41

The Hypothalamus and Pituitary Gland

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. Describe the structure and composition of the pituitary gland and its structural and functional relationship to magnocellular and parvocellular hypothalamic neurons.
2. Discuss the mechanisms by which the neurohormones antidiuretic hormone (ADH) and oxytocin are synthesized, transported, and released by magnocellular neurons.
3. Diagram a basic scheme illustrating the components and feedback loops of a typical endocrine axis, including central input, hypothalamic-releasing factors, pituitary hormones, and a peripheral endocrine gland. Explain the concept of a set point.
4. List the endocrine cell types of the adenohypophysis and the tropic hormones they produce, noting hormones that share a common subunit.
5. Contrast the axes of somatotropes and lactotropes with the classic endocrine axes and explain how they differ.
6. Discuss the actions of growth hormone (GH) and insulin-like growth factor I (IGF-I) in the regulation of growth, and the role of GH in the fasted state.
7. Describe the role of prolactin in the initiation and maintenance of lactation.

The **pituitary gland** (also called the **hypophysis**) is a small (≈0.5 g in weight) yet complex endocrine structure at the base of the forebrain (Fig. 41.1). It is composed of an epithelial component called the **adenohypophysis** and a neural structure called the **neurohypophysis.** The adenohypophysis is composed of five cell types that secrete six hormones. The neurohypophysis releases several neurohormones. All endocrine functions of the pituitary gland are regulated by the hypothalamus and by negative- and positive-feedback loops.

Anatomy

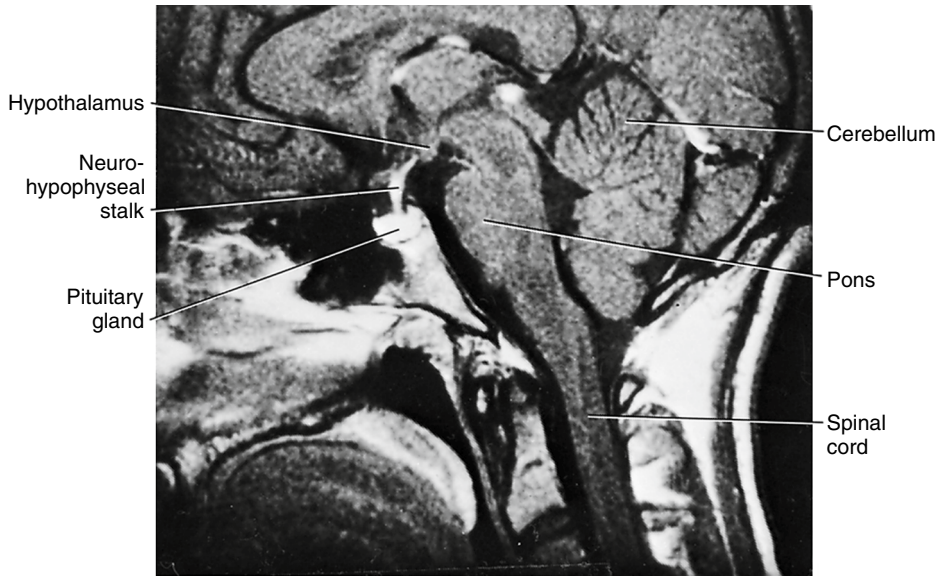
Microscopic examination of the pituitary reveals two distinct types of tissue: epithelial and neural (Fig. 41.2). The epithelial portion of the human pituitary gland is called the **adenohypophysis.** The adenohypophysis makes up the anterior portion of the pituitary and is often referred to as the **anterior lobe of the pituitary,** and its hormones are referred to as **anterior pituitary hormones.** The adenohypophysis is composed of three parts: (1) the **pars distalis,** which makes up about 90% of the adenohypophysis; (2) the pars tuberalis, which wraps around the stalk; and (3) the pars intermedia, which regresses and is absent in adult humans.

The neural portion of the pituitary is called the **neurohypophysis**, which represents a downgrowth of the hypothalamus. The most inferior portion of the neurohypophysis is called the **pars nervosa,** also called the **posterior lobe of the pituitary** (or simply **posterior pituitary**). At the superior end of the neurohypophysis, a funnel-shaped swelling called the **median eminence** develops. The portion of the neurohypophysis that extends from the median eminence down to the pars nervosa is called the **infundibulum.** The infundibulum and the pars tuberalis make up the pituitary stalk—a physical connection between the hypothalamus and pituitary gland (see Fig. 41.2).

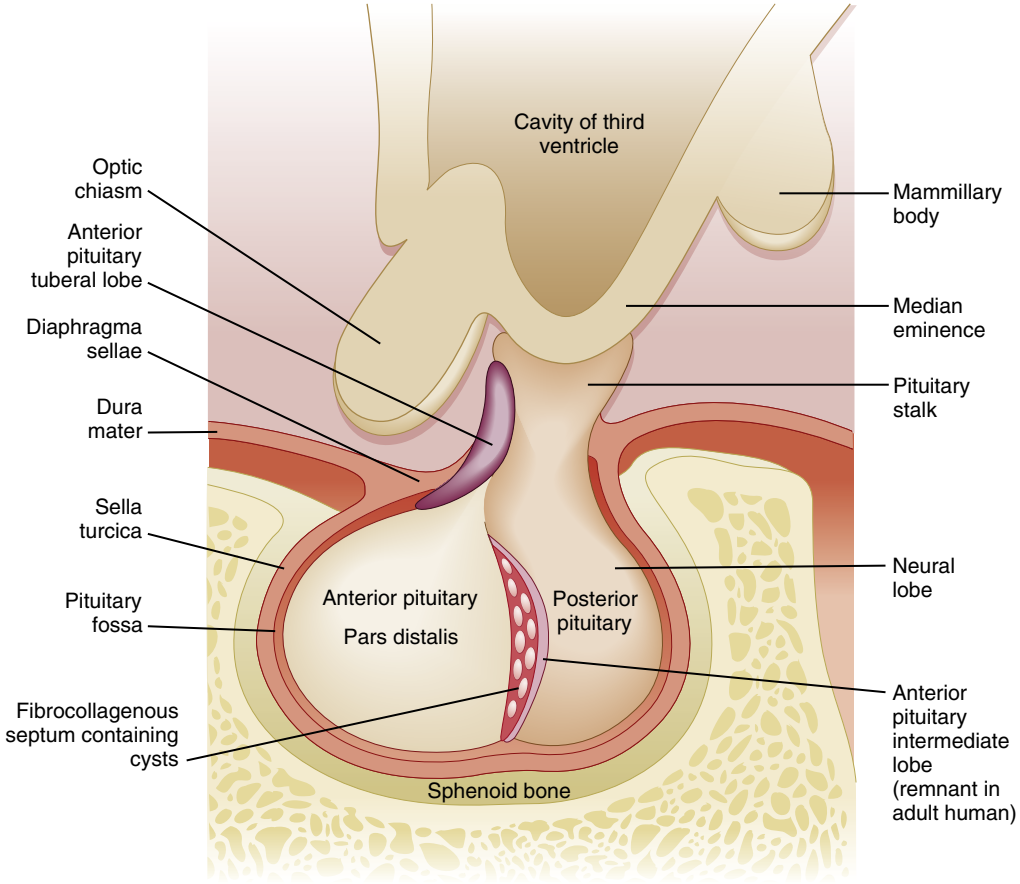
The pituitary gland (anterior and posterior lobes) is situated within a depression of the sphenoid bone called the **sella turcica.** Generally, tumors that arise in the pituitary are only able to expand in one direction, up into the brain and against the optic chiasma. Thus, any increase in size of the pituitary is commonly associated with visual field defects and headaches. The sella turcica is sealed off from the brain by a membrane called the **diaphragma sellae.**

The Neurohypophysis

The pars nervosa is a **neurovascular** structure that is the site of neurohormone release adjacent to a rich capillary bed. The peptide hormones that are released are **antidiuretic hormone (ADH, or arginine vasopressin)** and **oxytocin.** The cell bodies of the neurons that project to the pars nervosa are located in the **supraoptic nuclei (SON)** and **paraventricular nuclei (PVN)** of the **hypothalamus** (a *nucleus* refers to a collection of neuronal cell bodies residing within the central nervous system [CNS]; a *ganglion* is a collection of neuronal cell bodies residing outside the CNS). The large cell bodies of these neurons are described as **magnocellular,** and they project axons down the infundibular stalk as the **hypothalamohypophyseal tracts.** Individual magnocellular neurons are hormone specific, producing either ADH or oxytocin. These axons terminate in the pars nervosa (Fig. 41.3). In addition to axonal processes and termini from the SON and PVN, there are glial-like support cells called **pituicytes.** The posterior pituitary is extensively vascularized and the capillaries are

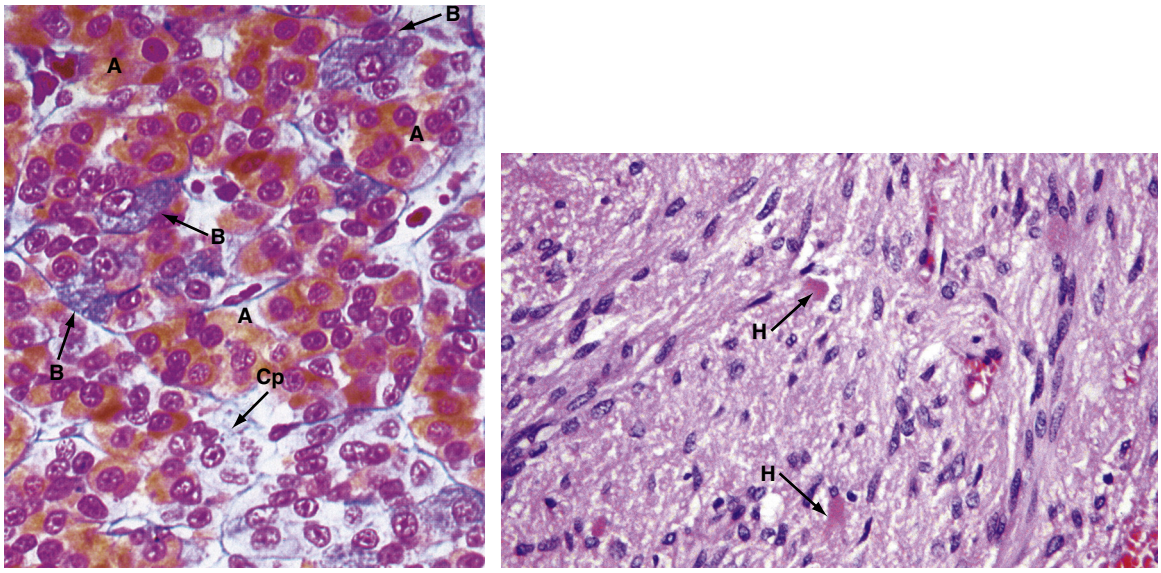


• **Fig. 41.1** Cross-sectional image of the head demonstrating the proximity of the hypothalamus and pituitary gland and their connection by a neurohypophyseal (pituitary) stalk.



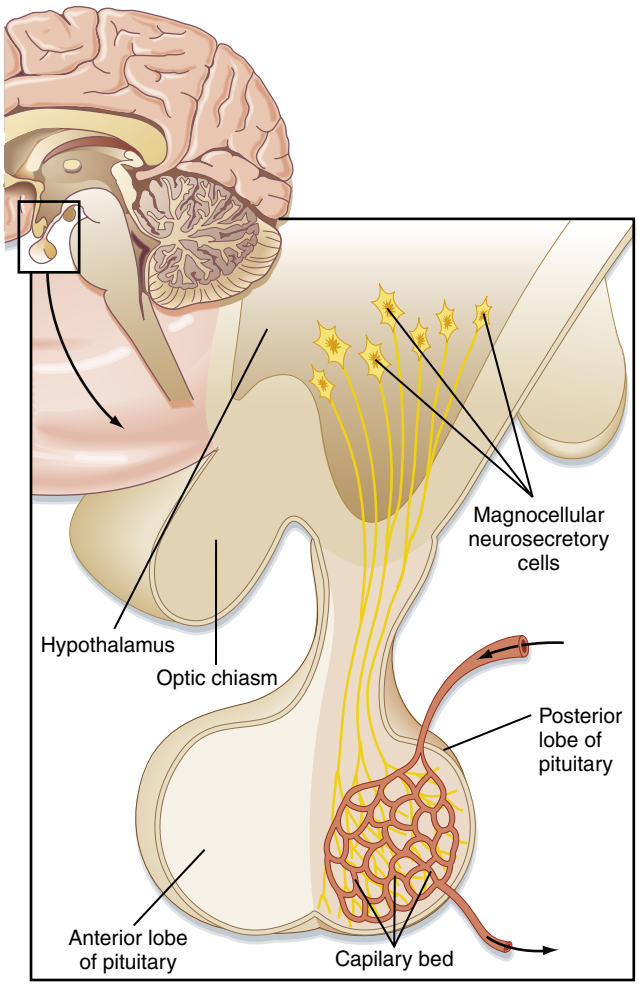
A

• **Fig. 41.2 A,** Gross structure of the pituitary gland. The pituitary gland is below the hypothalamus and is connected to it by the pituitary stalk. The gland sits within the sella turcica, a fossa within the sphenoid bone, and is covered by a dural reflection, the diaphragma sellae. The pars distalis makes up most of the anterior pituitary. **B,** The pars distalis is derived from epithelial tissue that is composed of acidophils *(A)* (somatotropes and lactotropes) and basophils *(B)* (thyrotropes, gonadotropes, and corticotropes). **C,** The posterior pituitary is derived from neural tissue and has a histological appearance of nonmyelinated nerves. *Cp*, Chromophobes; *H,* Herring bodies. (**A,** Modified from Stevens A, Lowe JS. *Human Histology.* 3rd ed. Philadelphia: Elsevier; 2005. **B and C,** From Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology.* 5th ed. Philadelphia: Churchill Livingstone; 2006.)

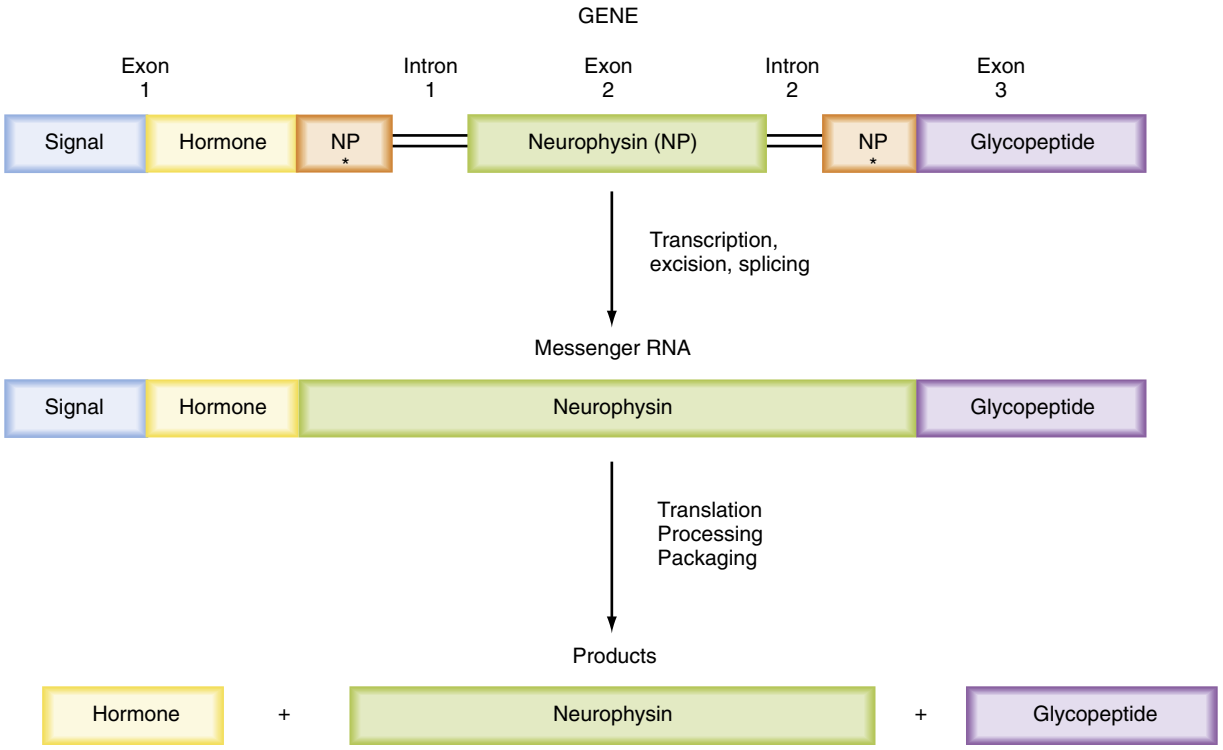


B C

• **Fig. 41.2** cont'd



• **Fig. 41.3** Magnocellular neurons of the hypothalamus (paraventricular and supraoptic nuclei) project their axons down the infundibular process and terminate in the pars nervosa (posterior lobe), where they release their hormones (either ADH or oxytocin) into a capillary bed. (Modified from Larsen PR, Kronenberg HM, Melmed S, et al. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: Saunders; 2003.)



• **Fig. 41.4** Synthesis and processing of preprovasopressin or preprooxytocin.

fenestrated, thereby facilitating diffusion of hormones into the systemic circulation.

Synthesis of ADH and Oxytocin

ADH and oxytocin are small peptides (nine amino acids) that differ in only two amino acids, yet they have limited overlapping activity. ADH and oxytocin are synthesized as preprohormones (Fig. 41.4). Each prohormone harbors the structure of oxytocin or ADH and a co-secreted peptide, either **neurophysin I** (associated with ADH) or **neurophysin II** (associated with oxytocin). These preprohormones are called **preprovasophysin** and **preprooxyphysin.** The N-terminal signal peptide is cleaved as the peptide is transported into the endoplasmic reticulum. In cell bodies within the SON and PVN, the prohormones are packaged in the endoplasmic reticulum and Golgi apparatus in membrane-bound secretory granules (Fig. 41.5). The secretory granules are conveyed through a "fast" (i.e., millimeters per hour) adenosine triphosphate (ATP)-dependent axonal transport mechanism down the infundibular stalk to axonal termini in the pars nervosa. During transit of the secretory granule, the prohormones are proteolytically cleaved to produce equimolar amounts of hormone and neurophysin. Secretory granules containing fully processed peptides are stored in the axonal termini. Expansions of the termini due to the presence of stored secretory granules can be observed by light microscopy and are termed **Herring bodies.**

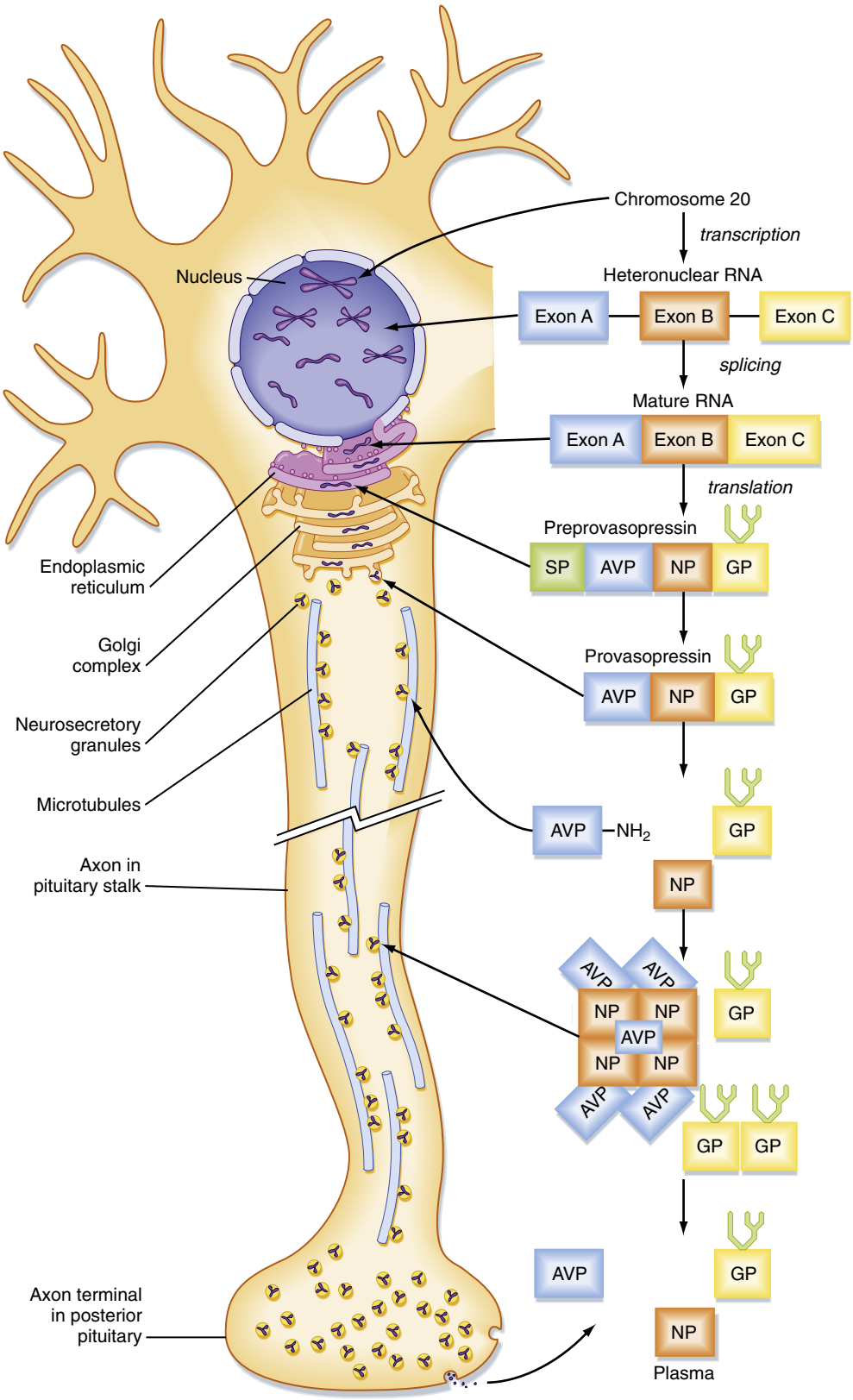
ADH and oxytocin are released from the pars nervosa in response to stimuli that are primarily detected at the cell body and its dendrites in the SON and PVN. These stimuli are mainly in the form of neurotransmitters released from hypothalamic interneurons. With sufficient stimulus the neurons will depolarize and propagate an action potential down the axon. At the axonal termini the action potential increases intracellular [Ca^{++}] and results in a stimulus-secretion response, with exocytosis of ADH or oxytocin along with neurophysins into the extracellular fluid of the pars nervosa (see Fig. 41.5). Hormones and neurophysins enter the peripheral circulation, and both can be measured in blood.

Actions and Regulation of ADH and Oxytocin

ADH acts primarily at the kidney to retain water (antidiuresis). The actions of ADH and regulation of ADH secretion are described in Chapter 35. Oxytocin primarily acts on the pregnant uterus to induce labor and on myoepithelial cells of the breast to promote milk letdown during nursing. The actions and regulation of oxytocin are discussed in Chapter 44.

IN THE CLINIC

Because posterior pituitary hormones are synthesized in the hypothalamus rather than the pituitary, **hypophysectomy** (pituitary removal) does not necessarily permanently disrupt synthesis and secretion of these hormones. Immediately after hypophysectomy, secretion of the hormones decreases. However, over a period of weeks the severed proximal end of the tract will show histological modification and pituicytes will form around the neuron terminals. Secretory vacuoles are seen, and secretion of hormone resumes from this proximal end. Secretion of hormone can even potentially return to normal levels. In contrast, a lesion higher up on the pituitary stalk can lead to loss of neuronal cell bodies in the PVN and SON.



• **Fig. 41.5** Synthesis, processing, and transport of preprovasopressin. Human ADH (also called *arginine vasopressin [AVP]*) is synthesized in the hypothalamic magnocellular cell bodies and packaged into neurosecretory granules. During intraaxonal transport of the granules down the infundibular process to the pars nervosa, provasopressin is proteolytically cleaved into the active hormone (AVP = ADH), neurophysin *(NP)*, and a C-terminal glycoprotein *(GP)*. NP arranges into tetramers that bind five AVP molecules. All three fragments are secreted from axonal termini in the pars nervosa (posterior pituitary) and enter the systemic blood. Only AVP (ADH) is biologically active. *SP*, signal peptide. (Modified from Larsen PR, Kronenberg HM, Melmed S, et al. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: Saunders; 2003.)

TABLE 41.1 Adenohypophysis Cell Types: Hormonal Production and Action, Hypothalamic Regulation, and Feedback Regulation

	Basophils			Acidophils	
	Corticotrope	**Thyrotrope**	**Gonadotrope**	**Somatotrope**	**Lactotrope**
Primary hypothalamic regulation	Corticotropin-releasing hormone (CRH): 41–amino acid peptide, stimulatory	Thyrotropin-releasing hormone (TRH): tripeptide, stimulatory	Gonadotropin-releasing hormone (GnRH): decapeptide, stimulatory	Growth hormone–releasing hormone (GHRH): 44–amino acid peptide, stimulatory Somatostatin: tetradecapeptide, inhibitory	Dopamine (catecholamine): inhibitory PRL-releasing factor?: stimulatory
Tropic hormone secreted	Adrenocorticotropic hormone (ACTH): 4.5-kDa protein	Thyroid-stimulating hormone (TSH): 28-kDa glycoprotein hormone	Follicle-stimulating hormone and luteinizing hormone (FSH, LH): 28- and 33-kDa glycoprotein hormones	Growth hormone (GH): ≈22-kDa protein	Prolactin (PRL): ≈23-kDa protein)
Receptor	MC2R (Gs-linked GPCR)	TSH receptor (Gs-linked GPCR)	FSH and LH receptors (Gs-linked GPCRs)	GH receptor (JAK/STAT-linked cytokine receptor)	PRL receptor (JAK/STAT-linked cytokine receptor)
Target endocrine gland	Zona fasciculata and zona reticularis of adrenal cortex	Thyroid epithelium	Ovary (theca and granulosa[a]) Testis (Leydig and Sertoli cells)	Liver (but also direct actions—especially in terms of metabolic effects)	No endocrine target organ—not part of an endocrine axis
Peripheral hormone involved in negative feedback	Cortisol	Triiodothyronine	Estrogen,[b] progesterone, testosterone, and inhibin[c]	IGF-I GH (short loop)	None

[a]Both follicular and luteinized thecal and granulosa cells.
[b]Estrogen can also have a positive feedback in women.
[c]Inhibin selectively inhibits release of FSH from the gonadotrope.

The Adenohypophysis

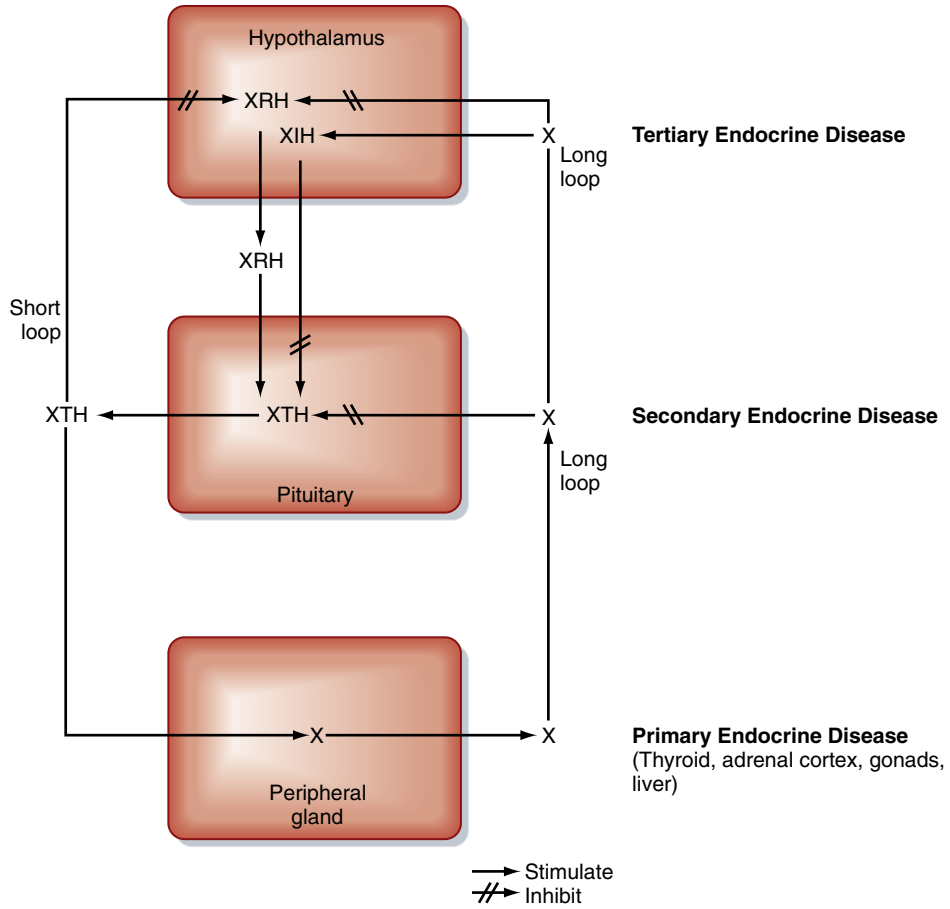
The pars distalis is composed of five endocrine cell types that produce six hormones (Table 41.1). Because of the histological staining properties of the cell types, the corticotropes, thyrotropes, and gonadotropes are referred to as pituitary **basophils,** whereas the somatotropes and lactotropes are referred to as pituitary **acidophils** (see Fig. 41.2B).

Endocrine Axes

Before discussing the individual hormones of the adenohypophysis, it is important to understand the structural and functional organization of the adenohypophysis in the context of the **endocrine axes** (Fig. 41.6; also see Table 41.1 and Chapter 38). Each endocrine axis is composed of three levels of endocrine cells: (1) hypothalamic neurons, (2) anterior pituitary cells, and (3) peripheral endocrine glands. Hypothalamic neurons release specific **hypothalamic-releasing hormones** (designated XRH in this generic scheme) that stimulate secretion of specific **pituitary tropic hormones** (XTH). In some cases, production of a pituitary tropic hormone is secondarily regulated by a **release-inhibiting hormone** (XIH). Pituitary tropic hormones then act on specific peripheral target endocrine glands and stimulate them to release peripheral hormones (X). The peripheral hormone X has two general functions: it regulates several aspects of human physiology, and it negatively feeds back on the pituitary gland and hypothalamus to inhibit production and secretion of tropic hormones and releasing hormones, respectively (see Fig. 41.6).

AT THE CELLULAR LEVEL

Significant progress has been made in understanding the differentiation of the five endocrine cells of the pars distalis from one precursor cell. The homeodomain transcription factor **PROP-1** is expressed soon after Rathke's pouch (the embryological precursor of the adenohypophysis) forms and

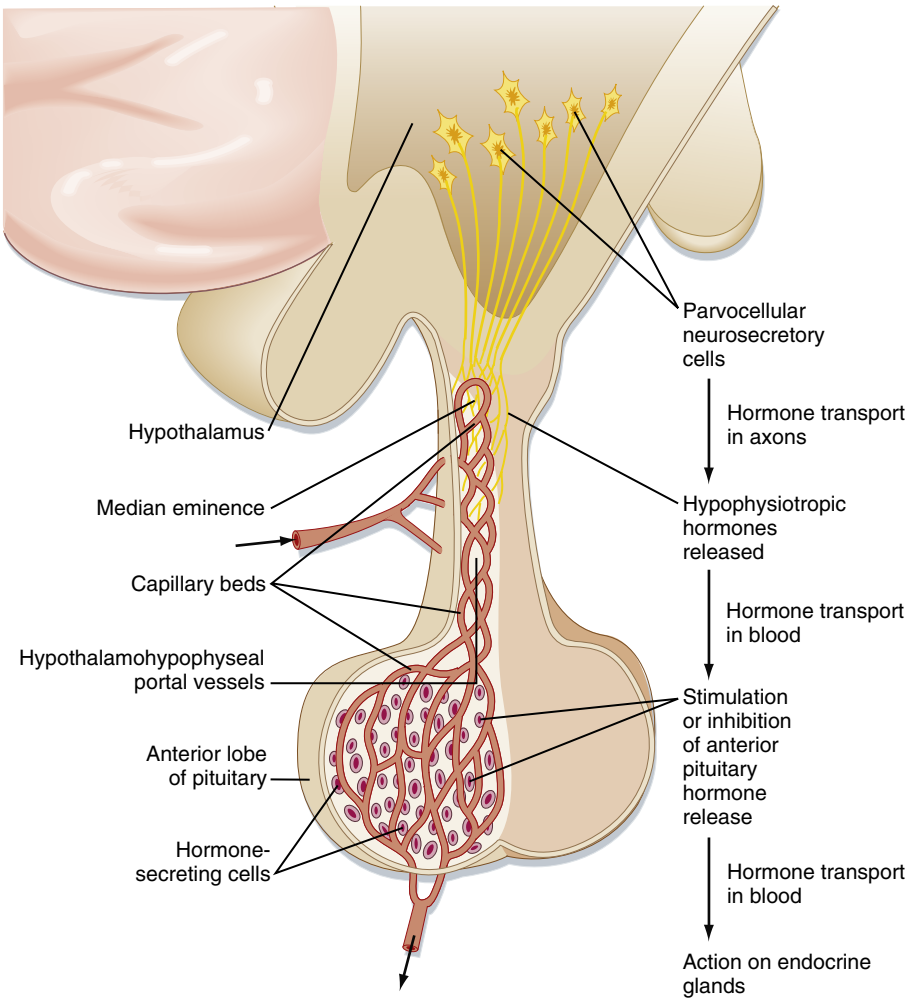


• **Fig. 41.6** Negative-feedback loops regulating hormone secretion in a typical hypothalamus-pituitary-peripheral gland axis. *X*, Peripheral gland hormone; *XIH*, hypothalamic-inhibiting hormone; *XRH*, hypothalamic-releasing hormone; *XTH*, pituitary tropic hormone.

promotes the cell lineages of somatotropes, lactotropes, thyrotropes, and gonadotropes. In humans, rare mutations in the *PROP1* gene result in a type of **combined pituitary hormone deficiency.** These individuals display dwarfism due to lack of GH, cognitive deficits secondary to hypothyroidism, and infertility due to lack of gonadotropins. A subsequently expressed pituitary-specific homeodomain transcription factor called **POU1F1** (formerly known as *Pit-1*) is required for differentiation of thyrotropes, somatotropes, and lactotropes, and it directly stimulates transcription and expression of TSH, GH, and prolactin (PRL). Affected individuals with *POU1F1* mutations have dwarfism and intellectual disability. The nuclear hormone receptor–related transcription factor **steroidogenic factor-1 (SF-1)** was originally identified in the adrenal cortex and gonads as a regulator of steroidogenic enzyme gene expression. SF-1 is also expressed in GnRH neurons in the hypothalamus and in pituitary gonadotropes, where it regulates transcription of LH and FSH. Mutations in the *SF1* gene disrupt adrenal and gonadal function, including loss of gonadotropes in the pituitary gland. **TPIT** is a transcription factor involved in the differentiation of corticotropes. TPIT, acting with other transcription factors, promotes differentiation of corticotropes and expression of the *POMC* gene (see Corticotropes section). Mutations in the human *TPIT* gene result in **isolated ACTH deficiency.** This results in a form of **secondary adrenal insufficiency** that requires lifelong replacement with glucocorticoids (see Chapter 43).

The hypothalamic regulation of anterior pituitary function is neurohormonal. An area of the hypothalamus collectively referred to as the **hypophysiotropic** (i.e., stimulatory to the hypophysis) **region** contains nuclei composed of small, or **parvocellular,** cell bodies that project axons to the median eminence. They are distinct from the magnocellular neurons of the PVN and SON that project to the pars nervosa. Parvocellular neurons secrete **releasing hormones** from their axonal termini at the median eminence (Fig. 41.7). The releasing hormones enter a primary plexus of fenestrated capillaries and are then conveyed to a second capillary plexus located in the pars distalis by the **hypothalamohypophyseal portal vessels** (a *portal vessel* is defined as a vessel that begins and ends in capillaries without going through the heart). At the secondary capillary plexus, the releasing hormones diffuse out of the vasculature and bind to their cognate receptors on specific cell types within the pars distalis. The neurovascular link (i.e., pituitary stalk) between the hypothalamus and pituitary is somewhat fragile and can be disrupted by physical trauma, surgery, or hypothalamic disease. Damage to the stalk and subsequent functional isolation of the anterior pituitary result in a decline in all anterior pituitary tropic hormones except PRL (discussed later).

The cells of the adenohypophysis make up the intermediate level of the endocrine axes. The adenohypophysis secretes

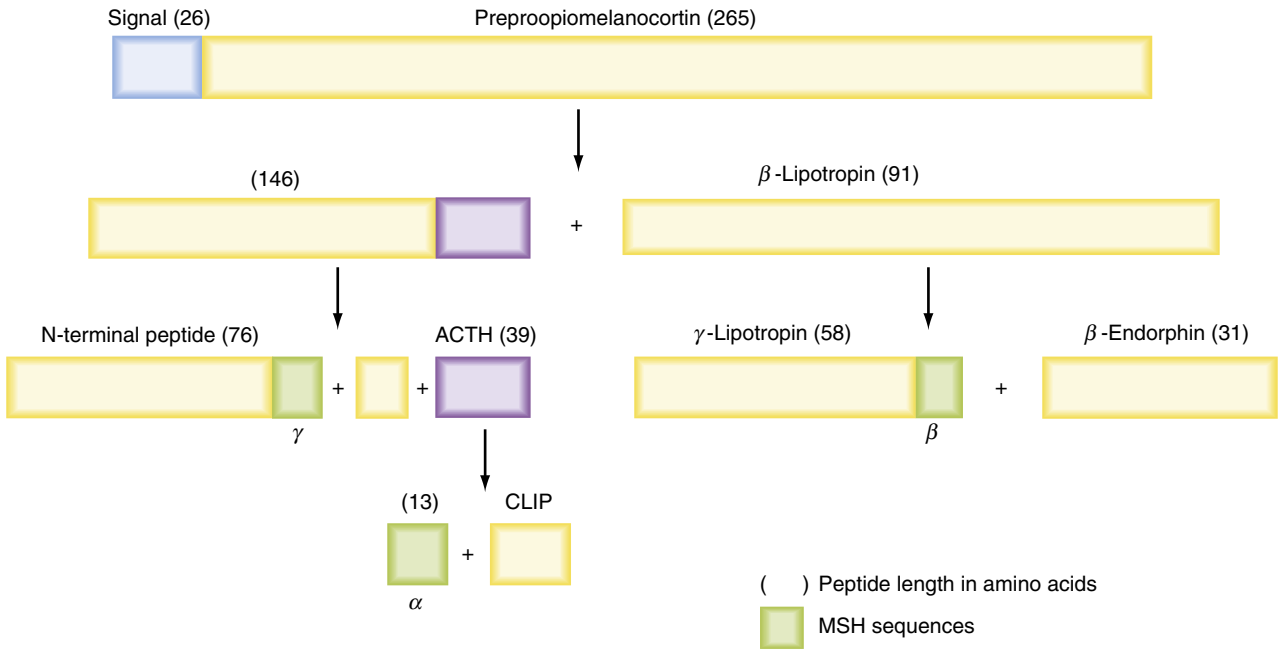


• **Fig. 41.7** Neurovascular link between the hypothalamus and the anterior lobe (pars distalis) of the pituitary. Parvocellular "hypophysiotropic" neurosecretory neurons within various hypothalamic nuclei project axons to the median eminence, where they secrete releasing hormones (RHs). RHs flow down the pituitary stalk in the hypothalamohypophyseal portal vessels to the anterior pituitary. RHs (and release-inhibiting hormones [see text]) regulate secretion of tropic hormones from the five cell types of the anterior pituitary. (From Larsen PR, Kronenberg HM, Melmed S, et al. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: Saunders; 2003.)

protein hormones that are referred to as **tropic hormones**—adrenocorticotropic hormone (ACTH, also called *corticotropin*), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), and prolactin (PRL) (see Table 41.1). With a few exceptions, tropic hormones bind to their cognate receptors on peripheral endocrine glands. Because of this arrangement, pituitary tropic hormones generally do not directly regulate physiological responses (see Chapter 38).

The endocrine axes have the following important features:

1. The activity of a specific axis is normally maintained at a **set point,** which varies from individual to individual, usually within a normal range. The set point is determined by the integration of hypothalamic stimulation and peripheral hormone negative feedback. Importantly, negative feedback generally is not exerted by the physiological responses regulated by a specific endocrine axis but by the peripheral hormone itself acting on the pituitary and hypothalamus (see Fig. 41.6). Thus, if the level of a peripheral hormone drops, secretion of hypothalamic-releasing hormones and pituitary tropic hormones will increase. As the level of peripheral hormone rises, the hypothalamus and pituitary will decrease secretion because of negative feedback. Although certain nonendocrine physiological parameters (e.g., acute hypoglycemia) can regulate some endocrine axes, the axes function semiautonomously with respect to the physiological changes they produce. This configuration means that a peripheral hormone (e.g., thyroid hormone) can regulate multiple organ systems without these organ systems exerting competing negative-feedback regulation of the hormone. Clinically this partial autonomy means that multiple aspects of a patient's physiology are at the mercy of whatever derangements might exist within a specific axis.
2. Hypothalamic hypophysiotropic neurons are often secreted in a **pulsatile** manner and are entrained to daily and seasonal rhythms through CNS input. Additionally, hypothalamic nuclei receive a variety of neuronal inputs from higher and lower levels of the brain. These can be short-term



• **Fig. 41.8** The original gene transcript of proopiomelanocortin contains structures of multiple bioactive compounds. *ACTH*, Adrenocorticotropic hormone; *CLIP*, corticotropin-like intermediate peptide; *MSH*, melanocyte-stimulating hormone. Note that ACTH is the only bioactive peptide released by the human corticotrope.

(e.g., various stresses/infections) or long-term (e.g., onset of reproductive function at puberty) inputs. Thus, inclusion of the hypothalamus in an endocrine axis allows integration of a considerable amount of information for setting or changing the set point of that axis. Clinically this means a broad range of complex neurogenic states can alter pituitary function. **Psychosocial dwarfism** is a striking example in which children subject to abuse or intense emotional stress have lower growth rates as a result of decreased GH secretion by the pituitary gland.

3. Abnormally low or high levels of a peripheral hormone (e.g., thyroid hormone) may be due to a defect at the level of the peripheral endocrine gland (e.g., thyroid), the pituitary gland, or the hypothalamus. Such lesions are referred to as **primary, secondary, and tertiary endocrine disorders,** respectively (see Fig. 41.6). A thorough understanding of the feedback relationships within an axis allows the physician to determine where the defect lies. Primary endocrine deficiencies tend to be the most severe because they often involve complete absence of the peripheral hormone.

Endocrine Function of the Adenohypophysis

The adenohypophysis consists of the following endocrine cell types: **corticotropes, thyrotropes, gonadotropes, somatotropes,** and **lactotropes** (see Table 41.1).

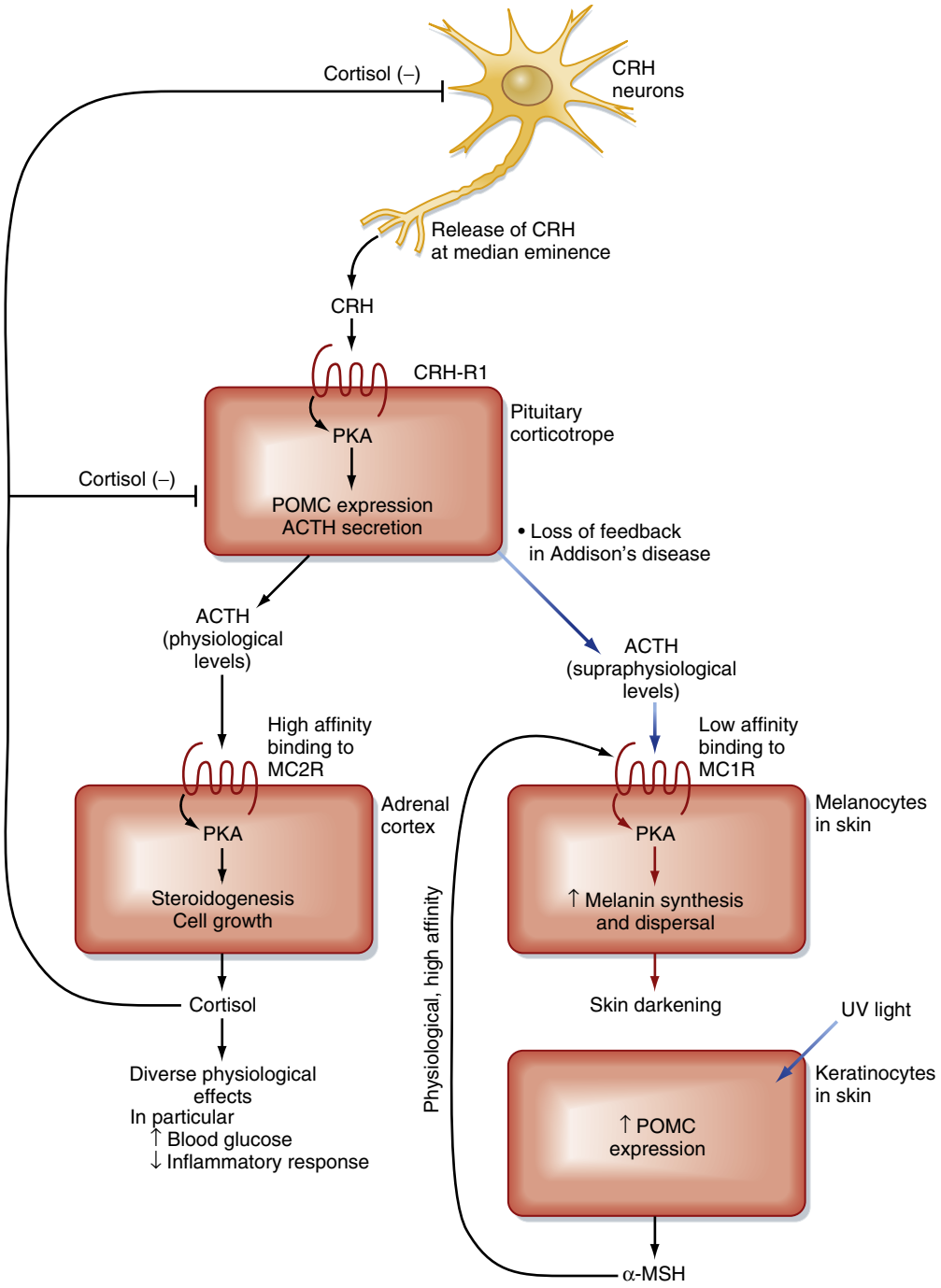
Corticotropes

Corticotropes stimulate the adrenal cortex as part of the **hypothalamic-pituitary-adrenal (HPA) axis.** Corticotropes produce the hormone **ACTH (corticotropin),** which stimulates two zones of the adrenal cortex (see Chapter 43). ACTH is a 39–amino acid peptide that is synthesized as part of a larger prohormone called **proopiomelanocortin (POMC).** Thus, corticotropes are also referred to as **POMC cells.** POMC harbors the peptide sequence for ACTH, two isoforms of melanocyte-stimulating hormone (MSH), endorphins (endogenous opioids), and enkephalins (Fig. 41.8). However, the human corticotrope expresses only prohormone convertase-1, which produces ACTH as the sole active hormone secreted by these cells. The other fragments that are cleaved from POMC are the N-terminal fragment and β-lipotropic hormone (β-LPH), neither of which plays a physiological role in humans.

ACTH circulates as an unbound hormone and has a short half-life of about 10 minutes. It binds to the **melanocortin-2 receptor (MC2R)** on cells in the adrenal cortex (Fig. 41.9). ACTH acutely increases cortisol and adrenal androgen production by increasing expression of steroidogenic enzyme genes. In the long term, ACTH promotes growth and survival of two zones within the adrenal cortex (see Chapter 43).

AT THE CELLULAR LEVEL

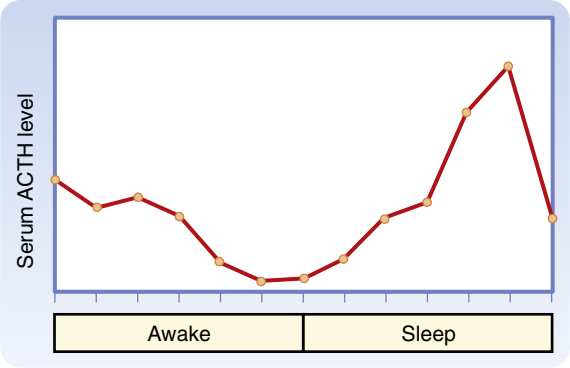
At supraphysiological levels, **ACTH** causes darkening of the skin (e.g., in Cushing's disease). Keratinocytes in the basal layer of the epidermis also express the POMC gene but process it to **α-MSH** instead of ACTH. Keratinocytes secrete α-MSH in response to ultraviolet light, and α-MSH acts as a paracrine factor on neighboring melanocytes to darken the skin. α-MSH binds to the **MC1R** on melanocytes. At very high levels, ACTH can cross-react with the MC1R receptor on skin melanocytes (see Fig. 41.9). Thus, increased skin pigmentation is one indicator of excess circulating ACTH.



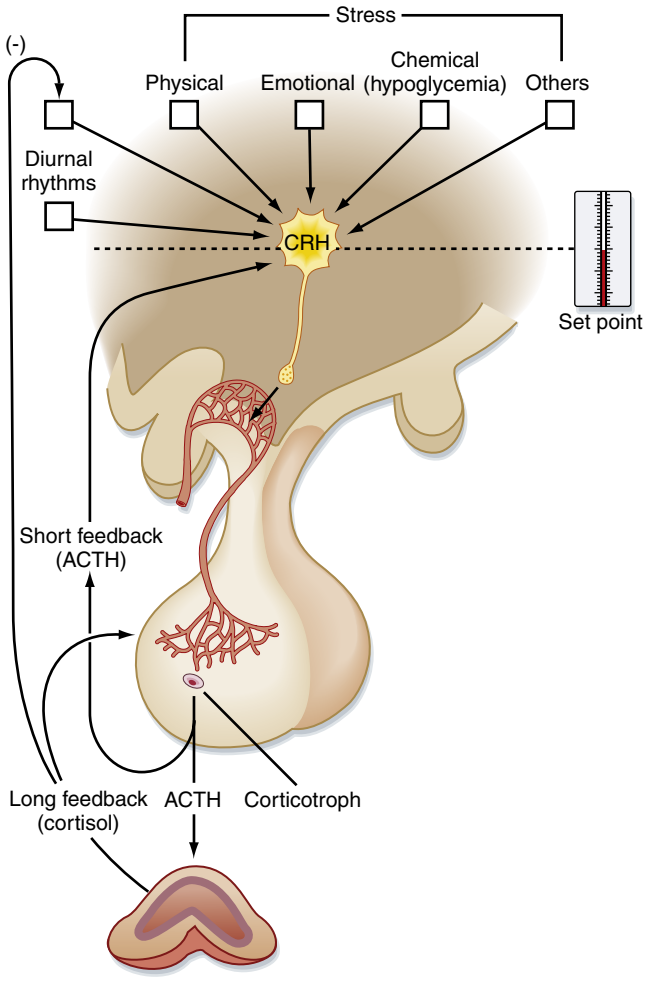
• **Fig. 41.9** Normal levels of ACTH act on the MC2R to increase cortisol. Supraphysiological levels of ACTH due to decreased cortisol production act on both the MC2R and the MC1R on melanocytes and cause skin darkening. *ACTH*, Adrenocorticotropic hormone; *CRH*, corticotropin-releasing hormone; *MC1R*, melanocortin receptor-1; *MC2R*, melanocortin receptor-2 *MSH*, melanocyte-stimulating hormone; *PKA*, protein kinase A; *POMC*, proopiomelanocortin. (Modified from Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)

ACTH is under stimulatory control by the hypothalamus. A subset of parvocellular hypothalamic neurons expresses the peptide **procorticotropin-releasing hormone (pro-CRH)** (see Table 41.1). Pro-CRH is processed to **CRH,** an amidated 41–amino acid peptide. CRH acutely stimulates ACTH secretion and increases transcription of the *POMC* gene. The parvocellular neurons that express CRH also express ADH, which potentiates the action of CRH on corticotropes. ACTH secretion has a pronounced diurnal pattern, with a peak in early morning and a nadir in late afternoon (Fig. 41.10). In addition, secretion of CRH—and hence secretion of ACTH—is pulsatile.

There are multiple regulators of the HPA axis, and many of them are mediated through the CNS (Fig. 41.11). Many types of stress, both neurogenic (e.g., fear) and systemic (e.g., infection), stimulate ACTH. The stress effects



• **Fig. 41.10** Diurnal pattern of serum adrenocorticotropic hormone *(ACTH)*. (Modified from Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)



• **Fig. 41.11** Hypothalamic-pituitary-adrenal axis illustrating factors regulating secretion of corticotropin-releasing hormone *(CRH)*. *ACTH*, Adrenocorticotropic hormone. (Modified from Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)

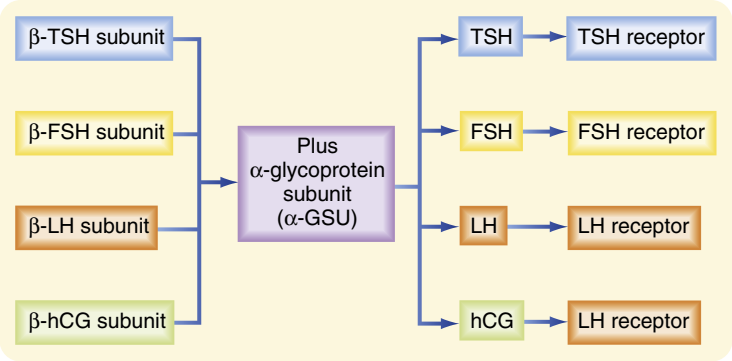
are mediated through CRH and ADH via the CNS. The response to many forms of severe stress can persist despite negative feedback from high cortisol levels. This means the hypothalamus has the ability to alter the set point of the HPA axis in response to stress. Severe chronic depression can reset the HPA axis as a result of hypersecretion of CRH and is a factor in the development of **tertiary hypercortisolism.** Cortisol exerts negative feedback on the pituitary, where it suppresses *POMC* gene expression and ACTH secretion, and on the hypothalamus, where it decreases pro-CRH gene expression and release of CRH. Because cortisol has profound effects on the immune system (see Chapter 43), the HPA axis and the immune system are closely coupled. Moreover, cytokines—particularly interleukin (IL)-1, IL-2, and IL-6—stimulate the HPA axis.

Thyrotropes

Thyrotropes regulate thyroid function by secreting the hormone **TSH (thyrotropin)** as part of the **hypothalamic-pituitary-thyroid axis.** TSH is one of three **pituitary glycoprotein hormones** (see Table 41.1) that also include **FSH** and **LH** (discussed later). TSH is a heterodimer composed of an α subunit, called the **α-glycoprotein subunit (α-GSU),** and a β subunit **(β-TSH)** (Fig. 41.12). The α-GSU is common to TSH, FSH, and LH, whereas the β subunit is hormone specific (i.e., β-TSH, β-FSH, and β-LH are all unique). Glycosylation of the subunits increases their stability in circulation and enhances the affinity and specificity of the hormones for their receptors. The half-lives of TSH, FSH, and LH (and an LH-like placental glycoprotein hormone, **human chorionic gonadotropin [hCG]**) are relatively long, ranging from tens of minutes to several hours.

TSH binds to the TSH receptor on thyroid follicle cells (see Chapter 42). As discussed in Chapter 42, production of thyroid hormones is a complex multistep process, and TSH stimulates essentially every aspect of thyroid function. TSH also has a strong tropic effect and stimulates hypertrophy, hyperplasia, and survival of thyroid epithelial cells. In geographical regions where the availability of iodide is limited (iodide is required for the synthesis of thyroid hormone), TSH levels are elevated because of reduced negative feedback. Elevated TSH levels can produce striking growth of the thyroid, producing a bulge in the neck called a **goiter.**

The pituitary thyrotrope is stimulated by the releasing hormone **thyrotropin-releasing hormone (TRH)** (see Table 41.1). TRH, produced by a subset of parvocellular hypothalamic neurons, is a tripeptide with cyclization of a glutamine at its N-terminus (pyro-Glu) and an amidated C-terminus. TRH is synthesized as a larger prohormone that contains six copies of TRH within its sequence. It binds to the TRH receptor on thyrotropes (Fig. 41.13). TRH neurons are regulated by numerous CNS-mediated stimuli, and TRH is released according to a diurnal rhythm (highest during overnight hours, lowest around dinner time). TRH secretion is also regulated by stress, but in contrast to CRH, stress inhibits secretion of TRH. This includes physical stress, starvation, and severe illness. Triiodothyronine (T_3) and thyroxine (T_4) (the latter via type 2 deiodinase-mediated conversion to T_3; see Chapter 42) negatively feed back on both pituitary thyrotropes and TRH-producing neurons. Thyroid hormone represses both β-TSH expression and the sensitivity of pituitary thyrotropes to TRH while



• **Fig. 41.12** Pituitary glycoprotein hormones. hCG is made by the placenta (see Chapter 44) and binds to the LH receptor. *FSH*, Follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *TSH*, thyroid-stimulating hormone.

also inhibiting TRH production and secretion by parvocellular neurons.

IN THE CLINIC

During embryonic development, GnRH neurons migrate to the mediobasal hypothalamus from the nasal placode. Patients with **Kallmann syndrome** have **tertiary hypogonadotropic hypogonadism,** often associated with loss of the sense of smell (anosmia). This is due to a mutation in the ***KAL* gene,** which results in failure of the GnRH neuronal precursors to properly migrate to the hypothalamus and establish a neurovascular link to the pars distalis.

The Gonadotrope

The gonadotrope secretes FSH and LH (collectively called *gonadotropins*) and regulates the function of the gonads in both sexes. As such, the gonadotrope plays an integral role in the **hypothalamic-pituitary-testis axis** and the **hypothalamic-pituitary-ovarian axis** (Fig. 41.14).

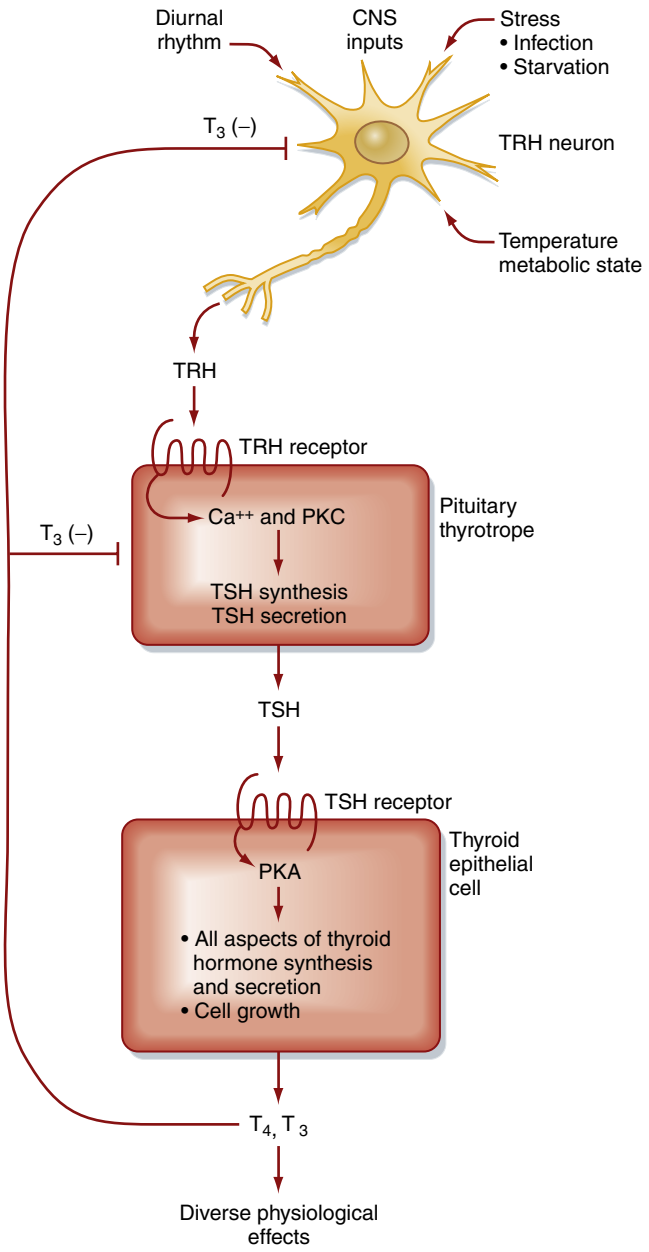
FSH and LH are segregated into different secretory granules and are not co-secreted in equimolar amounts (in contrast to ADH and neurophysin, for example). This allows independent regulation and secretion of FSH/LH by gonadotropes. The actions of FSH and LH on gonadal function are complex, especially in women, and will be discussed in detail in Chapter 44. In general, gonadotropins promote testosterone secretion in men and estrogen and progesterone secretion in women. FSH also increases secretion of a transforming growth factor (TGF)-β–related protein hormone called **inhibin** in both sexes.

FSH and LH secretion are regulated by one hypothalamic-releasing hormone, **gonadotropin-releasing hormone (GnRH;** formerly called **LHRH**). GnRH is a 10–amino acid peptide produced by a subset of parvocellular hypothalamic GnRH neurons (see Fig. 41.14). GnRH is produced as a larger prohormone and, as part of its processing to a decapeptide, is modified with a cyclized glutamine (pyro-Glu) at its N-terminus and an amidated C-terminus.

GnRH is released in a pulsatile manner (Fig. 41.15), and both the pulsatile secretion and the frequency of the pulses have important effects on the gonadotrope. Continuous infusion of GnRH downregulates the GnRH receptor, thereby resulting in a decrease in FSH and LH secretion. In contrast, pulsatile secretion does not desensitize the gonadotrope to GnRH, and results in normal FSH and LH secretion. At a frequency of one pulse per hour, GnRH preferentially increases LH secretion (Fig. 41.16). At a slower frequency of one pulse per 3 hours, GnRH preferentially increases FSH secretion. Gonadotropins increase sex steroid synthesis (see Fig. 41.14). In men, testosterone and estrogen negatively feed back at the level of the pituitary and the hypothalamus. Exogenous progesterone also inhibits gonadotropin function in men and has been considered as a possible component of a male contraceptive pill. Additionally, inhibin negatively feeds back selectively on FSH secretion in men and women. In women, progesterone and testosterone negatively feed back on gonadotropic function at the level of the hypothalamus and pituitary. At low doses, estrogen also exerts negative feedback on FSH and LH secretion. However, high estrogen levels maintained for 3 days cause a surge in LH and, to a lesser extent, FSH secretion. This positive feedback, which is critical in promoting ovulation, is observed at the hypothalamus and pituitary. At the hypothalamus, GnRH pulse amplitude and frequency increase. At the pituitary, high estrogen levels greatly increase the sensitivity of the gonadotrope to GnRH, both by increasing GnRH receptor levels and by enhancing postreceptor signaling (see Chapter 44).

The Somatotrope

The somatotrope produces **GH (somatotropin)** and is part of the hypothalamic-pituitary-liver axis (Fig. 41.17). A major target of GH is the liver, where it stimulates production of **insulin-like growth factor (IGF)-I.** GH is a 191–amino acid protein that is similar to **PRL** and **human placental lactogen (hPL);** accordingly, there is some overlap in activity among these hormones. Multiple forms of GH are present in serum, with the 191–amino acid (22-kDa) form representing approximately 75% of circulating GH. The GH receptor (GHR) is a member of the cytokine/GH/PRL/erythropoietin receptor family and as such is



• **Fig. 41.13** Hypothalamic-pituitary-thyroid axis. *PKA*, Protein kinase A; *PKC*, protein kinase C; T_3, triiodothyronine (active form of thyroid hormone); T_4, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone. (Modified from Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)

linked to the JAK/STAT signaling pathway (see Chapter 3). Human GH can also act as an agonist of the PRL receptor. About 50% of the 22-kDa form of GH in serum is bound to **GH-binding protein (GHBP),** which is derived from the N-terminal portion (the extracellular domain) of the GHR. Individuals with Laron syndrome, who lack normal GHRs, do not have detectable GHBP in their serum. GHBP reduces renal clearance and thus increases the biological half-life of GH, which is about 20 minutes. The liver and kidney are major sites of GH degradation.

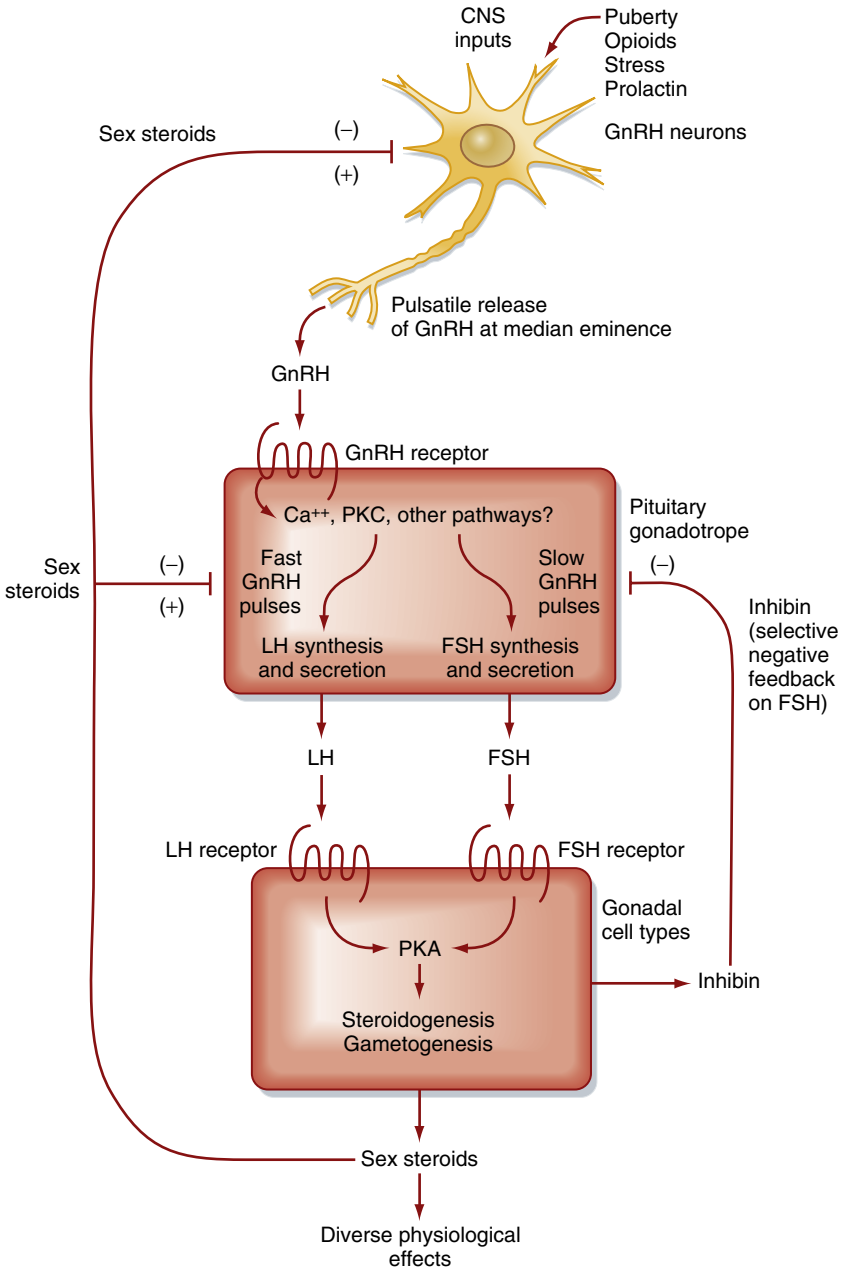
GH secretion is under dual positive/negative control by the hypothalamus (see Fig. 41.17). The hypothalamus predominantly stimulates GH secretion via the peptide **growth hormone–releasing hormone (GHRH).** This hormone is a member of the vasoactive intestinal polypeptide (VIP)/secretin/glucagon family and is processed from a larger prohormone into a 44–amino acid peptide with an amidated C-terminus. GHRH enhances GH secretion and GH gene expression. The hypothalamus inhibits pituitary GH synthesis and release via the peptide **somatostatin.** In the anterior pituitary, somatostatin inhibits release of GH and TSH. GH secretion is also stimulated by **ghrelin,** which acts through the GH secretagogue receptor on somatotropes. Ghrelin is primarily produced by the stomach but is also expressed in the hypothalamus. Ghrelin increases appetite and may serve as a signal to coordinate nutrient acquisition with growth.

The primary negative feedback on the somatotrope is exerted by IGF-I (see Fig. 41.17). GH stimulates IGF-I production by the liver, and IGF-I then inhibits GH synthesis and secretion by the pituitary and hypothalamus in a classic "long feedback" loop. In addition, GH itself exerts negative feedback on release of GHRH through a "short feedback" loop. GH also increases somatostatin release.

GH secretion, like ACTH, shows prominent diurnal rhythms, with peak secretion occurring in the early morning just before awakening. Its secretion is stimulated during deep slow-wave sleep (stages III and IV). GH secretion is lowest during the day. This rhythm is entrained to sleep-wakefulness patterns rather than light-dark patterns, so a phase shift occurs in people who work night shifts. As is typical of anterior pituitary hormones, GH secretion is pulsatile. Levels of GH in serum vary widely (0–30 ng/mL, with most values usually falling between 0 and 3). Because of this marked variation and the heterogeneity of circulating GH, measurement of serum GH levels is of limited clinical utility. Since IGF-I secretion is regulated by GH and possesses a longer half-life that buffers pulsatile and diurnal changes in GH secretion, it may be used to assess the status of the GH axis, especially in young patients.

GH secretion is differentially regulated depending on the physiological state. GH is classified as one of the **"stress hormones"** and is increased by neurogenic and physical stress. It promotes lipolysis, increases protein synthesis, and antagonizes the ability of insulin to reduce blood glucose levels. It is not surprising, therefore, that acute hypoglycemia is a stimulus for GH secretion and GH is classified as a **hyperglycemic hormone.** A rise in the serum concentration of some amino acids also stimulates GH secretion; administration of arginine is used for provocative testing of GH secretion. In contrast, an increase in blood glucose or free fatty acids inhibits secretion of GH. Obesity also inhibits GH secretion, in part because of insulin resistance (relative hyperglycemia) and increased circulating free fatty acids. Conversely, exercise and starvation stimulate GH secretion.

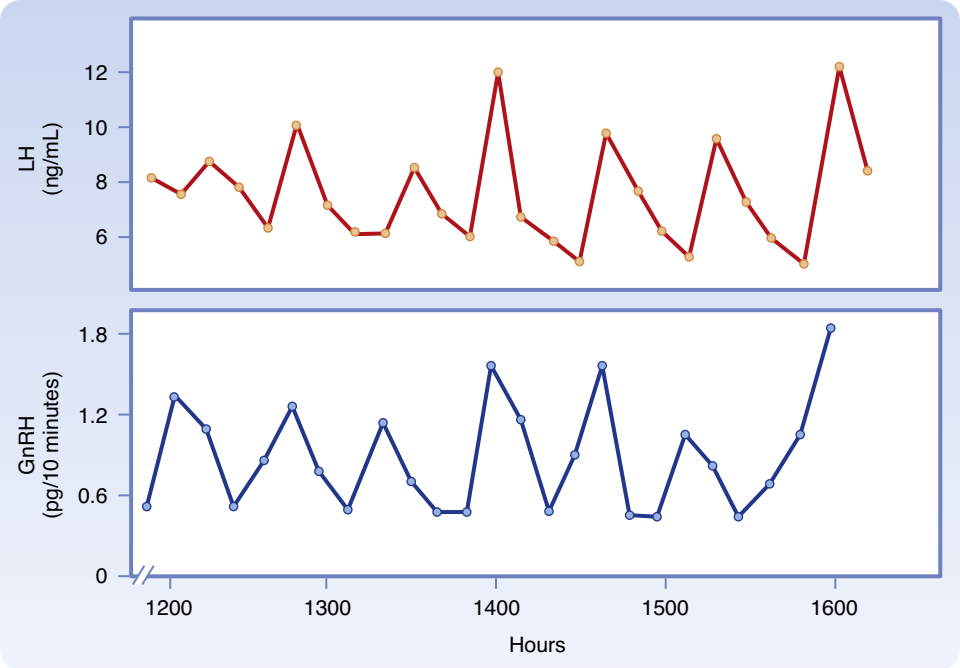
The lifetime pattern of GH secretion is shown in Fig. 41.18. GH secretion increases in the neonatal period as growth becomes GH and IGF-I dependent. It remains high throughout childhood and peaks during puberty, when



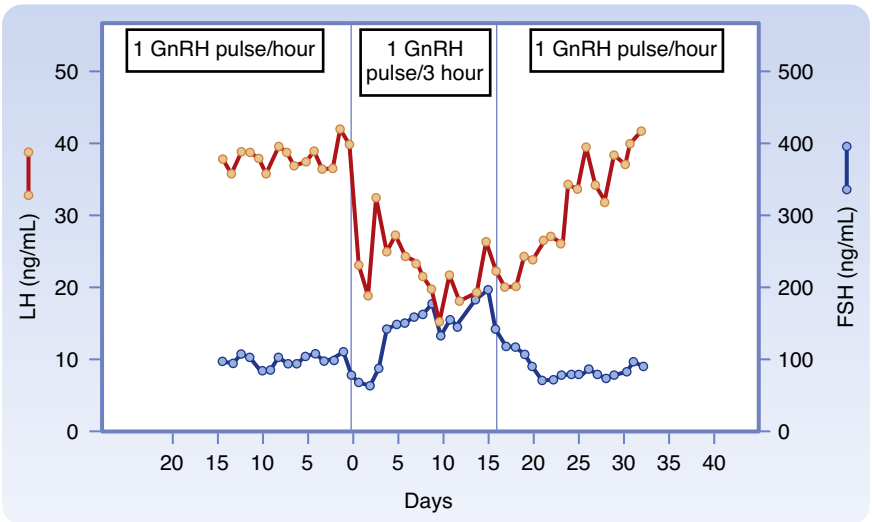
• **Fig. 41.14** Hypothalamic-pituitary-gonadal axis. *FSH*, Follicle-stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone; *PKA*, Protein kinase A; *PKC*, protein kinase C. (Modified from Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)

estrogen (in females and also in males via aromatization of testosterone) promotes even higher rates of GH secretion. Thyroid hormone also enhances GH and IGF-I secretion to support bone growth and maturation. After growth ceases, adults continue to produce GH, consistent with its role in metabolism. GH levels then fall during senescence.

IGFs are multifunctional hormones that regulate cellular proliferation, differentiation, and metabolism. These protein hormones resemble insulin in structure and function. The two hormones in this family, IGF-I and IGF-II, are produced in many tissues and have autocrine, paracrine, and endocrine actions. IGF-I is the major form produced in most adult tissues. IGF-II is the major form produced in the fetus, where it regulates growth of both the fetus and the placenta in a GH-independent manner. Both hormones are structurally similar to proinsulin, with IGF-I exhibiting 42% structural homology with proinsulin. IGFs and insulin show receptor cross-reactivity; IGFs in high concentration mimic the metabolic actions of insulin. Both IGF-I and IGF-II act through type I IGF receptors, which are similar to insulin and epidermal growth factor receptors and contain intrinsic tyrosine kinase activity. However, IGF-II also binds to the type II IGF/mannose-6-phosphate receptor. This receptor does not resemble the insulin receptor, does not have intrinsic tyrosine kinase activity, and probably functions to limit IGF-II signaling through the type

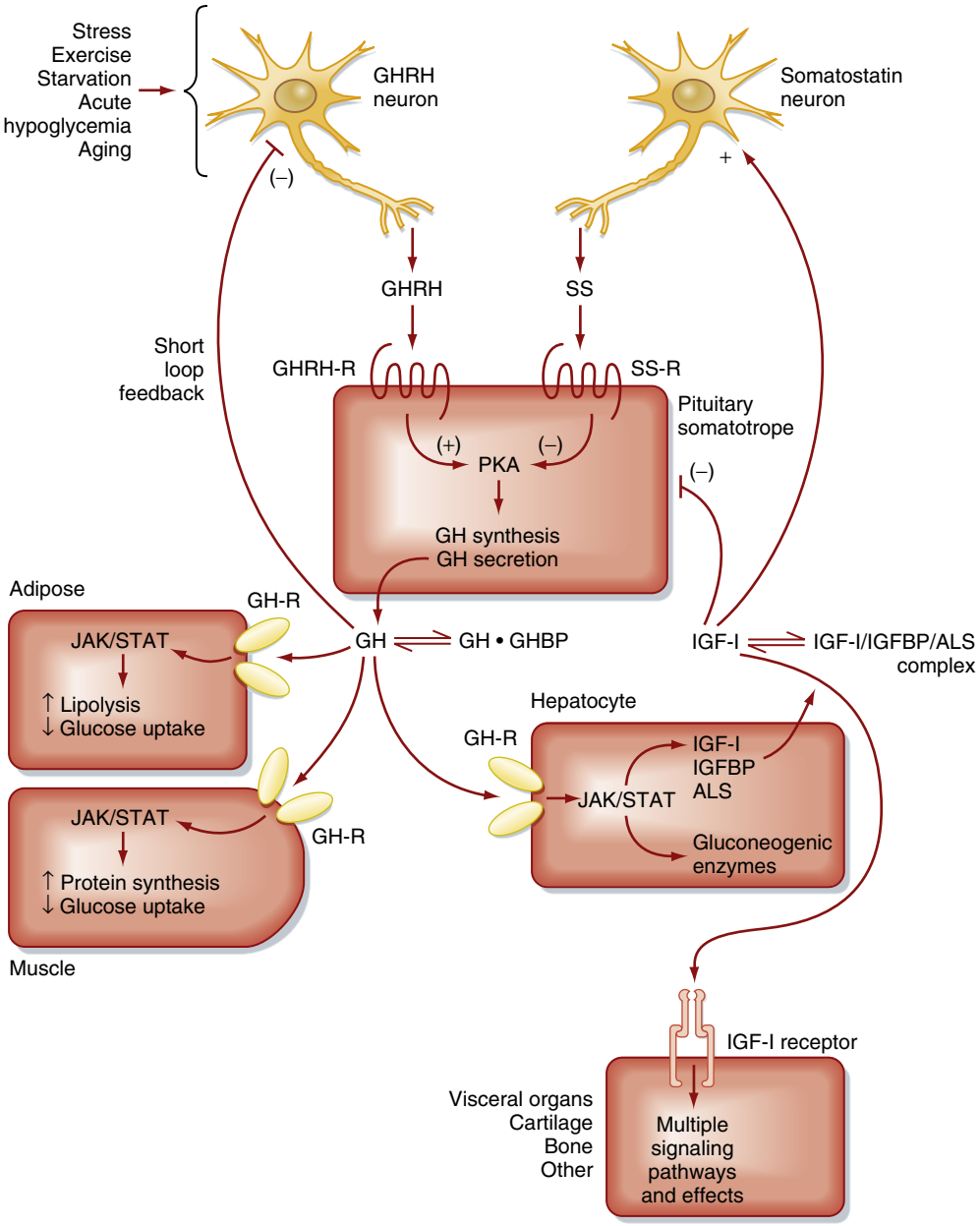


• **Fig. 41.15** Fluctuation of peripheral vein plasma LH levels and portal vein plasma GnRH levels in unanesthetized, ovariectomized female sheep. Each pulse of LH is coordinated with a pulse of GnRH. This supports the view that pulsatility of LH release is dependent on pulsatile stimulation of the pituitary by GnRH. *GnRH*, Gonadotropin-releasing hormone; *LH*, luteinizing hormone. (From Levine J, et al. *Endocrinology*. 1982;111:1449.)

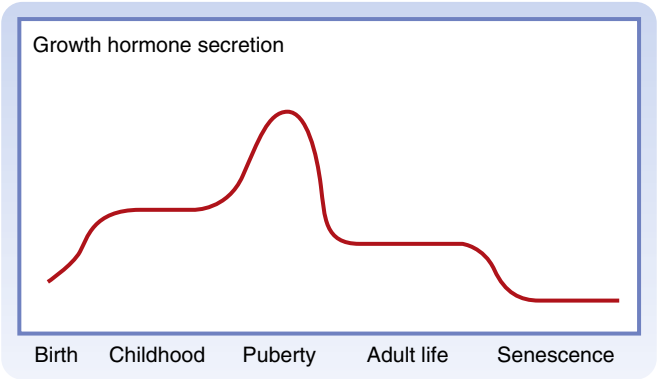


• **Fig. 41.16** Frequency-encoded regulation of FSH and LH secretion from gonadotropes. A high frequency of GnRH (1 pulse/hour) preferentially stimulates LH secretion, whereas a slower frequency of GnRH promotes FSH secretion. *FSH*, Follicle-stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone. (From Larsen PR, Kronenberg HM, Melmed S, et al. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: Saunders; 2003.)

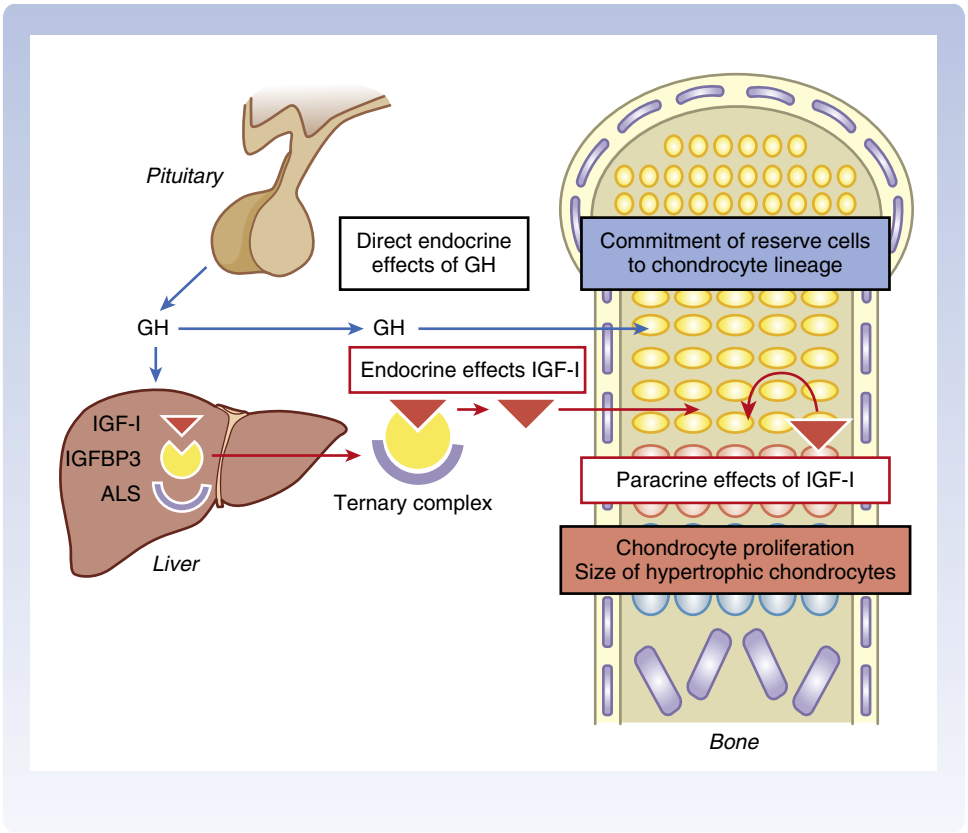
I receptor. IGFs stimulate glucose and amino acid uptake, and protein and DNA synthesis. They were initially called **somatomedins** because of their growth-mediating actions on cartilage, bone, and other organs. It was originally proposed that IGF-I is produced exclusively in the liver upon GH stimulation. During puberty, when GH levels increase (Fig. 41.19), IGF-I levels increase in parallel. However, it is now known that IGFs are produced in many extrahepatic tissues, exhibiting both autocrine and paracrine actions. Some of these are under the control of GH, whereas others are not. In bone, for example, IGF-I has both endocrine and paracrine effects on linear growth, some of which are GH-independent. Hormones such as parathyroid hormone (PTH) and estradiol are also effective stimuli for IGF-I production by osteoblasts. At the same time, GH exerts stimulatory effects on the growth plate that are independent of



• **Fig. 41.17** Hypothalamic-pituitary-liver axis. *ALS*, Acid labile subunit; *GHBP*, growth hormone–binding protein; *GHRH*, growth hormone–releasing hormone; *IGFBP*, insulin-like growth factor–binding protein; *IGF-I*, insulin-like growth factor I; *SS*, somatostatin. (From Porterfield SP, White BA. *Endocrine Physiology.* 3rd ed. Philadelphia: Mosby; 2007.)



• **Fig. 41.18** Lifetime pattern of GH secretion. GH levels are higher in children than in adults, with a peak period during puberty. GH secretion declines with aging.



• **Fig. 41.19** Relationship of GH and IGF-I. GH has direct endocrine actions on growth and stimulates the production of IGF-I, IGFBP-3, and ALS in the liver. Circulating IGF-I exerts endocrine actions on target organs. IGF-1 is also produced locally in bone, where it exerts paracrine effects. Part, but not all of this local IGF-I production is GH-dependent. *ALS*, Acid labile subunit; *IGF-I*, insulin-like growth factor I.

IGF-I. The liver appears to be the predominant source of the circulating pool of IGF-I (see Fig. 41.19).

Essentially all circulating IGFs are transported in serum bound to **IGF binding proteins (IGFBP).** IGFBP-3 binds to IGF and then associates with another protein called the **acid labile subunit (ALS)** (see Fig. 41.19). GH stimulates hepatic production of IGF-I, IGFBP-3, and ALS. The IGFBP-3/ALS/IGF-I complex mediates transport and bioavailability of IGF-I. Although IGFBPs generally inhibit IGF action, they greatly increase the biological half-life of IGFs (up to 12 hours). **IGFBP proteases** degrade IGFBP and play a role in local generation of free (i.e., active) IGFs. This is of interest in the context of IGF-responsive cancers (e.g., prostate cancer), which may overexpress one or more IGFBP proteases.

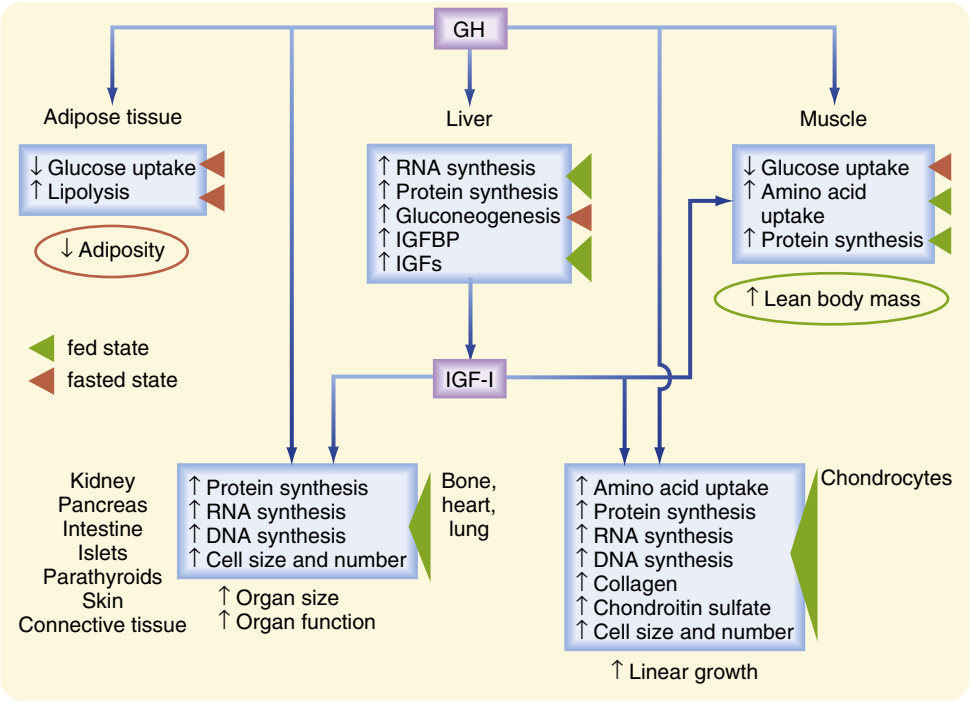
Growth Hormone Actions

GH plays a dual role in metabolism that is highly dependent on physiological context. At the risk of oversimplification, its dual roles are to: (1) promote growth and protein anabolism when nutritional status is favorable and (2) switch fuel consumption to lipids, thereby sparing glucose in the fasted state.

GH acts through a specific **GHR** that is a member of the cytokine receptor family. A GHR dimer binds to GH, which triggers activation of the JAK/STAT signaling pathway (see Fig. 41.17). This results in phosphorylation of STAT5b, which translocates to the nucleus to stimulate transcription of GH-responsive genes. Additional signaling pathways activated by GH include MAPK and PI3K, among others.

In the **fed state,** GH is a **protein anabolic hormone** that increases cellular amino acid uptake and incorporation into protein. Consequently, it causes nitrogen retention (positive nitrogen balance) and decreases urea production. The muscle wasting that occurs concomitant with aging has been proposed to be caused at least in part by the decrease in GH secretion that occurs during senescence. In children, GH increases skeletal, muscular, and visceral growth; children without GH show growth stunting or dwarfism. GH promotes cartilage growth and both linear and appositional growth of long bones (Fig. 41.20, *green arrowheads*).

Although GH is an effective stimulator of IGF production, this response requires insulin, which supports GHR expression and signaling in hepatocytes. When a balanced supply of nutrients is available, high serum glucose levels stimulate insulin secretion and high serum amino acid levels promote GH secretion (Fig. 41.21, *top*). These conditions are appropriate for growth, and GH in turn stimulates IGF-I production by the liver. IGFs are mitogenic and have profound anabolic effects on many organs and tissues, including muscle, cartilage, and bone. Together, GH and IGF-I promote chondrocyte proliferation, differentiation, and hypertrophy during the process of endochondral ossification (see Fig. 41.20, *green arrowheads*). After closure of



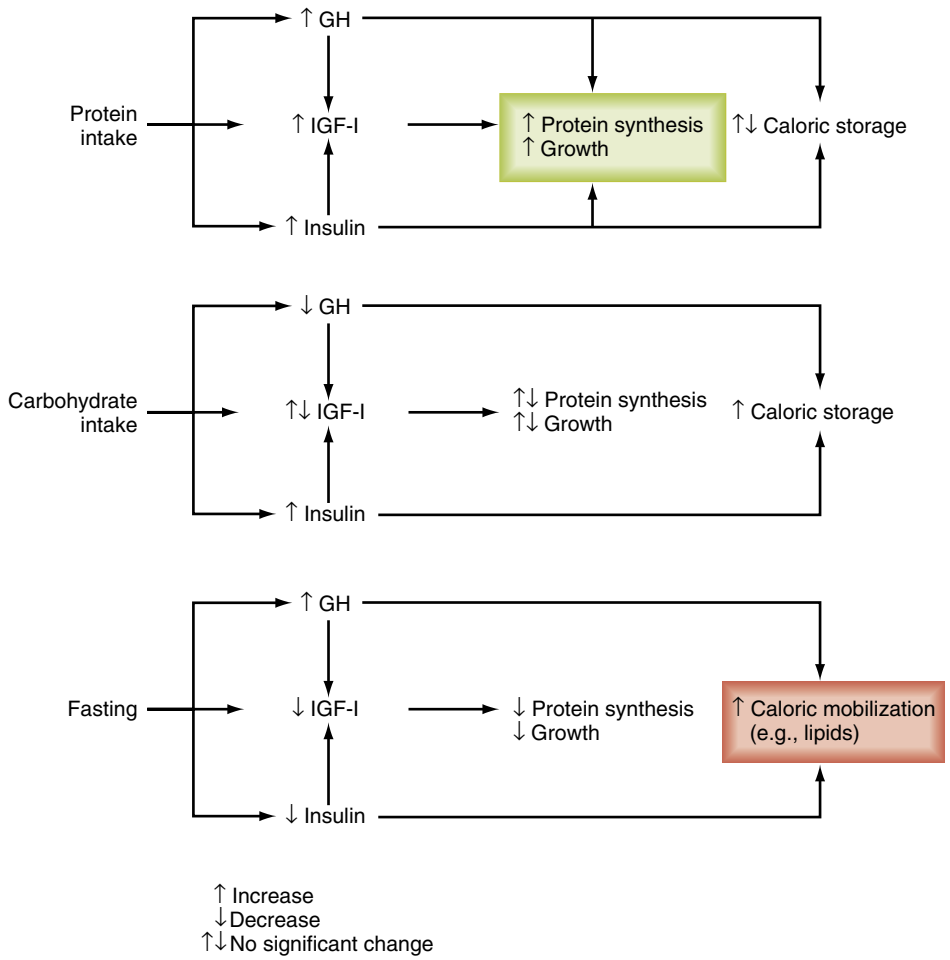
• **Fig. 41.20** Biological effects of GH and IGF-I. Anabolic growth-promoting effects that occur when nutritional status is favorable are indicated by *green arrowheads*. Metabolic effects of GH that mobilize fat while sparing glucose and protein during fasting are denoted by *red arrowheads*. *IGF-I*, Insulin-like growth factor I; *IGFBP*, insulin-like growth factor–binding protein.

the epiphyses, longitudinal growth ceases but appositional growth of long bones continues. IGF-I stimulates osteoblast replication and synthesis of collagen and bone matrix. Not surprisingly, serum IGF levels correlate well with growth in children. The role of GH changes with alteration of nutritional status. If the diet is high in calories but low in amino acids, for example, high carbohydrate availability promotes insulin secretion, but low serum amino acid levels inhibit GH and IGF production (see Fig. 41.21, *middle*). These responses allow dietary carbohydrates and fats to be stored, but conditions are unfavorable for growth.

In the **fasted state,** on the other hand, when nutrient availability wanes, serum GH levels rise and serum insulin levels fall in response to hypoglycemia (see Fig. 41.21, *bottom*). In the absence of insulin, peripheral glucose utilization decreases, thereby conserving glucose for essential tissues such as the brain. In these circumstances the rise in GH secretion is beneficial because it shifts metabolism to lipid as an energy source, thereby conserving carbohydrate and protein. This involves coordinated direct actions of GH on the liver, muscle, and adipose tissue (see Fig. 41.20, *red arrowheads*).

GH is a **lipolytic** hormone. In adipocytes it mobilizes fatty acids and glycerol from triacylglycerol by combined direct and indirect activation of adipocyte lipases. An important indirect action of GH is sensitization of adipocytes to the lipolytic actions of catecholamines, which are also elevated during fasting. Serum fatty acid levels rise as a result of GH action, and more fats are used for energy production. Fatty acid uptake and β-oxidation increase in skeletal muscle and liver. GH can be ketogenic as a result of the increase in fatty acid oxidation when insulin is absent. GH also alters carbohydrate metabolism, causing blood glucose levels to rise. Many of its actions may be secondary to increased fat mobilization and oxidation. For example, an increase in serum free fatty acids inhibits uptake of glucose in skeletal muscle and adipose tissue. The hyperglycemic effects of GH are mild and slower than those of glucagon and epinephrine. Liver glucose output increases, but this is not an effect of GH on glycogenolysis. The increase in fatty acid oxidation and hence the rise in liver acetyl CoA stimulate gluconeogenesis. GH also directly stimulates expression of the gluconeogenic enzyme PEPCK through activation of STAT5b. These actions increase glucose production by the liver from substrates such as lactate and glycerol. The latter is released into the circulation as a result of GH-induced lipolysis in adipocytes.

GH antagonizes the action of insulin at the postreceptor level in skeletal muscle and adipose tissue (but not the liver). **Hypophysectomy** (removal of the pituitary gland) can improve diabetic management because GH, like cortisol, decreases insulin sensitivity. Because GH produces **insulin insensitivity,** it is considered a **diabetogenic hormone.** Therefore, when secreted in excess (e.g., in acromegaly), GH can cause diabetes mellitus, and the insulin levels necessary to maintain normal metabolism increase. Excessive insulin secretion resulting from an excess of GH can cause damage to pancreatic beta cells. In the absence of GH, insulin



• **Fig. 41.21** Differential regulation of GH, insulin, and IGF-I secretion coordinates availability of nutrients with growth and protein anabolism, caloric storage, or caloric mobilization (primarily lipids). *IGF-I*, Insulin-like growth factor I

secretion declines. Thus, normal levels of GH are required for normal pancreatic function and insulin secretion.

IN THE CLINIC

GH is necessary for growth before adulthood. Unless treated, GH deficiencies can result in severe growth deficits, and excesses result in gigantism. Excess GH in adulthood after epiphyseal closure causes **acromegaly,** characterized by insidious enlargement of the hands and feet, coarsening of facial features, insulin resistance, and diabetes. Genetic disorders of the GH–IGF-I axis cause severe growth impairment. Identified mutations causing isolated GH deficiency most commonly occur in the GH and GHRH receptor genes. These patients can be treated with recombinant hGH to restore function of the downstream axis. In Laron syndrome, a mutation of the GH receptor causes GH resistance. In this instance, the liver does not produce IGF-I despite elevated GH levels due to the lack of long-loop feedback. A large cohort of people in Ecuador with Laron syndrome exhibit short stature and central obesity, but interestingly, both diabetes and cancer are very rare in this population. Other downstream genetic mutations that have been reported include those in STAT5B, IGF-I, and ALS.

GH deficiency in adults is becoming recognized as a pathological syndrome. If GH deficiency occurs after the epiphyses close, growth is not impaired. GH deficiency is one of many possible causes of hypoglycemia. Recent studies have shown that extended deficiencies of GH lead to changes in body composition. Fat as a percentage of body weight increases, whereas lean body mass declines. In addition, muscle weakness and early exhaustion are symptoms of GH deficiency. There has been interest in using GH in elderly populations to reverse age-related physical decline and body composition, but studies to date have shown small changes in body composition, no functional benefits, and increased risk of adverse events.

The Lactotrope

The lactotrope produces the hormone **prolactin,** which is a 199–amino acid single-chain protein. PRL is structurally related to GH and hPL (see Chapter 44). Like GH, the PRL receptor is a member of the cytokine family coupled to the JAK/STAT signaling pathways. Because the primary action of PRL in humans is related to breast development and function during pregnancy and lactation, the regulation and actions of PRL will be discussed in detail in Chapter 44.

In the context of the pituitary gland, it should be appreciated that the lactotrope differs from the other endocrine cell types of the adenohypophysis in two major ways:

1. The lactotrope is not part of an endocrine axis. This means PRL acts directly on nonendocrine cells (primarily of the breast) to induce physiological changes.
2. Production and secretion of PRL are predominantly under inhibitory control by the hypothalamus. Thus, disruption of the pituitary stalk and the hypothalamohypophyseal portal vessels (e.g., secondary to surgery or physical trauma) results in an increase in PRL levels but a decrease in ACTH, TSH, FSH, LH, and GH.

PRL circulates unbound to serum proteins and thus has a relatively short half-life of about 20 minutes. Normal basal serum concentrations are similar in men and women. Release of PRL is normally under tonic inhibition by the hypothalamus. This is exerted by dopaminergic tracts that secrete **dopamine** in the median eminence. There is also evidence for existence of a prolactin-releasing factor. The exact nature of this compound is not known, although many factors, including TRH and hormones in the glucagon family (secretin, glucagon, VIP, and gastric inhibitory polypeptide [GIP]), can stimulate release of PRL.

PRL is one of the many hormones released in response to **stress.** Surgery, fear, stimuli causing arousal, and exercise are all effective stimuli. As is the case with GH, sleep increases PRL secretion, and PRL has a pronounced sleep-associated diurnal rhythm. However, unlike GH, the rise in sleep-associated PRL is not associated with a specific sleep phase. Drugs that interfere with the synthesis or action of dopamine increase PRL secretion. Many commonly prescribed antihypertensive drugs and tricyclic antidepressants are dopamine inhibitors. Bromocriptine is a dopamine agonist that can be used to inhibit PRL secretion. Somatostatin, TSH, and GH also inhibit PRL secretion.

Key Concepts

1. The pituitary gland (also called the *hypophysis*) is composed of epithelial tissue (adenohypophysis [anterior lobe]) and neural tissue (neurohypophysis [posterior lobe]).
2. Magnocellular hypothalamic neurons in the paraventricular and supraoptic nuclei project axons down the infundibular stalk and terminate in the pars nervosa. The pars nervosa is a neurovascular organ from which neurohormones are released into the vasculature.
3. Two neurohormones, ADH and oxytocin, are synthesized in the hypothalamus in the magnocellular neuronal cell bodies. ADH and oxytocin are transported intraaxonally down the hypothalamohypophyseal tracts to the pars nervosa. Stimuli received at the cell bodies and dendrites in the hypothalamus control release of ADH and oxytocin at the pars nervosa.
4. The adenohypophysis secretes several tropic hormones that are part of endocrine axes. An endocrine axis includes the hypothalamus, the pituitary, and a peripheral endocrine gland. The set point of an axis is largely controlled by central input and negative feedback by the peripheral hormone on the pituitary and hypothalamus.
5. The adenohypophysis contains five endocrine cell types: corticotropes, thyrotropes, gonadotropes, somatotropes, and lactotropes. Corticotropes secrete ACTH, thyrotropes secrete TSH, gonadotropes secrete FSH and LH, somatotropes secrete GH, and lactotropes secrete PRL.
6. The hypothalamus regulates the anterior pituitary by secreting releasing hormones. These small peptides are carried via the hypophyseal portal system to the anterior pituitary, where they control synthesis and release of the pituitary hormones ACTH, TSH, FSH, LH, and GH. PRL secretion is inhibited by the hypothalamus through the catecholamine dopamine.
7. GH stimulates growth directly and via regulation of the growth-promoting hormone IGF-I. When nutritional status is favorable, GH promotes anabolic protein synthesis and growth. During fasting, GH stimulates lipolysis to mobilize fatty acids as an energy source, sparing glucose and protein. GH raises blood glucose by decreasing peripheral glucose uptake and stimulating hepatic gluconeogenesis.
8. PRL initiates and maintains lactation.