses in peripheral target tissues including the adrenal, thyroid, and gonads, as well as tissues involved in metabolism (e.g., liver, breast, bone). Elicited hormonal products of peripheral glands, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function (Fig. 390-1). Pituitary tumors cause characteristic hormone excess syn dromes. Hormone deficiency may be inherited or acquired. Fortunately, there are efficacious treatments for many pituitary hormone excess and deficiency syndromes. Nonetheless, these diagnoses are often elusive; this emphasizes the importance of recognizing subtle clinical manifes tations and performing the correct laboratory diagnostic tests. For dis cussion of disorders of the posterior pituitary or neurohypophysis, see Chap. 393.

TABLE 390-1 Anterior Pituitary Hormone Expression and Regulation CELL CORTICOTROPE SOMATOTROPE LACTOTROPE THYROTROPE GONADOTROPE Tissue-specific transcription factor T-Pit Prop-1, Pit-1 Prop-1, Pit-1 Prop-1, Pit-1, TEF SF-1, DAX-1 Developmental timing 6 weeks 8 weeks 12 weeks 12 weeks 12 weeks Hormone POMC GH PRL TSH FSH, LH Protein Polypeptide Polypeptide Polypeptide Glycoprotein α, β subunits Glycoprotein α, β subunits Amino acids 266 (ACTH 1–39)

210, 204 Stimulators CRH, AVP, cytokines GHRH, ghrelin Estrogen, TRH, VIP TRH GnRH, activins, estrogen Inhibitors Glucocorticoids Somatostatin, IGF-1 Dopamine T3, T4, dopamine, somatostatin, glucocorticoids PART 12 Endocrinology and Metabolism Target gland Adrenal Liver, bone, other tissues Breast, other tissues Thyroid Ovary, testis Trophic effect Steroid production IGF-1 production, growth induction, insulin antagonism Normal range ACTH, 4–22 pg/L <0.5 µg/La M <15 µg/L; F <20 µg/L 0.1–5 mU/L M, 5–20 IU/L; F (basal), 5–20 IU/L aHormone secretion integrated over 24 h. Abbreviations: F, female; M, male. For other abbreviations, see text. Source: Courtesy of Elsevier. ANATOMY AND DEVELOPMENT ■ ■ANATOMY The pituitary gland weighs ~600 mg and is located within the sella turcica ventral to the diaphragma sella; it consists of anatomically and functionally distinct anterior and posterior lobes. The bony sella is con tiguous to vascular and neurologic structures, including the cavernous sinuses, cranial nerves, and optic chiasm. Thus, expanding intrasellar pathologic processes may have significant central mass effects in addi tion to their endocrinologic impact. Hypothalamic neural cells synthesize specific releasing and inhibit ing hormones that are secreted directly into the portal vessels of the pituitary stalk. Blood supply of the pituitary gland comes from the superior and inferior hypophyseal arteries (Fig. 390-2). The hypotha lamic-pituitary portal plexus provides the major blood source for the anterior pituitary, allowing reliable transmission of hypothalamic pep tide pulses without significant systemic dilution; consequently, anterior pituitary cells are exposed to specific releasing or inhibiting factors and in turn release their respective hormones as discrete pulses into the systemic circulation (Fig. 390-3). The posterior pituitary is supplied by the inferior hypophyseal arter ies. In contrast to the anterior

pituitary, the posterior lobe is directly innervated by hypothalamic neurons (supraopticohypophyseal and tuberohypophyseal nerve tracts) via the pituitary stalk (Chap. 393). Thus, posterior pituitary production of arginine vasopressin (AVP) and oxytocin is particularly sensitive to neuronal damage by lesions that affect the pituitary stalk or hypothalamus. ■ ■PITUITARY DEVELOPMENT The embryonic differentiation and maturation of anterior pituitary cells have been elucidated in considerable detail. Pituitary develop ment from Rathke's pouch involves a complex interplay of lineagespecific transcription factors expressed in pluripotent Sox2-expressing precursor cells and gradients of locally produced growth factors (Table 390-1). The transcription factor Prop-1 induces pituitary development of Pit-1-specific lineages as well as gonadotropes. The transcrip tion factor Pit-1 determines cell-specific expression of GH, PRL, and TSH in somatotropes, lactotropes, and thyrotropes. Expression of high levels of estrogen receptors in cells that contain Pit-1 favors PRL expression, whereas thyrotrope embryonic factor (TEF) induces TSH expression. Pit-1 binds to GH, PRL, and TSH gene regulatory elements, providing a mechanism for determining specific pituitary hormone phenotypic stability. Gonadotrope cell development is fur ther defined by the cell-specific expression of the nuclear receptors steroidogenic factor (SF-1) and dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX-1). Devel opment of corticotrope cells, which express the proopiomelanocortin

Sex steroids, inhibin Milk production T4 synthesis and secretion Sex steroid production, follicle growth, germ cell maturation (POMC) gene, requires the T-Pit transcription factor. Abnormalities of pituitary development can be caused by inherited mutations of devel opmental transcription factors including Pit-1, Prop-1, SF-1, DAX-1, and T-Pit, resulting in selective or combined pituitary hormone deficit syndromes. ANTERIOR PITUITARY HORMONES Each anterior pituitary hormone is under unique control, and each exhibits highly specific normal and dysregulated secretory characteristics. ■ ■PROLACTIN Synthesis PRL consists of 198 amino acids and has a molecular mass of 21,500 kDa; it is weakly homologous to GH and human pla cental lactogen (hPL), reflecting the duplication and divergence of a common GH-PRL-hPL precursor gene. PRL is synthesized in lacto tropes, which constitute ~20% of anterior pituitary cells. Lactotropes and somatotropes are derived from a common precursor cell that may give rise to a tumor that secretes both PRL and GH. Lactotrope cell hyperplasia develops during pregnancy and the first few months of lactation. These transient functional changes in the lactotrope popula tion are induced by estrogen to increase PRL production. Secretion Normal adult serum PRL levels are about 10–25 μg/L in women and 10–20 μg/L in men. PRL secretion is pulsatile, with the highest secretory peaks occurring during non–rapid eye move ment (non-REM) sleep. Peak serum PRL levels (up to 30 μg/L) occur between 4:00 and 6:00 a.m. The circulating half-life of PRL is ~50 min. PRL is unique among the pituitary hormones in that the predomi nant hypothalamic control mechanism is inhibitory, reflecting tonic dopamine-mediated suppression of PRL release. This regulatory path way accounts for the spontaneous PRL hypersecretion that occurs with pituitary stalk section, often a consequence of head trauma or com pressive mass lesions at the skull base. Pituitary dopamine type 2 (D2) receptors mediate inhibition of PRL synthesis and secretion. Targeted disruption (gene knockout) of the murine D2 receptor in mice results in hyperprolactinemia and lactotrope proliferation. As discussed below, dopamine agonists play a central role in the management of hyperpro lactinemic disorders. Thyrotropin-releasing hormone (TRH) (pyro Glu-His-Pro-NH2) is a hypothalamic tripeptide that elicits PRL release within 15–30 min after intravenous injection. TRH primarily regulates TSH, and the physiologic relevance of TRH for PRL regulation is unclear (Chap. 394). Serum PRL levels rise transiently after exercise, meals, sexual intercourse, minor surgical

procedures, general anesthesia, chest wall injury, acute myocardial infarction, and other forms of acute stress. PRL levels increase markedly (about tenfold) during pregnancy and

TRH GHRH SRIF GnRH CRH Dopamine Hypothalamus – + – – + – + + Pituitary – ACTH Target organs + TSH Cortisol GH LH PRL Cell homeostasis and function Adrenal glands FSH + + + T4/T3 Thermogenesis metabolism Thyroid glands + Testosterone Inhibin Lactation Spermatogenesis Secondary sex characteristics Testes + Estradiol Progesterone Inhibin Chondrocytes Linear and organ growth Ovaries Ovulation Secondary sex characteristics IGF-1 FIGURE 390-1 Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary trophic hormones that in turn determine target gland secretion. Peripheral hormones feed back to negatively regulate hypothalamic and pituitary hormones. For abbreviations, see text. decline rapidly within 2 weeks of parturition. If breast-feeding is initi ated, basal PRL levels remain elevated; suckling stimulates transient reflex increases in PRL levels that last for ~30–45 min. Breast suckling activates afferent neural pathways in the hypothalamus that induce PRL release. With time, suckling-induced responses diminish and interfeeding PRL levels return to normal. Action The PRL receptor is a member of the type I cytokine recep tor family that also includes GH and interleukin (IL) 6 receptors. Ligand binding induces receptor dimerization and intracellular signal ing by Janus kinase (JAK), which stimulates translocation of the signal transduction and activators of transcription (STAT) family to activate target genes. Mutations of the PRL receptor result in PRL insensitivity, hyperprolactinemia, and oligomenorrhea. When homozygous, PRL receptor mutations cause agalactia, demonstrating that PRL action is necessary for lactation. In the breast, the lobuloalveolar epithelium proliferates in response to PRL, placental lactogens, estrogen, pro gesterone, and local paracrine growth factors, including insulin-like growth factor 1 (IGF-1).

Third ventricle Neuroendocrine cell nuclei Hypothalamus Physiology of Anterior Pituitary Hormones CHAPTER 390 Stalk Superior hypophyseal artery Inferior hypophyseal artery Long portal vessels Trophic hormone secreting cells Posterior pituitary Anterior pituitary Short portal vessel Hormone secretion FIGURE 390-2 Diagram of hypothalamic-pituitary vasculature. The hypothalamic nuclei produce hormones that traverse the portal system and impinge on anterior pituitary cells to regulate pituitary hormone production. Posterior pituitary hormones are derived from direct neural extensions. Liver PRL acts to induce and maintain lactation and to suppress both reproductive function and sexual drive. These functions are geared toward ensuring that maternal lactation is sustained and not inter rupted by pregnancy. PRL inhibits reproductive function by sup pressing hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary gonadotropin secretion and by impairing gonadal steroidogenesis in both women and men. In the ovary, PRL blocks fol liculogenesis and inhibits granulosa cell aromatase activity, leading to hypoestrogenism and anovulation. PRL also has a luteolytic effect, gen erating a shortened, or inadequate, luteal phase of the menstrual cycle. In men, attenuated LH secretion leads to low testosterone levels and decreased spermatogenesis. These hormonal changes decrease libido and reduce fertility in patients with hyperprolactinemia. ■ ■GROWTH HORMONE Synthesis GH is the most abundant anterior pituitary hormone, and GH-secreting somatotrope cells constitute up to 50% of the total anterior pituitary cell population. Mammosomatotrope cells, which coexpress PRL with GH, can be identified by using double immunos taining techniques. Somatotrope development and GH transcription LH mlU/mL GnRH pg/mL GnRH pulses LH pulses FIGURE 390-3 Hypothalamic gonadotropin-releasing hormone (GnRH) pulses induce secretory pulses of luteinizing hormone (LH).

are determined by expression of the cell-specific Pit-1 nuclear tran scription factor. Five distinct genes encode GH and related proteins. The pituitary GH gene (hGH-N) produces two alternatively spliced products that give rise to 22-kDa GH (191 amino acids) and a less abundant 20-kDa GH molecule with similar biologic activity. Placen tal syncytiotrophoblast cells express a GH variant (hGH-V) gene; the related hormone human chorionic somatotropin (HCS) is expressed by distinct members of the gene cluster.

Secretion GH secretion is controlled by complex hypothalamic and peripheral factors. GH-releasing hormone (GHRH) is a 44-amino-acid hypothalamic peptide that stimulates GH synthesis and release. Ghrelin, an octanoylated gastric-derived peptide, and synthetic ago nists of the GHS-R induce GHRH and also directly stimulate GH release. Somatostatin (somatotropin-release inhibiting factor [SRIF]) is synthesized in the medial preoptic area of the hypothalamus and inhibits GH secretion. GHRH is secreted in discrete spikes that elicit GH pulses, whereas SRIF sets basal GH secretory tone. SRIF also is expressed in many extrahypothalamic tissues, including the central nervous system (CNS), gastrointestinal tract, and pancreas, where it also acts to inhibit islet hormone secretion. IGF-1, the peripheral tar get hormone for GH, feeds back to inhibit GH; estrogen induces GH, whereas chronic glucocorticoid excess suppresses GH release, leading to growth delay in children. PART 12 Endocrinology and Metabolism Surface receptors on the somatotrope regulate GH synthesis and secretion. The GHRH receptor is a G protein–coupled receptor (GPCR) that signals through the intracellular cyclic AMP pathway to stimulate somatotrope cell proliferation as well as GH production. Inactivating mutations of the GHRH receptor cause profound growth deficiency (dwarfism). A distinct surface receptor for ghrelin, the gastric-derived GH secretagogue, is expressed in both the hypothalamus and pituitary. Somatostatin binds to five distinct receptor subtypes (SST1 to SST5); SST2 and SST5 subtypes preferentially suppress GH (and TSH) secre tion, while SST5 predominantly suppresses ACTH secretion. GH secretion is pulsatile, with highest peak levels occurring at night, generally correlating with sleep onset. GH secretory rates decline markedly with age so that hormone levels in middle age are ~15% of pubertal levels. These changes are paralleled by an age-related decline in lean muscle mass. GH secretion is also reduced in obese individuals, although IGF-1 levels may not be suppressed, suggesting a change in the setpoint for feedback control. Elevated GH levels occur within an hour of deep sleep onset as well as after exercise, physical stress, and trauma and during sepsis. Integrated 24-h GH secretion is higher in women and is also enhanced by estrogen replacement, likely reflective of increased peripheral GH resistance. Using standard assays, random GH measurements are undetectable in ~50% of daytime samples obtained from healthy subjects and are also undetectable (<1 μg/L) in most obese and elderly subjects. Thus, single random GH measure ments do not distinguish patients with adult GH deficiency from those with GH levels in the normal range. GH secretion is profoundly influenced by nutritional factors. Using ultrasensitive GH assays with a sensitivity of 0.002 μg/L, a glucose load suppresses GH to <0.7 μg/L in women and to <0.07 μg/L in men. Increased GH pulse frequency and peak amplitudes occur with chronic malnutrition or prolonged fasting. GH is stimulated by oral ghrelin receptor agonists, intravenous l-arginine, dopamine, and apo morphine (a dopamine receptor agonist), as well as by α-adrenergic pathways. β-Adrenergic blockade induces basal GH and enhances GHRH- and insulin-evoked GH release. Action The pattern of GH secretion may affect tissue responses. The higher GH pulsatility observed in men compared with the rela tively continuous basal GH secretion in women may be an important biologic determinant of linear growth patterns and liver enzyme induction. The 70-kDa peripheral GH receptor protein has structural homol ogy with the cytokine/hematopoietic

superfamily. A fragment of the receptor extracellular domain generates a soluble GH binding protein (GHBP) that binds to circulating GH. The liver and cartilage express

the greatest number of GH receptors. GH binding to preformed receptor dimers is followed by internal rotation and subsequent signal ing through the JAK/STAT pathway. Activated STAT proteins translo cate to the nucleus, where they modulate expression of GH-regulated target genes. GH analogues that bind to the receptor but are incapable of mediating receptor signaling are potent antagonists of GH action. A GH receptor antagonist (pegvisomant) is approved for treatment of acromegaly. GH induces protein synthesis and nitrogen retention and also impairs glucose tolerance by antagonizing insulin action. GH also stimulates lipolysis, leading to increased circulating fatty acid levels, reduced omental fat mass, and enhanced lean body mass. GH promotes sodium, potassium, and water retention and elevates serum levels of inorganic phosphate. Linear bone growth occurs as a result of complex hormonal and growth factor actions, including those of IGF-1. GH stimulates epiphyseal prechondrocyte differentiation. These precursor cells produce IGF-1 locally, and their proliferation is also responsive to the growth factor. Insulin-Like Growth Factors Although GH exerts direct effects in target tissues, many of its physiologic effects are mediated indirectly through IGF-1, a potent growth and differentiation factor. The liver is the major source of circulating IGF-1. In peripheral tissues, IGF-1 also exerts local paracrine actions that appear to be both dependent on and independent of GH. Thus, GH administration induces circulating IGF-1 as well as stimulating local IGF-1 production in multiple tissues. Both IGF-1 and IGF-2 are bound to high-affinity circulating IGFbinding proteins (IGFBPs) that regulate IGF availability and bioactiv ity. Levels of IGFBP3 are GH dependent, and it serves as the major carrier protein for circulating IGF-1. GH deficiency and malnutrition usually are associated with low IGFBP3 levels. IGFBP1 and IGFBP2 regulate local tissue IGF action but do not bind appreciable amounts of circulating IGF-1. Serum IGF-1 concentrations are profoundly affected by physi ologic factors. Levels increase during puberty, peak at 16 years, and subsequently decline by >80% during the aging process. IGF-1 con centrations are higher in women than in men. Because GH is the major determinant of hepatic IGF-1 synthesis, abnormalities of GH synthesis or action (including pituitary failure, GHRH receptor defect, GH receptor defect, or pharmacologic GH receptor blockade) lead to reduced IGF-1 levels. Hypocaloric states are associated with GH resistance; IGF-1 levels are therefore low with cachexia, malnutrition, and sepsis. In acromegaly, IGF-1 levels are high and reflect a log-linear relationship with circulating GH concentrations. IGF-1 PHYSIOLOGY Injected IGF-1 (100 µg/kg) induces hypoglyce mia, and lower doses improve insulin sensitivity in patients with severe insulin resistance and diabetes. In cachectic subjects, IGF-1 infusion (12 µg/kg per h) enhances nitrogen retention and lowers cholesterol levels. Longer-term subcutaneous IGF-1 injections enhance protein synthesis and are anabolic. Although bone formation markers are induced, bone turnover also may be stimulated by IGF-1. IGF-1 is approved for use in patients with GH-resistance syndromes. IGF-1 side effects are dose dependent, and overdose may result in hypoglycemia, hypotension, fluid retention, temporomandibular jaw pain, and increased intracranial pressure, all of which are revers ible. Retinal damage and avascular femoral head necrosis have been reported. Chronic excess IGF-1 administration presumably would result in features of acromegaly. ■ ■ADRENOCORTICOTROPIC HORMONE (See also Chap. 398). Synthesis ACTH-secreting corticotrope cells constitute ~20% of the pituitary cell population. ACTH (39 amino acids) is derived from the POMC precursor protein (266 amino acids) that also generates several other peptides, including β-lipotropin, β-endorphin, met-enkephalin, α-melanocyte-stimulating hormone (α-MSH), and corticotropin-like intermediate lobe protein (CLIP). The POMC gene is

potently sup pressed by glucocorticoids and induced by corticotropin-releasing

hormone (CRH), AVP, and proinflammatory cytokines, including IL-6, as well as leukemia inhibitory factor. CRH, a 41-amino-acid hypothalamic peptide synthesized in the paraventricular nucleus as well as in higher brain centers, is the predominant stimulator of ACTH synthesis and release. The CRH receptor is a GPCR that is expressed on the corticotrope and signals to induce POMC transcription. Secretion ACTH secretion is pulsatile and exhibits a characteristic circadian rhythm, peaking at about 6:00 a.m. and reaching a nadir about midnight. Adrenal glucocorticoid secretion, which is driven by ACTH, follows a parallel diurnal pattern. ACTH circadian rhythmicity is determined by variations in secretory pulse amplitude rather than changes in pulse frequency. Superimposed on this endogenous rhythm, ACTH levels are increased by physical and psychological stress, exer cise, acute illness, and insulin-induced hypoglycemia. Glucocorticoid-mediated negative regulation of the hypothalamicpituitary-adrenal (HPA) axis occurs as a consequence of both hypotha lamic CRH suppression and direct attenuation of pituitary POMC gene expression and ACTH release. In contrast, loss of cortisol feedback inhibition, as occurs in primary adrenal failure, results in extremely high ACTH levels. Acute inflammatory or septic insults activate the HPA axis through the integrated actions of proinflammatory cytokines, bacterial toxins, and neural signals. The overlapping cascade of ACTH-inducing cyto kines (tumor necrosis factor [TNF]; IL-1, -2, and -6; and leukemia inhibitory factor) activates hypothalamic CRH and AVP secretion, pituitary POMC gene expression, and local pituitary paracrine cytokine networks. The resulting cortisol elevation restrains the inflammatory response and enables host protection. Concomitantly, cytokine-mediated central glucocorticoid receptor resistance impairs glucocorticoid sup pression of the HPA. Thus, the neuroendocrine stress response reflects the net result of highly integrated hypothalamic, intrapituitary, and peripheral hormone and cytokine signals acting to regulate cortisol secretion. Action The major function of the HPA axis is to maintain meta bolic homeostasis and mediate the neuroendocrine stress response, largely by inducing adrenal cortisol production. ACTH induces adre nocortical steroidogenesis by sustaining adrenal cell proliferation and function. The receptor for ACTH, designated melanocortin-2 receptor, is a GPCR that induces steroidogenesis by stimulating a cascade of steroidogenic enzymes (Chap. 398). ■ ■GONADOTROPINS: FSH AND LH Synthesis and Secretion Gonadotrope cells constitute ~10% of anterior pituitary cells and produce two gonadotropin hormones—LH and FSH. Like TSH and human chorionic gonadotropin, LH and FSH are glycoprotein hormones that contain α and β subunits. The α subunit is common to these glycoprotein hormones; specificity of hormone function is conferred by the β subunits, which are expressed by separate genes. Gonadotropin synthesis and release are dynamically regulated. This is particularly true in women, in whom rapidly fluctuating gonadal steroid levels vary throughout the menstrual cycle. Hypo thalamic GnRH, a 10-amino-acid peptide, regulates the synthesis and secretion of both LH and FSH. Brain kisspeptin, a product of the KISS1 gene, regulates hypothalamic GnRH release. GnRH is secreted in discrete pulses every 60–120 min, and the pulses in turn elicit LH and FSH pulses (Fig. 390-3). The pulsatile mode of GnRH input is essen tial to its action; pulses prime gonadotrope responsiveness, whereas continuous GnRH exposure induces desensitization. Based on this phenomenon, long-acting GnRH agonists are used to suppress gonad otropin levels in children with precocious puberty and in men with prostate cancer (Chap. 92) and are used in some ovulation-induction protocols to reduce levels of endogenous gonadotropins (Chap. 404). Estrogens act at both the hypothalamus and the pituitary to modulate gonadotropin secretion. Chronic estrogen exposure is inhibitory,

whereas rising estrogen levels, as occur during the preovulatory surge, exert positive feedback to enhance pituitary responsiveness and to increase gonadotropin pulse frequency and amplitude. Progesterone slows GnRH pulse frequency but enhances gonadotropin responses to GnRH. Testosterone feedback in men also occurs at the hypotha lamic and pituitary levels and is mediated in part by its conversion to estrogens.

Although GnRH is the main regulator of LH and FSH secretion, FSH synthesis is also under distinct control by the gonadal peptides inhibin and activin, members of the transforming growth factor β (TGF-β) family. Inhibin selectively suppresses FSH, whereas activin stimulates FSH synthesis (Chap. 404). Physiology of Anterior Pituitary Hormones CHAPTER 390 Action The gonadotropin hormones interact with their respective GPCRs expressed in the ovary and testis, evoking germ cell develop ment and maturation and steroid hormone biosynthesis. In women, FSH regulates ovarian follicle development and stimulates ovarian estrogen production. LH mediates ovulation and maintenance of the corpus luteum. In men, LH induces Leydig cell testosterone synthesis and secretion, and FSH stimulates seminiferous tubule development and regulates spermatogenesis. ■ ■THYROID-STIMULATING HORMONE Synthesis and Secretion TSH-secreting thyrotrope cells consti tute 5% of the anterior pituitary cell population. TSH shares a common α subunit with LH and FSH but contains a specific TSH β subunit. TRH is a hypothalamic tripeptide (pyroglutamyl histidylprolinamide) that acts through a pituitary GPCR to stimulate TSH synthesis and secretion; it also stimulates the lactotrope cell to secrete PRL. TSH secretion is stimulated by TRH, whereas thyroid hormones, dopamine, somatostatin, and glucocorticoids suppress TSH by overriding TRH induction. Thyroid hormones are the predominant negative regulator of TSH production. Thyrotrope cell proliferation and TSH secretion are both induced when negative feedback inhibition by thyroid hormones is removed. Thus, thyroid damage (including surgical thyroidectomy), radia tion-induced hypothyroidism, chronic thyroiditis, and prolonged goitrogen exposure are associated with increased TSH levels. Longstanding untreated hypothyroidism can lead to elevated TSH levels, which may be associated with thyrotrope hyperplasia and pituitary enlargement and may sometimes be evident on magnetic resonance imaging. Action TSH is secreted in pulses, although the excursions are modest in comparison to other pituitary hormones because of the low amplitude of the pulses and the relatively long half-life of TSH. Consequently, single determinations of TSH suffice to precisely assess its circulating levels. TSH binds to a GPCR on thyroid follicular cells to stimulate thyroid hormone synthesis and release (Chap. 394). ■ ■FURTHER READING Bernard V et al: Prolactin: A pleiotropic factor in health and disease. Nat Rev Endocrinol 15:356, 2019. Das N, Kumar TR: Molecular regulation of follicle-stimulating hor mone synthesis, secretion and action. J Mol Endocrinol 60:R131, 2018. Langlais D et al: Adult pituitary cell maintenance: Lineage-specific contribution of self-duplication. Mol Endocrinol 27:1103, 2013. Le Tissier P et al: The process of anterior pituitary hormone pulse generation. Endocrinology 159:3524, 2018. Ho KY et al: The physiology of growth hormone (GH) in adults: Translational journey to GH replacement therapy. J Endocrinol 257:e220197, 2023. Ranke MB, Wit JM: Growth hormone: Past, present and future. Nat Rev Endocrinol 14:285, 2018. Zhang S et al: Single-cell transcriptomics identifies divergent develop mental lineage trajectories during human pituitary development. Nat Commun 11:5275, 2020.

Revision #1
Created 2026-01-06 16:35:09 UTC by Omar Ayman
Updated 2026-01-06 16:35:09 UTC by Omar Ayman