CHAPTER 32

The Hypothalamus and the Pituitary Gland

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CHAPTER OUTLINE

- HYPOTHALAMIC-PITUITARY AXIS
- HORMONES OF THE POSTERIOR PITUITARY
- HORMONES OF THE ANTERIOR PITUITARY

KEY CONCEPTS

1. The hypothalamic-pituitary axis is composed of the hypothalamus, infundibular stalk, posterior pituitary, and anterior pituitary
2. Arginine vasopressin (AVP) and oxytocin are synthesized in hypothalamic neurons whose axons terminate in the posterior pituitary.
3. AVP increases water reabsorption by the kidneys in response to a rise in blood osmolality or a fall in blood volume.
4. Oxytocin stimulates milk letdown in the breast in response to suckling and muscle contraction in the uterus in response to cervical dilation during labor.
5. The hormones ACTH, TSH, GH, FSH, LH, and PRL are synthesized in the anterior pituitary and secreted in response to hypothalamic releasing hormones carried in the hypophyseal portal circulation.
6. Hypothalamic CRH stimulates ACTH release from corticotrophs, which, in turn, stimulates glucocorticoid release from the adrenal cortex, to comprise the hypothalamic-pituitary-adrenal axis.
7. ACTH secretion is regulated by glucocorticoids, physical and emotional stress, AVP, and the sleep-wake cycle.
8. Hypothalamic TRH stimulates TSH release from thyrotrophs, which, in turn, stimulates T_3 and T_4 release from the thyroid follicles, to comprise the hypothalamic-pituitary-thyroid axis.
9. TSH secretion is regulated by the thyroid hormones, cold temperatures, and the sleep-wake cycle.
10. Hypothalamic GHRH increases and hypothalamic SRIF decreases GH secretion from somatotrophs.
11. GH secretion is regulated by the GH, IGF-I, aging, deep sleep, stress, exercise, and hypoglycemia.
12. LHRH stimulates the secretion of FSH and LH from the anterior pituitary. These hormones, in turn, affect functions of the ovaries and testes.
13. Dopamine inhibits the secretion of prolactin.

The pituitary gland is a complex endocrine organ that secretes an array of peptide hormones that have important actions on almost every aspect of body function. Some pituitary hormones influence key cellular processes involved in preserving the volume and composition of body fluids. Others bring about changes in body function, which enable the individual to grow, reproduce, and respond appropriately to stress and trauma. The pituitary hormones produce these physiological effects by either acting directly on their target cells or stimulating other endocrine glands to secrete hormones, which, in turn, bring about changes in body function.

Stimuli that affect the secretion of pituitary hormones may originate within or outside the body. These stimuli are perceived and processed by the brain, which signals the pituitary gland to increase or decrease the rate of secretion of a particular hormone. Thus, the brain links the pituitary gland to events occurring within or outside the body, which call for changes in pituitary hormone secretion. This important functional connection between the brain and the pituitary, in which the hypothalamus plays a central role, is called the **hypothalamic-pituitary axis**.

HYPOTHALAMIC-PITUITARY AXIS

The human pituitary is composed of two morphologically and functionally distinct glands connected to the hypothalamus. The **pituitary gland** or **hypophysis** is located at the base of the brain and is connected to the hypothalamus by a stalk. It sits in a depression in the sphenoid bone of the skull called the **sella turcica**. The two morphologically and functionally distinct glands comprising the human pituitary are the adenohypophysis and the neurohypophysis (Fig. 32.1). The **adenohypophysis** consists of the **pars tuberalis**, which forms the outer covering of the pituitary

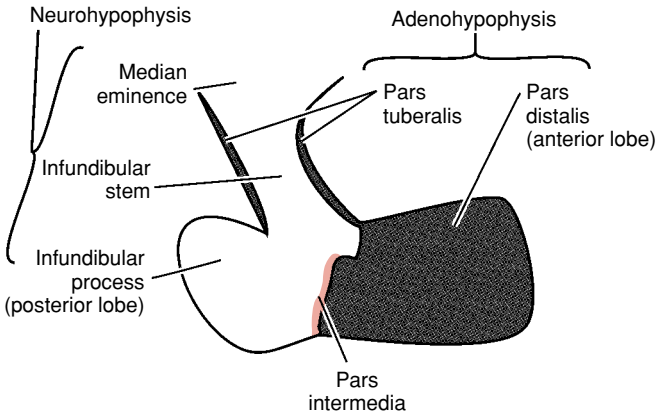

FIGURE 32.1 **A midsagittal section of the human pituitary gland.**

stalk, and the **pars distalis** or **anterior lobe**. The **neurohypophysis** is composed of the **median eminence** of the hypothalamus, the **infundibular stem**, which forms the inner part of the stalk, and the **infundibular process** or **posterior lobe**. In most vertebrates, the pituitary contains a third anatomically distinct lobe, the **pars intermedia** or **intermediate lobe**. In adult humans, only a vestige of the intermediate lobe is found as a thin diffuse region of cells between the anterior and posterior lobes.

The adenohypophysis and neurohypophysis have different embryological origins. The adenohypophysis is formed from an evagination of the oral ectoderm called **Rathke's pouch**. The neurohypophysis forms as an extension of the developing hypothalamus, which fuses with Rathke's pouch as development proceeds. The posterior lobe is, therefore, composed of neural tissue and is a functional part of the hypothalamus.

Posterior Pituitary Hormones Are Synthesized by Hypothalamic Neurons Whose Axons Terminate in the Posterior Lobe

The infundibular stem of the pituitary gland contains bundles of nonmyelinated nerve fibers, which terminate on the capillary bed in the posterior lobe. These fibers are the axons of neurons that originate in the **supraoptic nuclei** and **paraventricular nuclei** of the hypothalamus. The cell bodies of these neurons are large compared to those of other hypothalamic neurons; hence, they are called **magnocellular neurons**. The hormones arginine vasopressin (AVP) and oxytocin are synthesized as parts of larger precursor proteins (prohormones) in the cell bodies of these neurons. Prohormones are then packaged into granules and enzymatically processed to produce AVP and oxytocin. The granules are transported down the axons by axoplasmic flow; they accumulate at the axon terminals in the posterior lobe.

Stimuli for the secretion of posterior lobe hormones may be generated by events occurring within or outside the body. These stimuli are processed by the central nervous system (CNS), and the signal for the secretion of AVP or oxytocin is then transmitted to neurosecretory neurons in the hypothalamus. Secretory granules containing the hormone are then released into the nearby capillary circulation, from which they are carried into the systemic circulation.

Anterior Pituitary Hormones Are Synthesized and Secreted in Response to Hypothalamic Releasing Hormones Carried in the Hypophyseal Portal Circulation

The anterior lobe contains clusters of histologically distinct types of cells closely associated with blood sinusoids that drain into the venous circulation. These cells produce anterior pituitary hormones and secrete them into the blood sinusoids. The six well-known anterior pituitary hormones are produced by separate kinds of cells. **Adrenocorticotropic hormone** (ACTH), also known as **corticotropin**, is secreted by **corticotrophs**, **thyroid-stimulating hormone** (TSH) by **thyrotrophs**, **growth hormone** (GH) by **somatotrophs**, **prolactin** (PRL) by **lactotrophs**, and **follicle-stimulating hormone** (FSH) and **luteinizing hormone** (LH) by **gonadotrophs**.

The cells that produce anterior pituitary hormones are not innervated and, therefore, are not under direct neural control. Rather, their secretory activity is regulated by **releasing hormones**, also called **hypophysiotropic hormones**, synthesized by neural cell bodies in the hypothalamus. Granules containing releasing hormones are stored in the axon terminals of these neurons, located in capillary networks in the median eminence of the hypothalamus and lower infundibular stem. These capillary networks give rise to the principal blood supply to the anterior lobe of the pituitary.

The blood supply to the anterior pituitary is shown in Figure 32.2. Arterial blood is brought to the hypothalamic-pituitary region by the superior and inferior hypophyseal arteries. The **superior hypophyseal arteries** give rise to a rich capillary network in the median eminence. The capillaries converge into long veins that run down the pituitary stalk and empty into the blood sinusoids in the anterior lobe. They are considered to be portal veins because they deliver blood to the anterior pituitary rather than joining the venous circulation that carries blood back to the heart; therefore, they are called **long hypophyseal portal vessels**. The **inferior hypophyseal arteries** provide arterial blood to the posterior lobe. They also penetrate into the lower infundibular stem, where they form another important capillary network. The capillaries of this network converge into **short hypophyseal portal vessels**, which also deliver blood into the sinusoids of the anterior pituitary. The special blood supply to the anterior lobe of the pituitary gland is known as the **hypophyseal portal circulation**.

When a neurosecretory neuron is stimulated to secrete, the releasing hormone is discharged into the hypophyseal portal circulation (see Fig. 32.2). Releasing hormones travel only a short distance before they come in contact with their target cells in the anterior lobe. Only the amount of releasing hormone needed to control anterior pituitary hormone secretion is delivered to the hypophyseal portal circulation by neurosecretory neurons. Consequently, releasing hormones are almost undetectable in systemic blood.

A releasing hormone either stimulates or inhibits the synthesis and secretion of a particular anterior pituitary

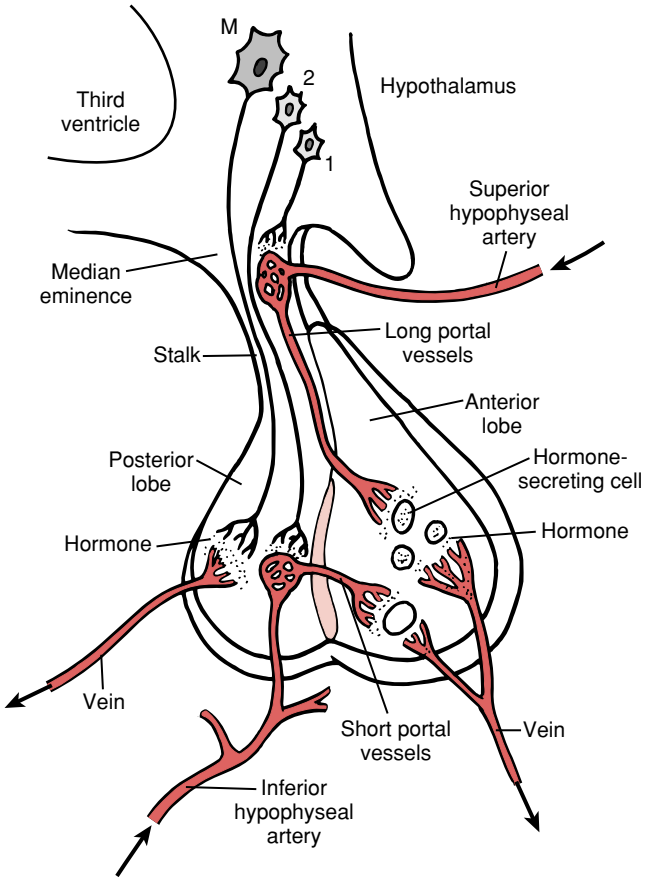

FIGURE 32.2 The blood supply to the anterior pituitary. This illustration shows the relationship of the hypothalamic magnocellular neurons and hypothalamic neurosecretory cells that produce releasing hormones to the pituitary blood vessels. M represents a magnocellular neuron releasing AVP or oxytocin at its axon terminals into capillaries that give rise to the venous drainage of the posterior lobe. Neurons 1 and 2 are secreting releasing factors into capillary networks that give rise to the long and short hypophyseal portal vessels, respectively. Releasing hormones are shown reaching the hormone-secreting cells of the anterior lobe via the portal vessels.

hormone. **Corticotropin-releasing hormone** (CRH), **thyrotropin-releasing hormone** (TRH), and **growth hormone-releasing hormone** (GHRH) stimulate the secretion and synthesis of ACTH, TSH, and GH, respectively (Table 32.1). **Luteinizing hormone-releasing hormone** (LHRH), also known as **gonadotropin-releasing hormone** (GnRH), stimulates the synthesis and release of FSH and LH. In contrast, **somatostatin**, also called **somatotropin release inhibiting factor** (SRIF), inhibits GH secretion. All of the releasing hormones are peptides, with the exception of **dopamine**, which is a catecholamine that inhibits the synthesis and secretion of PRL. Releasing hormones can be produced synthetically, and several are currently under study for use in the diagnosis and treatment of diseases of the endocrine system. For example, synthetic GnRH is now used for treating infertility in women.

Releasing hormones are secreted in response to neural inputs from other areas of the CNS. These signals are generated by external events that affect the body or by changes occurring within the body itself. For example, sensory nerve excitation, emotional or physical stress, biological rhythms, changes in sleep patterns or in the sleep-wake cycle, and changes in circulating levels of certain hormones or metabolites all affect the secretion of particular anterior pituitary hormones. Signals generated in the CNS by such events are transmitted to the neurosecretory neurons in the hypothalamus. Depending on the nature of the event and the signal generated, the secretion of a particular releasing hormone may be either stimulated or inhibited. In turn, this response affects the rate of secretion of the appropriate anterior pituitary hormone. The neural pathways involved in transmitting these signals to the neurosecretory neurons in the hypothalamus are not well defined.

HORMONES OF THE POSTERIOR PITUITARY

Arginine vasopressin (AVP), also known as ADH, antidiuretic hormone, and **oxytocin** are produced by magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Individual neurons make either AVP or

TABLE 32.1 Hypothalamic Releasing Hormones

Hormone	Chemistry	Actions on Anterior Pituitary
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates ACTH secretion by corticotrophs; stimulates expression of POMC gene in corticotrophs
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates TSH secretion by thyrotrophs; stimulates expression of genes for α and β subunits of TSH in thyrotrophs; stimulates PRL synthesis by lactotrophs
Growth hormone-releasing hormone (GHRH)	Two forms in human: single chain of 44 amino acids, single chain of 40 amino acids	Stimulates GH secretion by somatotrophs; stimulates expression of GH gene in somatotrophs
Luteinizing hormone-releasing hormone (LHRH), gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates FSH and LH secretion by gonadotrophs
Somatostatin, somatotropin release inhibiting factor (SRIF)	Single chain of 14 amino acids	Inhibits GH secretion by somatotrophs; inhibits TSH secretion by thyrotrophs
Dopamine	Catecholamine	Inhibits PRL synthesis and secretion by lactotrophs

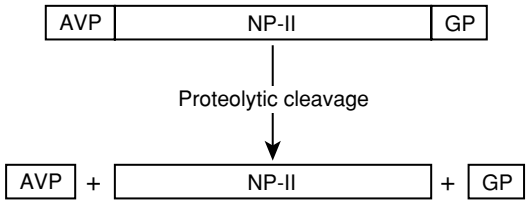

FIGURE 32.3 **The structural organization and proteolytic processing of AVP from its prohormone.**
AVP, arginine vasopressin; NP-II, neurophysin II; GP, glycoprotein.

oxytocin, but not both. The axons of these neurons form the infundibular stem and terminate on the capillary network in the posterior lobe, where they discharge AVP and oxytocin into the systemic circulation.

AVP and oxytocin are closely related small peptides, each consisting of nine amino acid residues. Two forms of vasopressin, one containing arginine and the other containing lysine, are made by different mammals. Arginine vasopressin is made in humans. Although AVP and oxytocin differ by only two amino acid residues, the structural differences are sufficient to give these two molecules very different hormonal activities. They are similar enough, however, for AVP to have slight oxytocic activity and for oxytocin to have slight antidiuretic activity.

The genes for AVP and oxytocin are located near one another on chromosome 20. They code for much larger prohormones that contain the amino acid sequences for AVP or oxytocin and for a 93-amino acid peptide called **neurophysin** (Fig. 32.3). The neurophysin coded by the AVP gene has a slightly different structure than that coded by the oxytocin gene. Neurophysin is important in the processing and secretion of AVP, and mutations in the neurophysin portion of the AVP gene are associated with **central diabetes insipidus**, a condition in which AVP secretion is impaired. Prohormones for AVP and oxytocin are synthesized in the cell bodies of magnocellular neurons and transported in secretory granules to axon terminals in the posterior lobe, as described earlier. During the passage of the granules from the Golgi apparatus to axon terminals, prohormones are cleaved by proteolytic enzymes to produce AVP or oxytocin and their associated neurophysins.

When magnocellular neurons receive neural signals for AVP or oxytocin secretion, action potentials are generated in these cells, triggering the release of AVP or oxytocin and neurophysin from the axon terminals. These substances diffuse into nearby capillaries and then enter the systemic circulation.

AVP Increases the Reabsorption of Water by the Kidneys

Two physiological signals, a rise in the osmolality of the blood and a decrease in blood volume, generate the CNS stimulus for AVP secretion. Chemical mediators of AVP release include catecholamines, angiotensin II, and atrial natriuretic peptide (ANP). The main physiological action of AVP is to increase water reabsorption by the collecting ducts of the kidneys. The result is decreased water excretion and the formation of osmotically concentrated urine (see Chapter 23). This action of AVP works to counteract the conditions that stimulate its secretion. For example, reducing water loss in the urine limits a further rise in the osmolality of the blood and conserves blood volume. Low blood AVP levels lead to diabetes insipidus and the excessive production of dilute urine (see Chapter 24).

Oxytocin Stimulates the Contraction of Smooth Muscle in the Mammary Glands and Uterus

Two physiological signals stimulate the secretion of oxytocin by hypothalamic magnocellular neurons. Breast-feeding stimulates sensory nerves in the nipple. Afferent nerve impulses enter the CNS and eventually stimulate oxytocin-secreting magnocellular neurons. These neurons fire in synchrony and release a bolus of oxytocin into the bloodstream. Oxytocin stimulates the contraction of **myoepithelial cells**, which surround the milk-laden alveoli in the lactating mammary gland, aiding in milk ejection.

Oxytocin secretion is also stimulated by neural input from the female reproductive tract during childbirth. Cervical dilation before the beginning of labor stimulates stretch receptors in the cervix. Afferent nerve impulses pass through the CNS to oxytocin-secreting neurons. Oxytocin release stimulates the contraction of smooth muscle cells in the uterus during labor, aiding in the delivery of the newborn and placenta. The actions of oxytocin on the mammary glands and the female reproductive tract are discussed further in Chapter 39.

HORMONES OF THE ANTERIOR PITUITARY

The anterior pituitary secretes six protein hormones, all of which are small, ranging in molecular size from 4.5 to 29 kDa. Their chemical and physiological features are given in Table 32.2.

Four of the anterior pituitary hormones have effects on the morphology and secretory activity of other endocrine glands; they are called *tropic* (Greek meaning "to turn to") or *trophic* ("to nourish") hormones. For example, ACTH maintains the size of certain cells in the adrenal cortex and stimulates these cells to synthesize and secrete **glucocorticoids**, the hormones **cortisol** and **corticosterone**. Similarly, TSH maintains the size of the cells of the thyroid follicles and stimulates these cells to produce and secrete the thyroid hormones **thyroxine** (T_4) and **triiodothyronine** (T_3). The two other tropic hormones, FSH and LH, are called **gonadotropins** because both act on the ovaries and testes. FSH stimulates the development of follicles in the ovaries and regulates the process of **spermatogenesis** in the testes. LH causes **ovulation** and **luteinization** of the ovulated **graafian follicle** in the ovary of the human female and stimulates the production of the female sex hormones **estrogen** and **progesterone** by the ovary. In the male, LH stimulates the **Leydig cells** of the testis to produce and secrete the male sex hormone, **testosterone**.

The two remaining anterior pituitary hormones, GH and PRL, are not usually thought of as tropic hormones because their main target organs are not human endocrine

TABLE 32.2 Hormones of the Anterior Pituitary

Hormone	Chemistry	Physiological Actions
Adrenocorticotropic hormone (ACTH, corticotropin)	Single chain of 39 amino acids 4.5 kDa	Stimulates production of glucocorticoids and androgens by adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyroid-stimulating hormone (TSH, thyrotropin)	Glycoprotein having two subunits, α and β; 28 kDa	Stimulates production of thyroid hormones, T_4 and T_3, by thyroid follicular cells; maintains size of follicular cells
Growth hormone (GH, somatotropin)	Single chain of 191 amino acids; 22 kDa	Stimulates postnatal body growth; stimulates triglyceride lipolysis; inhibits insulin action on carbohydrate and lipid metabolism
Follicle-stimulating hormone (FSH)	Glycoprotein having two subunits, α and β; 28–29 kDa	Stimulates development of ovarian follicles; regulates spermatogenesis in testes
Luteinizing hormone (LH)	Glycoprotein having two subunits, α and β; 28–29 kDa	Causes ovulation and formation of corpus luteum in ovaries; stimulates production of estrogen and progesterone by ovaries; stimulates testosterone production by testes
Prolactin (PRL)	Single chain of 199 amino acids	Essential for milk production by lactating mammary glands

glands. As discussed later, however, these two hormones have certain effects that can be regarded as "tropic." The main physiological action of GH is its stimulatory effect on the growth of the body during childhood. In humans, PRL is essential for the synthesis of milk by the mammary glands during **lactation**.

The following discussion focuses on ACTH, TSH, and GH. Regulation of the secretion of the gonadotropins and PRL, and descriptions of their actions, are given in greater detail in Chapters 37 to 39.

ACTH Regulates the Function of the Adrenal Cortex

The adrenal cortex produces the glucocorticoid hormones, cortisol and corticosterone, in the cells of its two inner zones, the **zona fasciculata** and the **zona reticularis**. These cells also synthesize **androgens** or male sex hormones, with the main androgen being **dehydroepiandrosterone**.

Glucocorticoids act on many processes, mainly by altering gene transcription and, thereby, changing the protein composition of their target cells. Glucocorticoids permit metabolic adaptations during fasting, which prevent the development of **hypoglycemia** or low blood glucose level. They also play an essential role in the body's response to physical and emotional stress. Other actions of glucocorticoids include their inhibitory effect on inflammation, their ability to suppress the immune system, and their regulation of vascular responsiveness to norepinephrine.

Aldosterone, the other physiologically important hormone made by the adrenal cortex, is produced by the cells of the outer zone of the cortex, the **zona glomerulosa**. It acts to stimulate sodium reabsorption by the kidneys.

Adrenocorticotropic hormone (ACTH) is the physiological regulator of the synthesis and secretion of glucocorticoids by the zona fasciculata and zona reticularis. ACTH stimulates the synthesis of these steroid hormones and promotes the expression of the genes for various enzymes involved in steroidogenesis. It also maintains the size and functional integrity of the cells of the zona fasciculata and zona reticularis. ACTH is not an important regulator of aldosterone synthesis and secretion.

The actions of ACTH on glucocorticoid synthesis and secretion and details about the physiological effects of glucocorticoids are described in Chapter 34.

The Structure and Synthesis of ACTH. ACTH, the smallest of the six anterior pituitary hormones, consists of a single chain of 39 amino acids and has a molecular size of 4.5 kDa. ACTH is synthesized in corticotrophs as part of a larger 30-kDa prohormone called **proopiomelanocortin** (POMC). Enzymatic cleavage of POMC in the anterior pituitary results in ACTH, an amino terminal protein, and **β-lipotropin** (Fig. 32.4). β-Lipotropin has effects on lipid metabolism, but its physiological function in humans has not been estab-

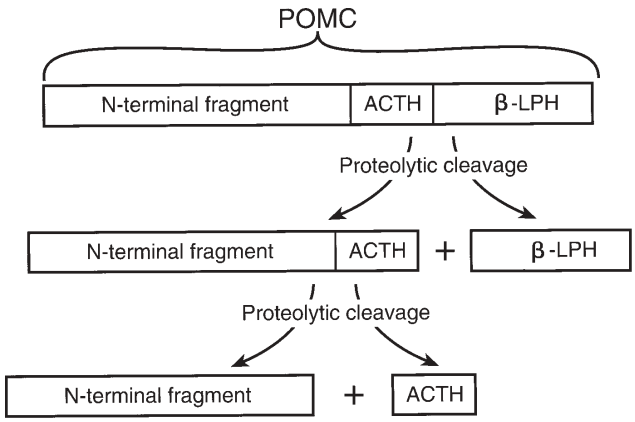

FIGURE 32.4 The proteolytic processing of proopiomelanocortin (POMC) by the human corticotroph. β-LPH, β-lipotropin.

lished. Although POMC can be cleaved into other peptides, such as β-endorphin, only ACTH and β-lipotropin are produced from POMC in the human corticotroph. Proteolytic processing of POMC occurs after it is packaged into secretory granules. Therefore, when the corticotroph receives a signal to secrete, ACTH and β-lipotropin are released into the bloodstream in a 1:1 molar ratio.

POMC is also synthesized by cells of the intermediate lobe of the pituitary gland and neurons in the hypothalamus. In the intermediate lobe, the ACTH sequence of POMC is cleaved to release a small peptide, **α-melanocyte-stimulating hormone** (α-MSH), and, therefore, very little ACTH is produced. α-MSH acts in lower vertebrates to produce temporary changes in skin color by causing the dispersion of melanin granules in pigment cells. As noted earlier, the adult human has only a vestigial intermediate lobe and does not produce and secrete significant amounts of α-MSH or other hormones derived from POMC. However, because ACTH contains the α-MSH amino acid sequence at its N-terminal end, it has melanocyte-stimulating activity when present in the blood at high concentrations. Humans who have high blood levels of ACTH, as a result of **Addison's disease** or an ACTH-secreting tumor are often hyperpigmented. In the hypothalamus, α-MSH is important in the regulation of feeding behavior.

CRH and ACTH Synthesis and Secretion. Corticotropin-releasing hormone is the main physiological regulator of ACTH secretion and synthesis. In humans, CRH consists of 41 amino acid residues in a single peptide chain.

CRH is synthesized in the paraventricular nuclei of the hypothalamus by a group of neurons with small cell bodies, called **parvicellular neurons**. The axons of parvicellular neurons terminate on capillary networks that give rise to hypophyseal portal vessels. Secretory granules containing CRH are stored in the axon terminals of these cells. Upon receiving the appropriate stimulus, these cells secrete CRH into the capillary network; CRH enters the hypophyseal portal circulation and is delivered to the anterior pituitary gland.

CRH binds to receptors on the plasma membranes of corticotrophs. These receptors are coupled to adenylyl cyclase by stimulatory G proteins. The binding of CRH to its receptor increases the activity of adenylyl cyclase, which catalyzes the formation of cAMP from ATP (Fig. 32.5). The rise in cAMP concentration in the corticotroph activates protein kinase A (PKA), which then phosphorylates cell proteins. PKA-mediated protein phosphorylation stimulates the corticotroph to secrete ACTH and β-lipotropin by unknown mechanisms.

Increased cAMP production in the corticotroph by CRH also stimulates expression of the gene for POMC, increasing the level of POMC mRNA in these cells (see Fig. 32.5). Thus, CRH not only stimulates ACTH secretion but also maintains the capacity of the corticotroph to synthesize the precursor for ACTH.

Glucocorticoids and ACTH Synthesis and Secretion. A rise in glucocorticoid concentration in the blood resulting from the action of ACTH on the adrenal cortex inhibits the secretion of ACTH. Thus, glucocorticoids have a negative-feedback effect on ACTH secretion, which, in turn, reduces the rate of secretion of glucocorticoids by the adrenal cortex. If the blood glucocorticoid level begins to fall for some reason, this negative-feedback effect is reduced, stimulating ACTH secretion and restoring the blood glucocorticoid level. This interactive relationship is called the **hypothalamic-pituitary-adrenal axis** (Fig. 32.6). This control loop ensures that the level of glucocorticoids in the blood remains relatively stable in the resting state, although there is a diurnal variation in glucocorticoid secretion. As discussed later, physical and emotional stress can alter the mechanism regulating glucocorticoid secretion.

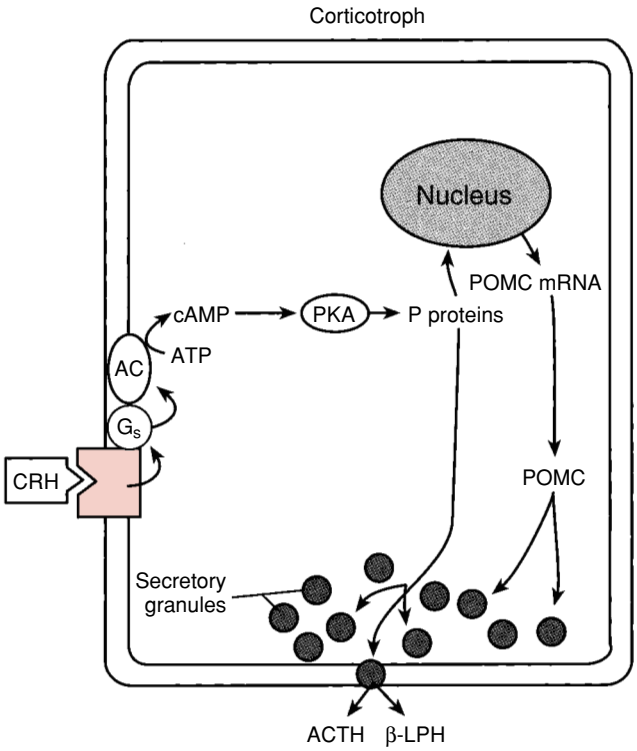

FIGURE 32.5 The main actions of corticotropin-releasing hormone (CRH) on a corticotroph. CRH binds to membrane receptors that are coupled to adenylyl cyclase (AC) by stimulatory G proteins (G_s). Adenylyl cyclase is stimulated, and cAMP rises in the cell. cAMP activates protein kinase A (PKA), which then phosphorylates proteins (P proteins) involved in stimulating ACTH secretion and the expression of the POMC gene.

The negative-feedback effect of glucocorticoids on ACTH secretion results from actions on both the hypothalamus and the corticotroph (see Fig. 32.6). When the concentration of glucocorticoids rises in the blood, CRH secretion from the hypothalamus is inhibited. As a result, the stimulatory effect of CRH on the corticotroph is reduced and the rate of ACTH secretion falls. Glucocorticoids act directly on parvicellular neurons to inhibit CRH release, and indirectly through neurons in the hippocampus that project to the hypothalamus, to affect the activity of parvicellular neurons. At the corticotroph, glucocorticoids inhibit the actions of CRH to stimulate ACTH secretion.

If the blood concentration of glucocorticoids remains high for a long period of time, expression of the gene for POMC is inhibited. As a result, the amount of POMC mRNA falls in the corticotroph, and gradually the produc-

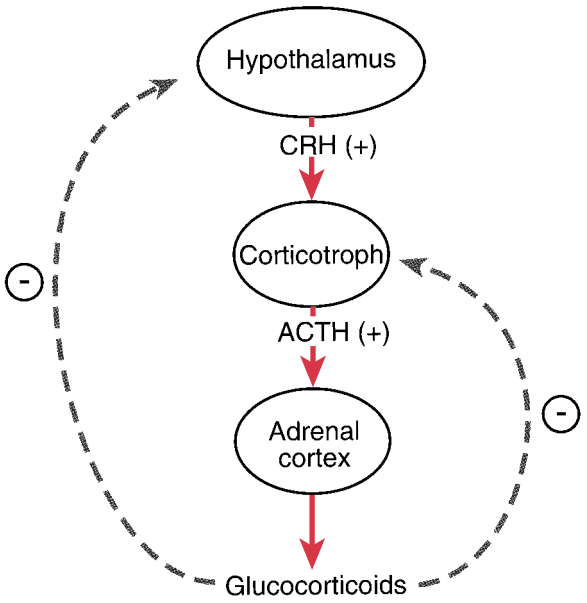

FIGURE 32.6 **The hypothalamic-pituitary-adrenal axis.** The negative-feedback actions of glucocorticoids on the corticotroph and the hypothalamus are indicated by dashed lines.

tion of ACTH and the other POMC peptides declines as well. Since CRH stimulates POMC gene expression and glucocorticoids inhibit CRH secretion, glucocorticoids inhibit POMC gene expression, in part, by suppressing CRH secretion. Glucocorticoids also act directly in the corticotroph itself to suppress POMC gene expression.

The negative-feedback actions of glucocorticoids are essential for the normal operation of the hypothalamic-pituitary-adrenal axis. This relationship is vividly illustrated by the disturbances that occur when blood glucocorticoid levels are changed drastically by disease or glucocorticoid administration. For example, if an individual's adrenal glands have been surgically removed or damaged by disease (e.g., Addison's disease), the resulting lack of glucocorticoids allows corticotrophs to secrete large amounts of ACTH. As noted earlier, this response may result in hyperpigmentation as a result of the melanocyte-stimulating activity of ACTH. Individuals with glucocorticoid deficiency caused by inherited genetic defects affecting enzymes involved in steroid hormone synthesis by the adrenal cortex have high blood ACTH levels from the absence of the lack of the negative-feedback effects of glucocorticoids on ACTH secretion. Because a high blood concentration of ACTH causes hypertrophy of the adrenal glands, these genetic diseases are collectively called **congenital adrenal hyperplasia** (see Chapter 34). By contrast, in individuals treated chronically with large doses of glucocorticoids, the adrenal cortex atrophies because the high level of glucocorticoids in the blood inhibits ACTH secretion, resulting in the loss of its trophic influence on the adrenal cortex.

Stress and ACTH Secretion. The hypothalamic-pituitary-adrenal axis is greatly influenced by stress. When an individual experiences physical or emotional stress, ACTH secretion is increased. As a result, the blood level of glucocorticoids rises rapidly. Regardless of the blood glucocorticoid concentration, stress stimulates the hypothalamic-pituitary-adrenal axis because stress-induced neural activity generated at higher CNS levels stimulates parvicellular neurons in the paraventricular nuclei to secrete CRH at a greater rate. Thus, stress can override the normal operation of the hypothalamic-pituitary-adrenal axis. If the stress persists, the blood glucocorticoid level remains high because the glucocorticoid negative-feedback mechanism functions at a higher set point.

AVP and ACTH Secretion. Glucocorticoid deficiency and certain types of stress also increase the concentration of arginine vasopressin (AVP) in hypophyseal portal blood. The physiological significance is that AVP, like CRH, can stimulate corticotrophs to secrete ACTH. Acting along with CRH, AVP amplifies the stimulatory effect of CRH on ACTH secretion.

AVP interacts with a specific receptor on the plasma membrane of the corticotroph. These receptors are coupled to the enzyme **phospholipase C** (PLC) by G proteins. The interaction of AVP with its receptor activates PLC, which, in turn, hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) present in the plasma membrane. This generates the intracellular second messengers **inositol trisphosphate** (IP_3) and **diacylglycerol** (DAG). IP_3 mobilizes intracellular calcium stores and DAG activates the phospholipid- and calcium-dependent protein kinase C (PKC) to mediate the stimulatory effect of AVP on ACTH secretion.

As noted earlier, AVP and oxytocin are produced by magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. These neurons terminate in the posterior lobe, where they secrete AVP and oxytocin into capillaries that feed into the systemic circulation. However, parvicellular neurons in the paraventricular nuclei also produce AVP, which they secrete into hypophyseal portal blood. It appears that much of the AVP secreted by parvicellular neurons is made in the same cells that produce CRH. It is assumed that the AVP in hypophyseal portal blood comes from these cells and from a small number of AVP-producing magnocellular neurons whose axons pass through the median eminence of the hypothalamus on their way to the posterior lobe.

The Sleep-Wake Cycle and ACTH Secretion. Under normal circumstances, the hypothalamic-pituitary-adrenal axis in humans functions in a pulsatile manner, resulting in several bursts of secretory activity over a 24-hour period. This pattern appears to be due to rhythmic activity in the CNS, which causes bursts of CRH secretion and, in turn, bursts of ACTH and glucocorticoid secretion (Fig. 32.7). A diurnal oscillation in secretory activity of the axis is thought to be due to changes in the sensitivity of CRH-producing neurons to the negative-feedback action of glucocorticoids, altering their rate of CRH secretion. As a result, there is a diurnal oscillation in the rate of ACTH and glucocorticoid secretion. This **circadian rhythm** is reflected in the daily pattern of glucocorticoid secretion. In individuals who are awake during the day and sleep at night, the blood gluco-

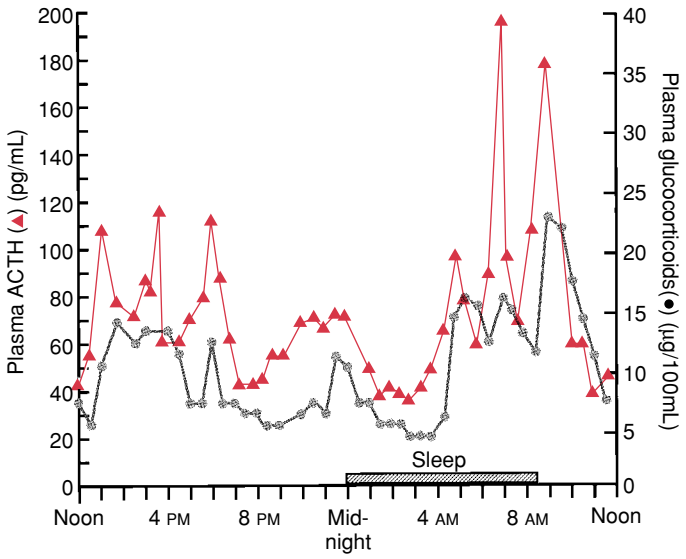

FIGURE 32.7 ACTH secretion and the sleep-wake cycle. Pulsatile changes in the concentrations of ACTH and glucocorticoids in the blood of a young woman over a 24-hour period. Note that the amplitude of the pulses in ACTH and glucocorticoids is lower during the evening hours and increases greatly during the early morning hours. This pattern is due to the diurnal oscillation of the hypothalamic-pituitary-adrenal axis. (Modified from Krieger DT. Rhythms in CRF, ACTH and corticosteroids. In: Krieger DT, ed. Endocrine Rhythms. New York: Raven, 1979.)

corticoid level begins to rise during the early morning hours, reaches a peak sometime before noon, and then falls gradually to a low level around midnight (see Fig. 32.7). This pattern is reversed in individuals who sleep during the day and are awake at night. This inherent biological rhythm is superimposed on the normal operation of the hypothalamic-pituitary-adrenal axis.

TSH Regulates the Function of the Thyroid Gland

The thyroid gland is composed of aggregates of **follicles**, which are formed from a single layer of cells. The follicular cells produce and secrete thyroxine (T_4) and triiodothyronine (T_3), thyroid hormones that are iodinated derivatives of the amino acid tyrosine. The thyroid hormones act on many cells by changing the expression of certain genes, changing the capacity of their target cells to produce particular proteins. These changes are thought to bring about the important actions of the thyroid hormones on the differentiation of the CNS, on body growth, and on the pathways of energy and intermediary metabolism.

Thyroid-stimulating hormone (TSH) is the physiological regulator of T_4 and T_3 synthesis and secretion by the thyroid gland. It also promotes nucleic acid and protein synthesis in the cells of the thyroid follicles, maintaining their size and functional integrity. The actions of TSH on thyroid hormone synthesis and secretion, and the physiological effects of the thyroid hormones, are described in detail in Chapter 33.

The Structure and Synthesis of TSH.

TSH is a glycoprotein consisting of two structurally different subunits. The α **subunit** of human TSH is a single peptide chain of 92 amino acid residues with two carbohydrate chains linked to its structure. The β **subunit** is a single peptide chain of 112 amino acid residues, to which a single carbohydrate chain is linked. The α and β subunits are held together by noncovalent bonds. The two subunits combined give the TSH molecule a molecular weight of about 28,000. Neither subunit has significant TSH activity by itself. The two subunits must be combined in a 1:1 ratio to form an active hormone. The gonadotropins FSH and LH are also composed of two noncovalently combined subunits. The α subunits of TSH, FSH, and LH are derived from the same gene and are identical, but the β subunit gives each hormone its particular set of physiological activities.

Thyrotrophs synthesize the peptide chains of the α and β subunits of TSH from separate mRNA molecules, which are transcribed from two different genes. The peptide chains of the α and β subunits are combined and undergo glycosylation in the rough ER. These processes are completed as TSH molecules pass through the Golgi apparatus and are packaged into secretory granules. Normally, thyrotrophs make more α subunits than β subunits. As a result, secretory granules contain excess α subunits. When a thyrotroph is stimulated to secrete TSH, it releases both TSH and free α subunits into the bloodstream. In contrast, very little free TSH β subunit is in the blood.

TRH and TSH Synthesis and Secretion.

Thyrotropin-releasing hormone (TRH) is the main physiological stimulator of TSH secretion and synthesis by thyrotrophs. TRH is a small peptide consisting of three amino acid residues produced by neurons in the hypothalamus. These neurons terminate on the capillary networks that give rise to the hypophyseal portal vessels. Normally, these neurons secrete TRH into the hypophyseal portal circulation at a constant or tonic rate. It is assumed that the TRH concentration in the blood that perfuses the thyrotrophs does not change greatly; therefore, the thyrotrophs are continuously exposed to TRH.

TRH binds to receptors on the plasma membranes of thyrotrophs. These receptors are coupled to PLC by G proteins (Fig. 32.8). The interaction of TRH with its receptor activates PLC, causing the hydrolysis of PIP_2 in the membrane. This action releases the intracellular messengers IP_3 and DAG. IP_3 causes the concentration of Ca^{2+} in the cytosol to rise, which stimulates the secretion of TSH into the blood.

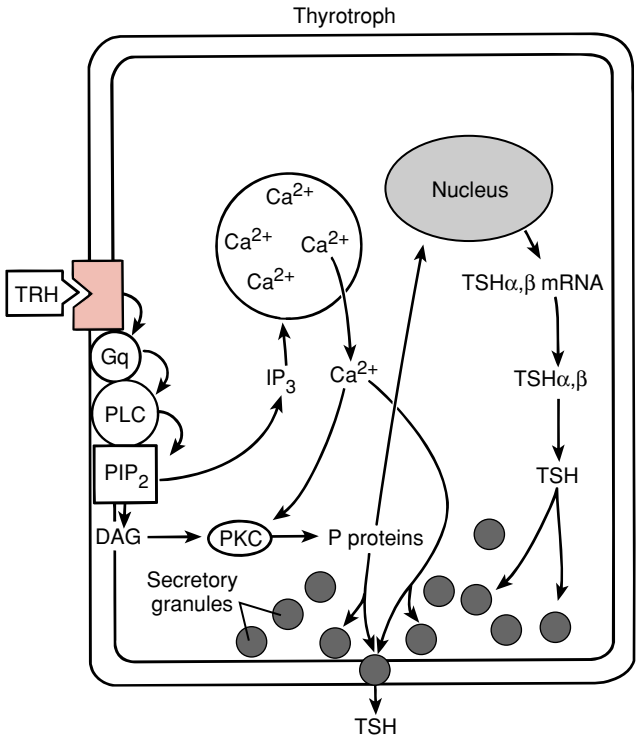

FIGURE 32.8 **The actions of TRH on a thyrotroph.** TRH binds to membrane receptors, which are coupled to phospholipase C (PLC) by G proteins (G_q). PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) in the plasma membrane, generating inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes intracellular stores of Ca^{2+}. The rise in Ca^{2+} stimulates TSH secretion. Ca^{2+} and DAG activate protein kinase C (PKC), which phosphorylates proteins (P proteins) involved in stimulating TSH secretion and the expression of the genes for the α and β subunits of TSH.

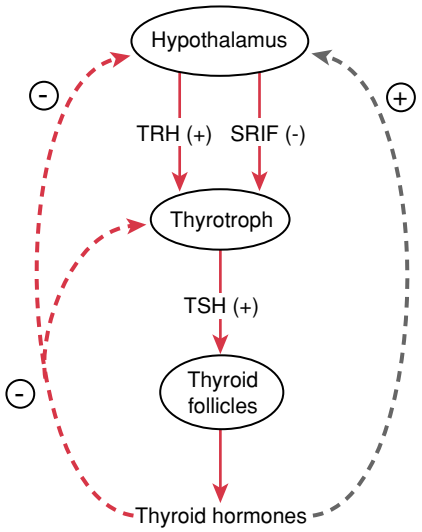

FIGURE 32.9 **The hypothalamic-pituitary-thyroid axis.** TRH stimulates and somatostatin (SRIF) inhibits TSH release by acting directly on the thyrotroph. The negative-feedback loops (-), shown in red, inhibit TRH secretion and action on the thyrotroph, causing a decrease in TSH secretion. The feedback loops (+), shown in gray, stimulate somatostatin secretion, causing a decrease in TRH secretion. SRIF, somatostatin, or somatotropin release inhibiting factor.

The rise in cytosolic Ca^{2+} and the increase in DAG activate PKC in thyrotrophs. PKC phosphorylates proteins that are in some way involved in stimulating TSH secretion.

TRH also stimulates the expression of the genes for the α and β subunits of TSH (see Fig. 32.8). As a result, the amount of mRNA for the α and β subunits is maintained in the thyrotroph and the production of TSH is fairly constant.

Thyroid Hormones and TSH Synthesis and Secretion. The thyroid hormones exert a direct negative-feedback effect on TSH secretion. For example, when the blood concentration of thyroid hormones is high, the rate of TSH secretion falls. In turn, the stimulatory effect of TSH on the follicular cells of the thyroid is reduced, resulting in a decrease in T_4 and T_3 secretion. However, when the circulating levels of T_4 and T_3 are low, their negative-feedback effect on TSH release is reduced and more TSH is secreted from thyrotrophs, increasing the rate of thyroid hormone secretion. This control system is part of the **hypothalamic-pituitary-thyroid axis** (Fig. 32.9).

The thyroid hormones exert negative-feedback effects on both the hypothalamus and the pituitary. In the hypothalamic TRH-secreting neurons, thyroid hormones reduce TRH mRNA and TRH prohormone to decrease TRH release. The thyroid hormones also increase the release of somatostatin from the hypothalamus. Somatostatin (SRIF) inhibits the release of TSH from the thyrotroph (see Fig. 32.9). In the pituitary, thyroid hormones reduce the sensitivity of the thyrotroph to TRH and inhibit TSH synthesis.

The negative-feedback effects of the thyroid hormones on thyrotrophs are produced primarily through the actions of T_3. Both T_4 and T_3 circulate in the blood bound to plasma proteins, with only a small percentage (less than 1%) unbound or free (see Chapter 33). The free T_4 and T_3 molecules are taken up by thyrotrophs, and T_4 is converted to T_3 by the enzymatic removal of one iodine atom. The newly formed T_3 molecules and those taken up directly from the blood enter the nucleus, where they bind to thyroid hormone receptors in the chromatin. The interaction of T_3 with its receptors changes the expression of specific genes in the thyrotroph, which decreases the cell's ability to produce and secrete TSH. For example, T_3 inhibits the expression of the genes for the α and β subunits of TSH, directly decreasing the synthesis of TSH. Also, T_3 influences the expression of other unidentified genes that code for proteins that decrease thyrotroph sensitivity to TRH. The loss in sensitivity is thought to be partly due to a reduction in the number of TRH receptors in thyrotroph plasma membranes.

Other Factors Affecting TSH Secretion. The exposure of certain animals to a cold environment stimulates TSH secretion. This makes sense from a physiological perspective because the thyroid hormones are important in regulating body heat production (see Chapter 33). Brief exposure of experimental animals to a cold environment stimulates the secretion of TSH, presumably a result of enhanced TRH se-

cretion. Newborn humans behave much the same way, in that they respond to brief cold exposure with an increase in TSH secretion. This response to cold does not occur in adult humans.

The hypothalamic-pituitary-thyroid axis, like the hypothalamic-pituitary-adrenal axis, follows a diurnal circadian rhythm in humans. Peak TSH secretion occurs in the early morning and a low point is reached in the evening. Physical and emotional stress can alter TSH secretion but the effects of stress on the hypothalamic-pituitary-thyroid axis are not as pronounced as on the hypothalamic-pituitary-adrenal axis.

GH Regulates Growth During Childhood and Remains Important Throughout Life

As its name implies, growth hormone (GH) promotes the growth of the human body. It does not appear to stimulate fetal growth, nor is it an important growth factor during the first few months after birth. Thereafter, it is essential for the normal rate of body growth during childhood and adolescence.

Growth hormone (also called somatotropin) is secreted by the anterior pituitary throughout life and remains physiologically important even after growth has stopped. In addition to its growth-promoting action, GH has effects on many aspects of carbohydrate, lipid, and protein metabolism. For example, GH is thought to be one of the physiological factors that counteract and, thus, modulate some of the actions of insulin on the liver and peripheral tissues.

The Structure and Synthesis of Human GH.

Human GH is a globular 22 kDa protein consisting of a single chain of 191 amino acid residues with two intrachain disulfide bridges. Human GH has considerable structural similarity to human PRL and placental lactogen.

Growth hormone is produced in somatotrophs of the anterior pituitary. It is synthesized in the rough ER as a larger prohormone consisting of an N-terminal signal peptide and the 191-amino acid hormone. The signal peptide is then cleaved from the prohormone, and the hormone traverses the Golgi apparatus and is packaged in secretory granules.

Hypothalamic growth hormone-releasing hormone (GHRH) regulates the production of GH by stimulating the expression of the GH gene in somatotrophs. Expression of the GH gene is also stimulated by thyroid hormones. As a result, the normal rate of GH production depends on these hormones. For example, a thyroid hormone deficient individual is also GH-deficient. This important action of thyroid hormones is discussed further in Chapter 33.

Regulation of GH Secretion by GHRH and Somatostatin.

The secretion of GH is regulated by two opposing hypothalamic releasing hormones. GHRH stimulates GH secretion and somatostatin inhibits GH secretion by inhibiting the action of GHRH. The rate of GH secretion is determined by the net effect of these counteracting hormones on somatotrophs. When GHRH predominates, GH secretion is stimulated. When somatostatin predominates, GH secretion is inhibited.

Human GHRH is a peptide composed of a single chain of 44 amino acid residues. A slightly smaller version of GHRH consisting of 40 amino acid residues is also present in humans. GHRH is synthesized in the cell bodies of neurons in the **arcuate nuclei** and **ventromedial nuclei** of the hypothalamus. The axons of these cells project to the capillary networks giving rise to the portal vessels. When these neurons receive a stimulus for GHRH secretion, they discharge GHRH from their axon terminals into the hypophyseal portal circulation.

GHRH binds to receptors in the plasma membranes of somatotrophs (Fig. 32.10). These receptors are coupled to adenylyl cyclase by a stimulatory G protein, G_s. The interaction of GHRH with its receptors activates adenylyl cyclase, increasing the concentration of cyclic AMP (cAMP) in the somatotroph. The rise in cAMP activates protein kinase A (PKA), which, in turn, phosphorylates proteins that stimulate GH secretion and GH gene expression. GHRH binding to its receptor also increases intracellular Ca^{2+}, which stimulates GH secretion. In addition, some evidence suggests that GHRH may stimulate PLC, causing the hy-

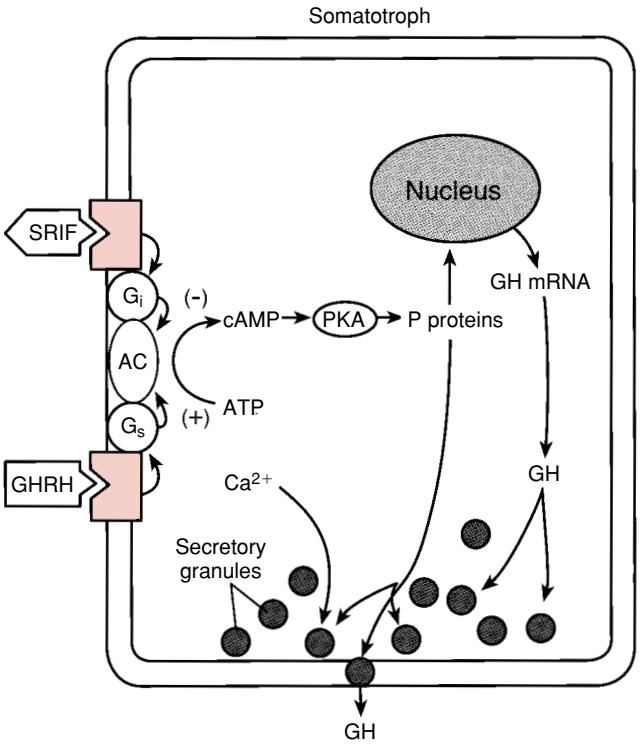

FIGURE 32.10 The actions of GHRH and somatostatin on a somatotroph. GHRH binds to membrane receptors that are coupled to adenylyl cyclase (AC) by stimulatory G proteins (G_s). Cyclic AMP (cAMP) rises in the cell and activates protein kinase A (PKA), which then phosphorylates proteins (P proteins) involved in stimulating GH secretion and the expression of the gene for GH. Ca^{2+} is also involved in the action of GHRH on GH secretion. The possible involvement of the phosphatidylinositol pathway in GHRH action is not shown. Somatostatin (SRIF) binds to membrane receptors that are coupled to adenylyl cyclase by inhibitory G proteins (G_i). This action inhibits the ability of GHRH to stimulate adenylyl cyclase, blocking its action on GH secretion.

drolysis of membrane PIP_2 in the somatotroph. The importance of this phospholipid pathway for the stimulation of GH secretion by GHRH is not established.

Somatostatin is a small peptide consisting of 14 amino acid residues. Although made by neurosecretory neurons in various parts of the hypothalamus, somatostatin neurons are especially abundant in the **anterior periventricular region** (i.e., close to the third ventricle). The axons of these cells terminate on the capillary networks giving rise to the hypophyseal portal circulation, where they release somatostatin into the blood.

Somatostatin binds to receptors in the plasma membranes of somatotrophs. These receptors, like those for GHRH, are also coupled to adenylyl cyclase, but they are coupled by an inhibitory G protein (see Fig. 32.10). The binding of somatostatin to its receptor decreases adenylyl cyclase activity, reducing intracellular cAMP. Somatostatin binding to its receptor also lowers intracellular Ca^{2+}, reducing GH secretion. When the somatroph is exposed to both somatostatin and GHRH, the effects of somatostatin are dominant and intracellular cAMP and Ca^{2+} are reduced. Thus, somatostatin has a negative modulating influence on the action of GHRH.

GH and Insulin-Like Growth Factor I. GH is not considered a traditional trophic hormone; however, it does stimulate the production of a trophic hormone called **insulin-like growth factor I** (IGF-I). IGF-I is a potent **mitogenic agent** that mediates the growth-promoting action of GH. IGF-I was originally called **somatomedin C** or somatotropin-mediating hormone because of its role in promoting growth. Somatomedin C was renamed IGF-I because of its structural similarity to proinsulin.

Insulin-like growth factor II (IGF-II), an additional growth factor induced by GH, is structurally similar to IGF-I and has many of the same metabolic and mitogenic actions. However, IGF-I appears to be the more important mediator of GH action.

IGF-I is a 7.5 kDa protein consisting of a single chain of 70 amino acids. Because of its structural similarity to proinsulin, IGF-I can produce some of the effects of insulin. IGF-I is produced by many cells of the body; however, the liver is the main source of IGF-I in the blood. Most IGF-I in the blood is bound to specific IGF-I-binding proteins; only a small amount circulates in the free form. The bound form of circulating IGF-I has little insulin-like activity, so it does not play a physiological role in the regulation of blood glucose level.

GH increases the expression of the genes for IGF-I in various tissues and organs, such as the liver, and stimulates the production and release of IGF-I. Excessive secretion of GH results in a greater than normal amount of IGF-I in the blood. Individuals with GH deficiency have lower than normal levels of IGF-I, but there is still some present, since the production of IGF-I by cells is regulated by a variety of hormones and factors in addition to GH.

IGF-I has a negative-feedback effect on the secretion of GH (Fig. 32.11). It acts directly on somatotrophs to inhibit the stimulatory action of GHRH on GH secretion. It also inhibits GHRH secretion and stimulates the secretion of somatostatin by neurons in the hypothalamus. The net effect of these actions is the inhibition of GH secretion. By stimulating IGF-I production, GH inhibits its own secretion. This mechanism is analogous to the way ACTH and TSH regulate their own secretion through the respective negative-feedback effects of the glucocorticoid and thyroid hormones. This interactive relationship involving GHRH, somatostatin, GH, and IGF-I comprises the **hypothalamic-pituitary-GH axis**.

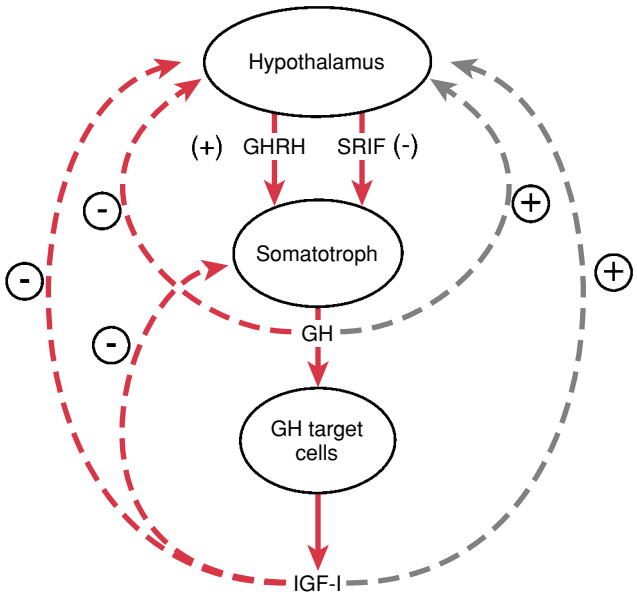

FIGURE 32.11 **The hypothalamic-pituitary-GH axis.** Growth hormone-releasing hormone (GHRH) stimulates, and somatostatin inhibits, GH secretion by acting directly on the somatotroph. The negative-feedback loops (−), shown in red, inhibit GHRH secretion and action on the somatotroph, causing a decrease in GH secretion. The feedback loops (+), shown in gray, stimulate somatostatin secretion, causing a decrease in GH secretion. IGF-I, insulin-like growth factor I.

Feedback Effects of GH on Its Own Secretion. An increase in the blood concentration of GH has direct feedback effects on its own secretion, independent of the production of IGF-I. These effects of GH are due to the inhibition of GHRH secretion and the stimulation of somatostatin secretion by hypothalamic neurons (see Fig. 32.11). GH circulating in the blood can enter the interstitial spaces of the median eminence of the hypothalamus because there is no blood-brain barrier in this area.

Pulsatile Secretion of GH. In humans, GH is secreted in periodic bursts, which produce large but short-lived peaks in GH concentration in the blood. Between these episodes of high GH secretion, somatotrophs release little GH; as a result, the blood concentration of GH falls to very low levels. It is believed that these periodic bursts of GH secretion are caused by an increase in the rate of GHRH secretion and a fall in the rate of somatostatin secretion. The intervals between bursts, when GH secretion is suppressed, are thought to be caused by increased somatostatin secretion. These changes in GHRH and somatostatin secretion result from neural activity generated in higher levels of the CNS,

which affects the secretory activity of GHRH and somatostatin producing neurons in the hypothalamus.

Bursts of GH secretion occur during both awake and sleep periods of the day; however, GH secretion is maximal at night. The bursts of GH secretion during sleep usually occur within the first hour after the onset of deep sleep (stages 3 and 4 of slow-wave sleep). Mean GH levels in the blood are highest during adolescence (peaking in late puberty) and decline in adults. The reduction in blood GH with aging is mainly due to decrease in the size of the GH secretory burst but not the number of pulses (Fig 32.12).

A variety of factors affect the rate of GH secretion in humans. These factors are thought to work by changing the secretion of GHRH and somatostatin by neurons in the hypothalamus. For example, emotional or physical stress causes a great increase in the rate of GH secretion. Vigorous exercise also stimulates GH secretion. Obesity results in reduced GH secretion.

Changes in the circulating levels of metabolites also affect GH secretion. A decrease in blood glucose concentration stimulates GH secretion, whereas hyperglycemia inhibits it. Growth hormone secretion is also stimulated by an increase in the blood concentration of the amino acids arginine and leucine.

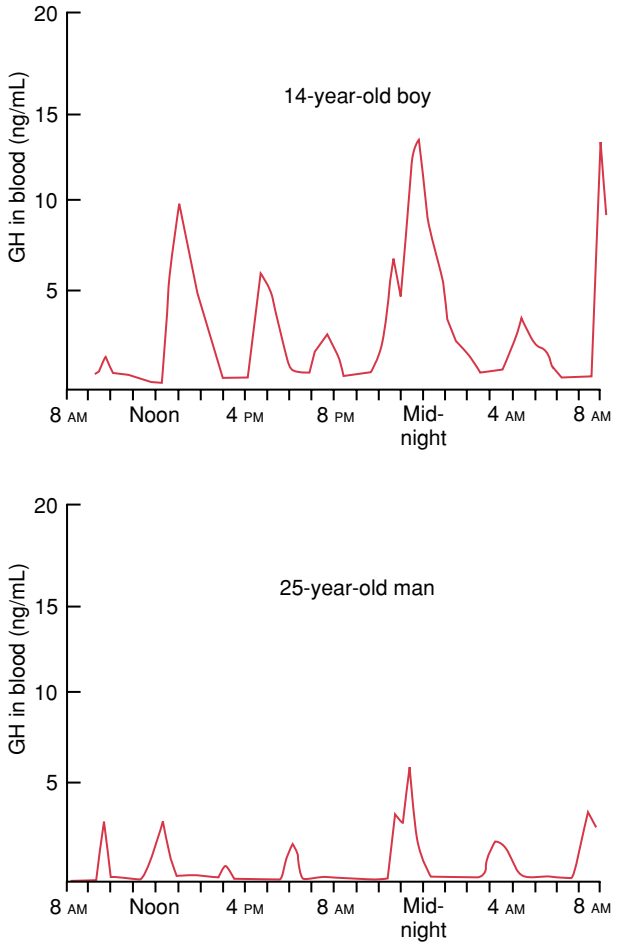

FIGURE 32.12 **Pulsatile GH secretion in an adolescent boy and in an adult.** In the adult, GH levels are reduced as a result of smaller pulse width and amplitude rather than a decrease in the number of pulses.

The Actions of GH. The cells of many tissues and organs of the body have receptors for GH in their plasma membranes. The interaction of GH with these receptors produces its growth-promoting and other metabolic effects, but the mechanisms that produce these effects are not fully understood. The binding of GH to its receptor activates a tyrosine kinase (JAK2), which initiates changes in the phosphorylation pattern of cytoplasmic and nuclear proteins. These phosphorylated proteins ultimately stimulate the transcription of specific genes, such as that for IGF-I.

Many of the mitogenic effects of GH are mediated by IGF-I; however, evidence indicates that GH has direct growth-promoting actions on **progenitor cells** or **stem cells**, such as **prechondrocytes** in the growth plates of bone and **satellite cells** of skeletal muscle. GH stimulates such progenitor cells to differentiate into cells with the capacity to undergo cell division. An important action of GH on the differentiation of progenitor cells is stimulation of the expression of the IGF-I gene; IGF-I is produced and released by these cells. IGF-I exerts an autocrine mitogenic action on the cells that produced it or a paracrine action on neighboring cells. In response to IGF-I, these cells undergo division, causing the tissue to grow mainly through cell replication.

As mentioned earlier, GH deficiency in childhood causes a decrease in the rate of body growth. If left untreated, the deficiency results in **pituitary dwarfism**. Individuals with this condition may be deficient in GH only, or they may have multiple anterior pituitary hormone deficiencies. GH deficiency can be caused by a defect in the mechanisms that control GH secretion or the production of GH by somatotrophs. In some individuals, the target cells for GH fail to respond normally to the hormone because of several different mutations in the GH receptor. See Clinical Focus Box 32.1 and the Case Study for further discussion of growth hormone deficiency, its detection and treatment.

The excessive secretion of GH during childhood, caused by a defect in the mechanisms regulating GH secretion or a GH-secreting tumor, results in **gigantism**. Affected individuals may grow to a height of 7 to 8 feet (2.1 to 2.4 m). When excessive GH secretion occurs in an adult, further linear growth does not occur because the growth plates of the long bones have calcified. Instead, it causes the bones of the face, hands, and feet to become thicker and certain organs, such as the liver, to undergo hypertrophy. This condition, known as **acromegaly**, can also be caused by the chronic administration of excessive amounts of GH to adults.

Although the main physiological action of GH is on body growth, it also has important effects on certain aspects of fat and carbohydrate metabolism. Its main action on fat metabolism is to stimulate the mobilization of triglycerides from the fat depots of the body. This process, known as **lipolysis**, involves the hydrolysis of triglycerides to fatty acids and glycerol by the enzyme **hormone-sensitive lipase**. The fatty acids and glycerol are released from adipocytes and enter the bloodstream. How GH stimulates lipolysis is not understood, but most evidence suggests that it causes adipocytes to be more responsive to other lipolytic stimuli, such as fasting and catecholamines.

CLINICAL FOCUS BOX 32.1

Recombinant Human Growth Hormone and GH Deficiency

Growth hormone (GH) is species-specific, and humans do not respond to GH derived from animals. In the past, the only human GH available for treating children who were GH-deficient was a very limited amount made from human pituitaries obtained at autopsy, but there was never enough to meet the need. This problem was solved when the gene for human GH was cloned in 1979 and then expressed in bacteria. The production of large amounts of recombinant human GH, with all the activities of the natural substance, was now possible. During the 1980s, careful clinical trials established that recombinant human GH was safe to use in GH-deficient children to promote growth. The hormone was approved for clinical use and is now produced and sold worldwide.

Despite the availability of recombinant GH, the diagnosis of **GH deficiency** has remained controversial. GH is released in periodic bursts, the greatest of which occur in the early morning hours. Between pulses of secretion, the blood concentration of GH is nearly undetectable by most techniques. For these reasons, a random measure of GH in the blood is not useful for diagnosing GH deficiency. However, a random blood sample may be useful to detect GH resistance, a syndrome in which the patient exhibits symptoms of GH deficiency but presents with high GH levels in the blood.

An alternative means of diagnosing GH deficiency is to measure the levels of IGF-I, IGF-II, and the IGF-binding protein 3 (IGFBP3) in the blood. The IGFs mediate many of the mitogenic effects of GH on tissues in the body. IGF-I and IGF-II bind to IGFBP3 in the blood. IGFBP3 extends the half-life of the IGFs, transports them to target cells, and facilitates their interaction with IGF receptors. GH stimulates the production of all three molecules, which are present in the blood at fairly constant, readily detectable levels in normal individuals. In children with GH deficiency, the concentration of IGFs and IGFBP3 are low. Treatment with recombinant GH will increase IGF-I, IGF-II, and IGFBP3 in the blood, which will result in increased long bone growth. The epiphyseal growth plate in the bone becomes less responsive to GH and IGF-I several years after puberty, and long bone growth stops in adulthood (see Chapter 36).

GH is also thought to function as one of the counterregulatory hormones that limit the actions of insulin on muscle, adipose tissue, and the liver. For example, GH inhibits glucose use by muscle and adipose tissue and increases glucose production by the liver. These effects are opposite those of insulin. Also, GH makes muscle and fat cells resistant to the action of insulin itself. Thus, GH normally has a tonic inhibitory effect on the actions of insulin, much like the glucocorticoid hormones (see Chapter 34).

The insulin-opposing actions of GH can produce serious metabolic disturbances in individuals who secrete excessive amounts of GH (people with acromegaly) or are given large amounts of GH for an extended time. They may develop insulin resistance and an elevated insulin level in the blood. They may also have hyperglycemia caused by the underutilization and overproduction of glucose. These disturbances are much like those in individuals with non-insulin-dependent (type 2) diabetes mellitus. For this reason, this metabolic response to excess GH is called its **diabetogenic action**.

In GH-deficient individuals, GH has a transitory **insulin-like action**. For example, intravenous injection of GH in a person who is GH-deficient produces hypoglycemia. The hypoglycemia is caused by the ability of GH to stimulate the uptake and use of glucose by muscle and adipose tissue and to inhibit glucose production by the liver. After about 1 hour, the blood glucose level returns to normal. If this person is given a second injection of GH, hypoglycemia does not occur because the person has become insensitive or refractory to the insulin-like action of GH and remains so for some hours. Normal individuals do not respond to the insulin-like action of GH, presumably because they are always refractory from being exposed to their own endogenous GH. The actions of GH in humans are summarized in Table 32.3.

Gonadotropins Regulate Reproduction

The testes and ovaries have two essential functions in human reproduction. The first is to produce sperm cells and ova (egg cells), respectively. The second is to produce an array of steroid and peptide hormones, which influence virtually every aspect of the reproductive process. The gonadotropic hormones FSH and LH regulate both of these functions. The production and secretion of the gonadotropins by the anterior pituitary is, in turn, regulated by the hypothalamic releasing hormone LHRH and the hormones produced by the testes and ovaries in response to gonadotropic stimulation. The regulation of human reproduction by this **hypothalamic-pituitary-gonad axis** is dis-

TABLE 32.3 The Actions of Growth Hormone

Growth-promoting	Stimulates IGF-I gene expression by target cells; IGF-I produced by these cells has autocrine or paracrine stimulatory effect on cell division, resulting in growth
Lipolytic	Stimulates mobilization of triglycerides from fat deposits
Diabetogenic	Inhibits glucose use by muscle and adipose tissue and increases glucose production by the liver
	Inhibits the action of insulin on glucose and lipid metabolism by muscle and adipose tissue
Insulin-like	Transitory stimulatory effect on uptake and use of glucose by muscle and adipose tissue in GH-deficient individuals
	Transitory inhibitory effect on glucose production by liver of GH-deficient individuals

cussed in Chapters 37 and 38. Here, we describe the chemistry and formation of the gonadotropins.

Like TSH, human FSH and LH are composed of two structurally different glycoprotein subunits, called α and β, which are held together by noncovalent bonds. The β subunit of human FSH consists of a peptide chain of 111 amino acid residues, to which two chains of carbohydrate are attached. The β subunit of human LH is a peptide of 121 amino acid residues. It is also glycosylated with two carbohydrate chains. The combined α and β subunits of FSH and LH give these hormones a molecular size of about 28 to 29 kDa.

As with TSH, the individual subunits of the gonadotropins have no hormonal activity. They must be combined with each other in a 1:1 ratio in order to have activity. Again, it is the β subunit that gives the gonadotropin molecule either FSH or LH activity because the α subunits are identical.

FSH and LH are produced by the same gonadotrophs in the anterior pituitary. There are separate genes for the α and β subunits in the gonadotroph; hence, the peptide chains of these subunits are translated from separate mRNA molecules. Glycosylation of these chains begins as they are synthesized and before they are released from the ribosome. The folding of the subunit peptides into their final three-dimensional structure, the combination of an α subunit and a β subunit, and the completion of glycosylation all occur as these molecules pass through the Golgi apparatus and are packaged into secretory granules. As with the thyrotroph, the gonadotroph produces an excess of α subunits over FSH and LH β subunits. Therefore, the rate of β subunit production is considered to be the rate-limiting step in gonadotropin synthesis.

The synthesis of FSH and LH is regulated by the hormones of the hypothalamic-pituitary-gonad axis. For example, gonadotropin production is stimulated by LHRH. It is also affected by the steroid and peptide hormones produced by the gonads in response to stimulation by the gonadotropins. Such hormonally regulated changes in gonadotropin production are caused mainly by changes in the expression of the genes for the gonadotropin subunits. More information about the regulation of gonadotropin synthesis and secretion is found in Chapters 37 and 38.

Prolactin Regulates the Synthesis of Milk

Lactation is the final phase of the process of human reproduction. During pregnancy, **alveolar cells** of the mammary glands develop the capacity to synthesize milk in response to stimulation by a variety of steroid and peptide hormones. Milk synthesis by these cells begins shortly after childbirth. To continue to synthesize milk, these cells must be stimulated periodically by prolactin (PRL), and this is thought to be the main physiological function of PRL in the human female. What role, if any, PRL has in the human male is unclear. It is known to have some supportive effect on the action of androgenic hormones on the male reproductive tract, but whether this is an important physiological function of PRL is not established.

Human PRL is a globular protein consisting of a single peptide chain of 199 amino acid residues with three intrachain disulfide bridges. Its molecular size is about 23 kDa. Human PRL has considerable structural similarity to human GH and to a PRL-like hormone produced by the human placenta called **placental lactogen** (hPL). It is thought that these hormones are structurally related because their genes evolved from a common ancestral gene during the course of vertebrate evolution. Because of its structural similarity to human PRL, human GH has substantial PRL-like or **lactogenic activity**. However, PRL and hPL have little GH-like activity. Human placental lactogen is discussed further in Chapter 39.

Prolactin is synthesized and secreted by lactotrophs in the anterior pituitary. PRL is synthesized in the rough ER as a larger peptide. Its N-terminal signal peptide sequence is then removed and the 199-amino acid protein passes through the Golgi apparatus and is packaged into secretory granules.

The synthesis and secretion of PRL is stimulated by estrogens and other hormones, such as TRH, which increase the expression of the PRL gene. However, dopamine inhibits the synthesis of PRL. Dopamine produced by hypothalamic neurons plays a major role in the regulation of PRL synthesis and secretion by the hypothalamic-pituitary axis. The regulation of the synthesis and secretion of PRL and its physiological actions are discussed in Chapter 39.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is the BEST in each case.

1. Which of the following conditions is consistent with a decreased rate of ACTH secretion?
   (A) Hyperosmolality of the blood
   (B) Low serum glucocorticoid
   (C) Loss of hypothalamic neurons
   (D) Primary adrenal insufficiency
   (E) Stress as a result of emotional trauma
   (F) Increased PKA activity in corticotrophs
2. Which of the following statements most accurately describes the feedback effects of thyroid hormones?
   (A) They increase the sensitivity of thyrotrophs to TRH
   (B) They stimulate transcription of the α and β subunits of TSH in thyrotrophs
   (C) They increase the secretion of TSH by thyrotrophs
   (D) They stimulate the expression of the GH gene in somatotrophs
   (E) They increase IP_3 in thyrotrophs
   (F) They increase ACTH release
3. A 30-year-old woman completed a routine pregnancy with the uncomplicated delivery of a normal-sized baby girl 6 months ago. The woman is currently experiencing galactorrhea (persistent discharge of milk-like secretions from the breast) and has not yet resumed regular menstrual periods. The baby had been bottle-fed since birth. What is the

(continued)

most likely explanation of the galactorrhea?
(A) Normal postpartum response
(B) Excess PRL secretion
(C) Insufficient TSH secretion
(D) Reduced GH secretion
(E) Increased dopamine synthesis in the hypothalamus

4. A decrease in blood volume would result in an increase in the secretion of
(A) Neurophysin
(B) Oxytocin
(C) β-Lipotropin
(D) Domatostatin
(E) ACTH
(F) POMC

5. A 50-year-old man complains of decreased muscle strength, libido, and exercise intolerance. Examination reveals a 10% reduction in lean body mass and an increase in body fat, primarily localized to the abdominal region. Thyroid hormone levels are normal. Which diagnosis is most consistent with these symptoms?
(A) Glucocorticoid deficiency
(B) Addison's disease
(C) GH deficiency
(D) PRL deficiency
(E) Acromegaly

6. For evaluation of possible adrenocortical dysfunction in a middle-aged man, ACTH and cortisol were measured in blood samples taken at 8 AM, 8:30 AM, 8 PM, and 8:30 PM. The values obtained for ACTH were 110, 90, 120, and 200 pg/mL, respectively. The values obtained for cortisol were 10, 15, 25, and 20 μg/dL. These concentrations of ACTH demonstrate
(A) Normal circadian pulsatile release
(B) Primary adrenal insufficiency
(C) Inverted circadian pulsatile release
(D) Secondary adrenal insufficiency
(E) Normal circadian nonpulsatile release
(F) ACTH-secreting tumor

7. Which treatment would provide the greatest therapeutic benefit in patients with acromegaly?
(A) Glucocorticoid
(B) Somatostatin
(C) Growth hormone
(D) Insulin
(E) GHRH
(F) Thyroid hormone

8. Which of the following is mediated by a rise in cAMP?
(A) Inhibition of GH secretion by somatostatin
(B) Stimulation of GH gene expression by GHRH
(C) Stimulation of TSH secretion by TRH
(D) Inhibition of TSH α and β subunit gene expression by TRH
(E) Release of AVP
(F) Inhibition of ACTH synthesis in corticotrophs

SUGGESTED READING

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