9.2 Hypothalamus and Pituitary Gland

Learning Objectives

- Identify the anatomical location of the pituitary gland, hypothalamus, and parts of the gland including the adenohypophysis and neurohypophysis
- List the hormones secreted by the posterior lobe of the pituitary and state their chemical nature
- Trace the route of posterior pituitary hormones from their point of synthesis to point of secretion
- List the signals leading to oxytocin release
- List the major actions of oxytocin
- List the signals leading to ADH release
- List the major actions of ADH
- List the hormones released from the anterior pituitary
- Describe in general how the hypothalamus controls release of anterior pituitary hormones
- Describe in particular the signals for control of GH release by somatotrophs including GHRH, SST, ghrelin, IGF, and GH
- Summarize the effects of GH
- Name the diseases associated with GH excess or deficit

THE *PITUITARY GLAND* LIES BELOW THE BRAIN AND CONNECTS TO THE HYPOTHALAMUS BY A NARROW STALK

The pituitary gland, also called the **hypophysis**, sits below the brain in a depression of the sphenoid bone called the **sella turcica** or "Turkish saddle" (see Figure 9.2.1). Its name derives from the Greek "ptuo" and the Latin "pituita," meaning phlegm. It has two basic parts, the **adenohypophysis** and the **neurohypophysis**. The adenohypophysis derives from an evagination of the pharyngeal cavity, whereas the neurohypophysis derives from an invagination of the brain tissue. The two coalesce to form the pituitary gland. They remain connected to the hypothalamus through a narrow stalk called the **hypophyseal stalk**.

The adenohypophysis is further divided into three parts: the **pars distalis** is the largest and is also called the **anterior lobe** of the pituitary. The **pars tuberalis** forms the outer covering of the hypophyseal stalk. The third part is the **pars intermedia**, a specialized group of cells lying between the adenohypophysis and the neurohypophysis. In humans, the pars intermedia is small and consists of a thin, diffuse region of cells.

The neurohypophysis consists of the **median eminence**, the bottom part of the hypothalamus, the **infundibular stem** that forms the core of the hypophyseal stalk, and the **infundibular process**, also called the **posterior lobe**. The word "infundibulum" describes "funnel" from which these structures derive their names (see Figure 9.2.1).

CELLS IN THE HYPOTHALAMUS SYNTHESIZE ADH AND OXYTOCIN AND SECRETE THEM IN THE POSTERIOR PITUITARY

The two hormones secreted by the posterior pituitary are **antidiuretic hormone**, or **ADH**, also known as **vasopressin**, and **oxytocin**. Their structures are shown in Figure 9.2.2. Both hormones are synthesized in large cells in the hypothalamus, transported into nerve terminals in the posterior pituitary, and released in response to stimulation of the cell bodies in the hypothalamus. These magnocellular neurons are located in the **supraoptic nucleus** just above the optic chiasm and in the **paraventricular nucleus** on the side of the hypothalamus. The cells that synthesize oxytocin are distinct from those that secrete ADH.

OXYTOCIN AND ADH ARE CHAINS OF NINE AMINO ACIDS

Cells in the hypothalamus synthesize ADH as a large precursor, propressophysin, that contains four separate functional regions: a signal peptide that directs the protein into ER, a 9 amino acid section that becomes the active hormone, a 93–95 amino acid polypeptide that is cleaved off to form **neurophysin**, and a 39 amino acid glycopeptide. ADH is stored in secretory granules bound to neurophysin, which is a 10-kDa protein that binds to other neurophysin molecules and to ADH. The complex of ADH, neurophysin, and glycoprotein is stored within secretory vesicles, and transported down the axon to its terminal in the posterior pituitary. On stimulation, all three are released and then ADH dissociates from the neurophysin in the blood (see Figures 9.2.2 and 9.2.3). Oxytocin is synthesized similarly to vasopressin, except the neurophysin analog is different and there is no glycopeptide.

DOI: http://dx.doi.org/10.1016/B978-0-12-800883-6.00085-9

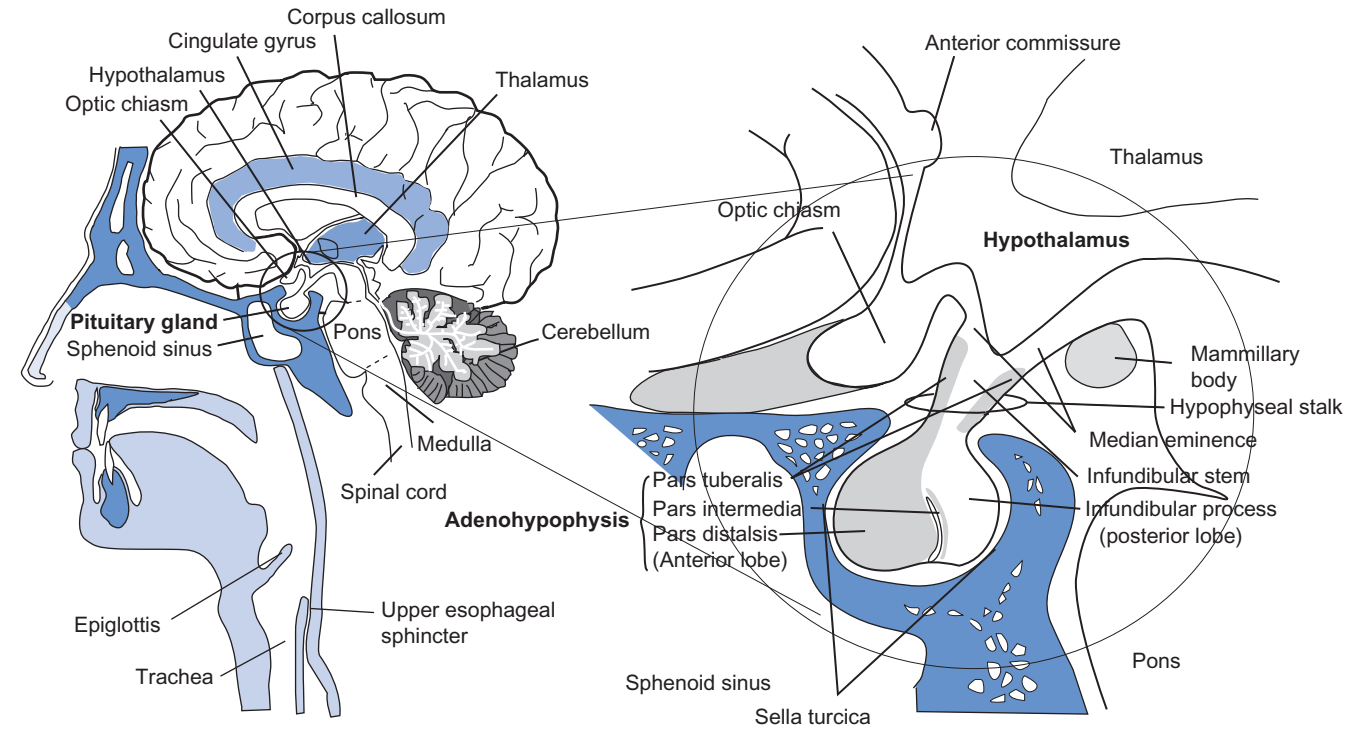

FIGURE 9.2.1 Location and identification of parts of the pituitary gland. The gland lies below the hypothalamus and is connected to it by a hypophyseal stalk. Its mass is about 0.5 g in adult males and is slightly larger in females. It is about 1.2−1.5 cm from side to side, about 1 cm long, and about 0.5 cm thick. The pituitary consists of the adenohypophysis and neurohypophysis. The adenohypophysis in turn consists of the pars tuberalis that covers the hypophyseal stalk, the pars distalis (also called the anterior lobe) and the pars intermedia, which in humans is small. The neurohypophysis consists of the median eminence at the base of the hypothalamus, the infundibular stem in the core of the hypophyseal stalk, and the infundibular process, also called the posterior pituitary. The sphenoid bone surrounds the pituitary with a structure called the sella turcica.

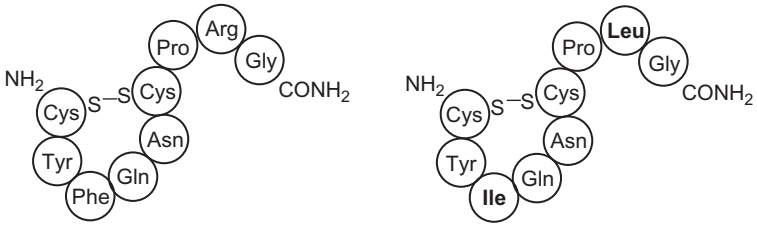

FIGURE 9.2.2 Chemical structures of vasopressin and oxytocin. The two 9 amino acid polypeptides differ only in positions 3 and 8. The terminal carboxyl group is amidated in both hormones.

OXYTOCIN CONTRACTS THE UTERUS AND MYOEPITHELIAL CELLS OF ALVEOLI CELLS IN THE BREAST

Oxytocin has no known humoral function in human males. In females, oxytocin causes the uterus to contract and it causes the "milk ejection reflex," and it may be involved in some maternal behaviors. Stretch or dilation of the cervix and vagina are strong stimuli for oxytocin secretion, mediated by neural pathways called the **Ferguson reflex**. During birth, oxytocin in the mother is released explosively in pulses, causing contraction of the uterus and aiding delivery of the baby. The density of oxytocin receptors increases as much as 200-fold as parturition approaches, which markedly increases the sensitivity of the uterus to oxytocin. Oxytocin binds to oxytocin receptor, OXTR, that is a G-protein-coupled receptor, working through a G_q mechanism. Occupancy of OXTR activates phospholipase C, which releases IP_3, which in turn increases plasma $[Ca^{2+}]$ by release of Ca^{2+} through IP_3 receptors on the ER, which then activates MLKC within smooth muscle cells to activate contraction.

Suckling of an infant at the breast excites sensory afferents that cross in the medulla and eventually connect to the oxytocinergic magnocellular neurons in the supraoptic nucleus and paraventricular nucleus. This sensory information causes a synchronous pulsatile release of oxytocin that pumps milk out of the breast by stimulating the glandular cells of the breast that produce the milk and contraction of myoepithelial cells that empty the alveoli that contain the milk. This effect is called the **milk ejection reflex** or the **milk let-down reflex**. In humans, the release of oxytocin can be elicited by psychological stimuli such as preparing for nursing or hearing the baby cry. Suckling causes pulsatile release of oxytocin, whereas breast massage causes a more continuous oxytocin release (see Figure 9.2.4).

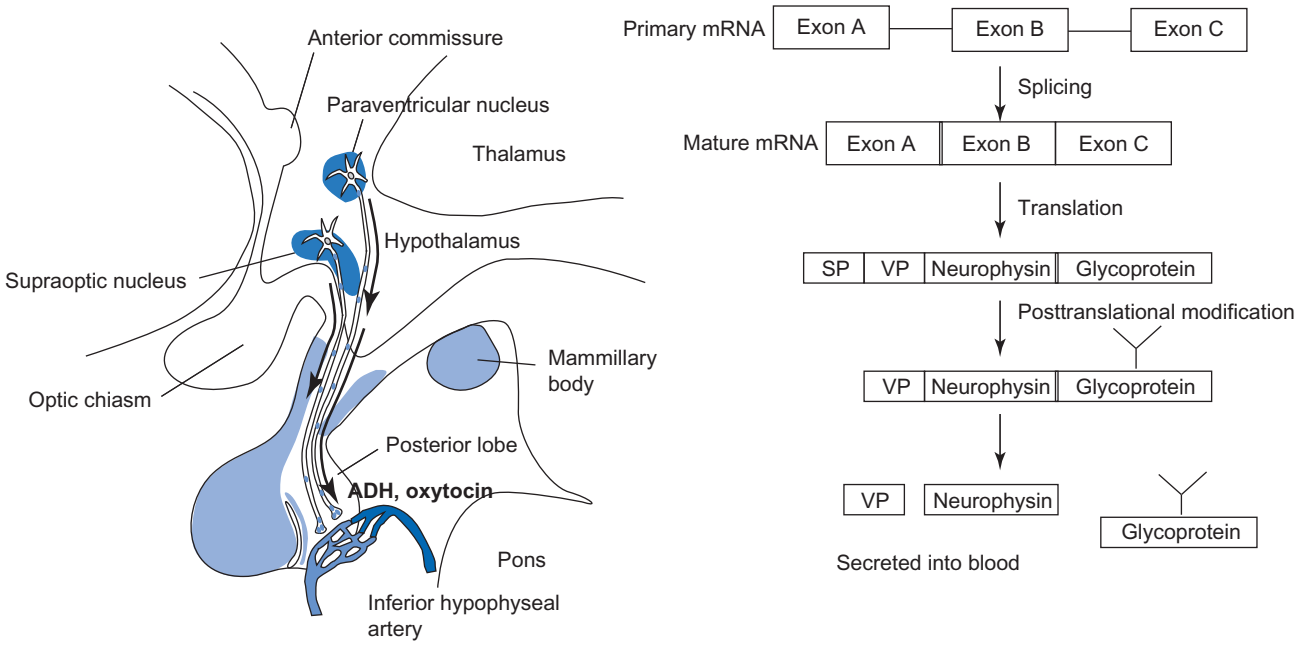

FIGURE 9.2.3 Processing of ADH. Chromosome 20 has three exons that code for ADH in magnocellular neurons located in the supraoptic nucleus and paraventricular nucleus of the hypothalamus. Transcription of the DNA results in a primary mRNA transcript which is then spliced to form a mature mRNA. Translation of the mRNA produces a single peptide strand that contains four functional regions: a signal peptide, ADH (also known as vasopressin, VP), neurophysin, and glycoprotein. The signal sequence is removed and the peptide is cleaved into ADH, neurophysin, and glycoprotein. The neurophysin binds ADH in vesicles that are transported from the soma to its axon terminals in the posterior pituitary where it is released on excitation. Neuroendocrine cells in the supraoptic nucleus and paraventricular nucleus make either ADH or oxytocin, but not both. The same basic mechanism as shown here also applies to oxytocin, except there is no glycoprotein.

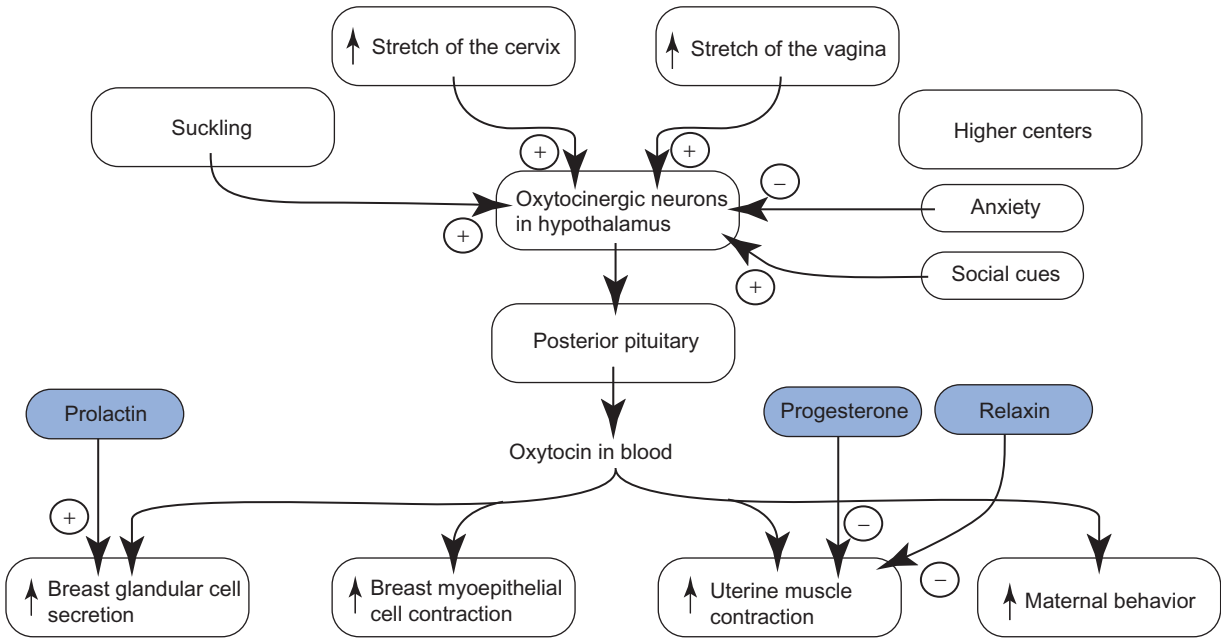

FIGURE 9.2.4 Control and effects of oxytocin. Oxytocin is synthesized in the hypothalamus but released in the posterior pituitary. Its release is stimulated by afferent sensation from the breast caused by suckling, by stretch of the cervix or vagina, and by higher centers. Its main effects are on uterine contraction and lactation. Uterine contraction prior to parturition is inhibited by progesterone and relaxin.

OXYTOCIN HAS BECOME KNOWN AS THE "TRUST HORMONE" OR "LOVE HORMONE"

Oxytocin that is produced by cells in the hypothalamus and released into the blood is a hormone. Oxytocin that is released at nerve terminals elsewhere in the brain is a neurotransmitter, and this release results in detectable increases in plasma levels of oxytocin. Increased plasma levels of oxytocin have been detected in prosocial environments, and administration of oxytocin by nasal sprays promotes a variety of prosocial

behaviors. Oxytocin inhibits fear responses in the amygdala, and this reduction in fear thereby promotes prosocial interactions. For this reason, the hormone has become known as the "trust hormone."

INCREASED PLASMA OSMOLARITY AND DECREASED BLOOD VOLUME STIMULATE ADH RELEASE

Increasing plasma osmolarity and decreasing blood volume independently increase ADH release (see Figure 9.2.5). Osmoreceptors in the anterior hypothalamus tonically stimulate magnocellular neurons to secrete ADH. Lowering the osmolarity reduces ADH secretion and increasing plasma osmolarity increases it. This forms a negative feedback loop, as ADH retains water by action on the kidneys, as described in Chapter 7.6. Briefly, ADH engages a G_s mechanism through V2 receptors that increase the water and urea permeability of principal cells of the collecting duct, by recruiting latent aquaporin-2 water channels to the apical membrane. High ADH increases reabsorption of water and produces a low volume of highly concentrated urine; low ADH is associated with a high volume of highly dilute urine. Lowered osmolarity decreases ADH secretion, causing loss of water over salt in the kidney and the blood osmolarity returns toward normal. Increased osmolarity increases ADH secretion, leading to reabsorption of water. Salt can be excreted in excess of water, leading to a return toward normal plasma osmolarity.

Reduction in blood volume and pressure also stimulates ADH release, but not as strongly as increased osmolarity. High-pressure receptors in the carotid sinus and aortic arch, and low-pressure receptors in the atria and pulmonary veins, inform the central nervous system of the state of the circulation. The afferents travel over cranial nerves IX (glossopharyngeal nerve) and X (vagus nerve) to the medulla. These inputs tonically inhibit ADH release. Reduction in blood volume reduces the firing rate of the stretch receptors, thereby reducing the tonic inhibition and increasing ADH release, causing water retention by the kidney. This cannot raise blood volume by itself, but it helps conserve water that is consumed. ADH also binds to V1 receptors on the blood vessels, causing vasoconstriction through a G_q mechanism and raising the pressure toward normal.

Although the adjustment of water and salt excretion can adjust plasma osmolarity and correct for excess plasma volume, conservation of water alone cannot correct reduced plasma volume. This requires drinking fluids and absorbing the fluid into the blood. **Thirst** is stimulated by the same sensory afferents that control ADH release: high-pressure and low-pressure receptors, and osmoreceptors in the anterior hypothalamus.

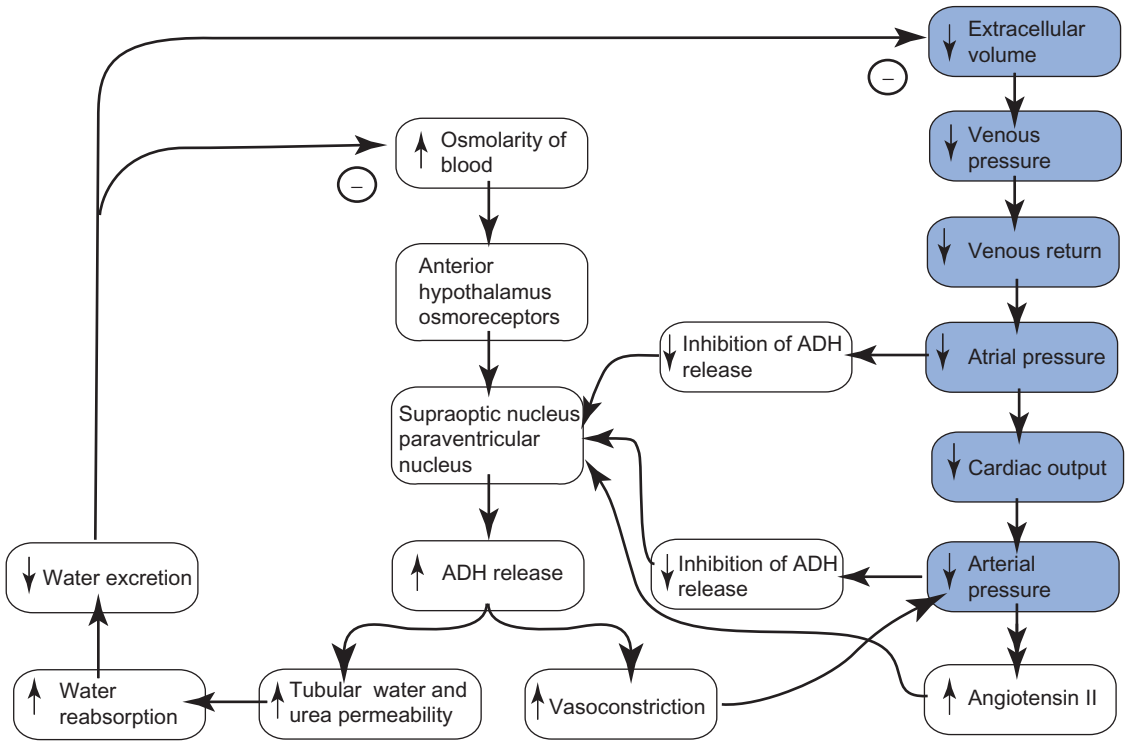

FIGURE 9.2.5 Control of ADH secretion by plasma osmolarity and blood volume. Increased plasma osmolarity increases ADH release. Decreased blood volume, sensed by stretch receptors in the great veins and atria, also increases ADH release. ADH increases water and urea permeability of the distal nephron, leading to excretion of a small volume of concentrated urine, thereby minimizing further loss of blood volume and decreasing the osmolarity of the plasma back toward normal.

THE HYPOTHALAMUS CONTROLS RELEASE OF HORMONES FROM THE ANTERIOR PITUITARY

The anterior pituitary releases hormones in response to stimulation by cells in the hypothalamus. These hormones include:

- thyroid stimulating hormone (TSH)
- adrenocorticotropic hormone (ACTH)
- growth hormone (GH)
- luteinizing hormone (LH)
- follicle stimulating hormone (FSH)
- prolactin (PRL).

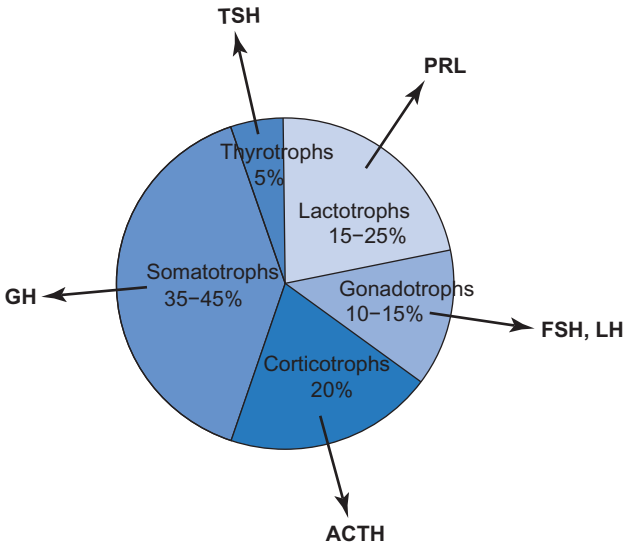

FIGURE 9.2.6 Hormone secreting cells of the anterior pituitary. The five distinct types of cells each secrete definite sets of hormones. The size of the slices reflects the approximate percentage of the cell type in the overall cell population of the anterior pituitary. The locations of the cells are also not arbitrary, being collected in regions. The thyrotrophs, for example, congregate in the anteromedial areas of the gland, whereas somatotrophs are predominantly located in the lateral wings of the gland.

These hormones are secreted in the anterior hypothalamus by five distinct cell types (see Figure 9.2.6). These are **trophic** cells because their hormones affect the growth of their target tissues. **Thyrotrophs** target the thyroid gland; **gonadotrophs** secrete FSH and LH that target cells in the gonads; **somatotrophs** secrete GH that influences overall body (soma) growth; **corticotrophs** secrete ACTH that stimulates secretions and size of the adrenal cortex; and **lactotrophs** secrete PRL that targets the mammary gland.

The superior hypophyseal artery supplies blood to the median eminence. It breaks up into a series of capillaries, forming long and short capillary loops. Neurons in the hypothalamus secrete small molecular weight factors that enter these capillaries. The blood vessels course down into the anterior pituitary, where they once again form an anastomosing network of capillaries. This is a **portal** circulation: a second set of capillaries between artery and vein. These capillaries are fenestrated and lie outside of the blood–brain barrier. The fenestrations allow relatively unrestricted diffusion of materials into the extracellular space. The releasing factors thus travel down to the anterior pituitary undiluted by the general circulation. In the anterior pituitary, these factors bind to receptors on the trophic cells, controlling their secretion of hormones. The anatomic arrangement of these cells and the portal circulation is illustrated in Figure 9.2.7. A summary of the releasing factors is given in Table 9.2.1.

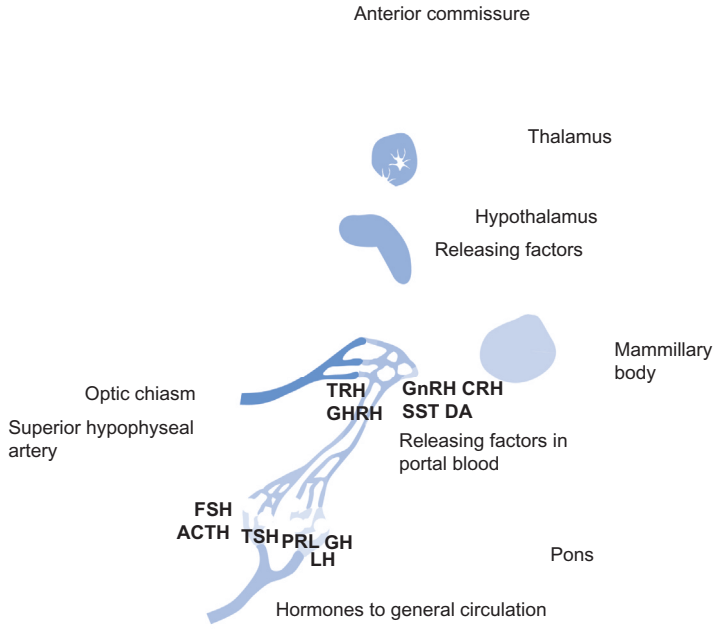

FIGURE 9.2.7 The blood supply to the anterior pituitary and control of anterior pituitary by hypothalamic factors. The superior hypophyseal artery enters the median eminence where it forms a capillary network. This drains into sinuses that form a portal circulation to the anterior pituitary. Neurons in the hypothalamus project axons to the capillary network in the median eminence, and release factors into the blood there. These factors travel down the portal circulation to the anterior pituitary, where they bind to the surface membrane of the trophic cells. The factors may either stimulate or inhibit hormone secretion by these cells. Hormones released in the anterior pituitary eventually travel into the systemic circulation.

TABLE 9.2.1 Hypothalamic Releasing Factors

Releasing Factor	Chemical Nature	Target Cells	Primary Action
TRH (thyrotropin releasing hormone)	3 aa chain	Thyrotrophs	Stimulates TSH release
CRH (corticotropin releasing hormone)	41 aa chain	Corticotrophs	Stimulates ACTH release
GHRH (growth hormone releasing hormone)	40 or 44 aa chain	Somatotrophs	Stimulates GH release
SST (somatostatin)	28 aa chain or 1–12, 14–28 fragments	Somatotrophs	Inhibits GH release
GnRH (gonadotropin releasing hormone)	10 aa chain	Gonadotrophs	Stimulates FSH and LH release
DA (Dopamine)	Neurotransmitter	Lactotrophs	Inhibits PRL release

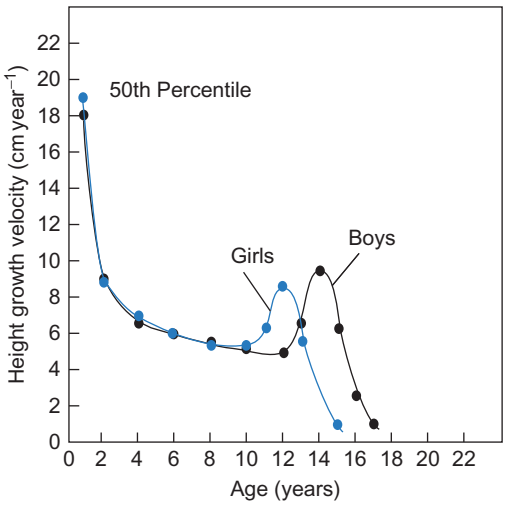

FIGURE 9.2.8 Growth velocity curves for humans as a function of age in years. The curves show the growth rate of height for British boys and girls who were followed longitudinally. Note that the growth spurt for girls occurs earlier and is smaller. This accounts for the difference in average heights between adult men and women. The lines show the 50th percentile. *Adapted from E.O. Reiter and R.G. Rosenfeld, "Normal and Aberrant Growth", in* Williams Textbook of Endocrinology, *10th ed., Saunders, 2003.*

MULTIPLE SIGNALS PRODUCE PULSATILE RELEASE OF GH

GH is a 191 amino acid polypeptide (22 kDa) that is synthesized and secreted by somatotrophs located in the lateral aspects of the anterior pituitary. Circulating GH levels show profound diurnal variation, with peak GH secretion during the night. This is true regardless of the onset of sleep, though GH secretion is further stimulated during slow wave sleep. GH secretion also varies with age. The velocity of growth is shown graphically in Figure 9.2.8, which represents data from British youth followed longitudinally. The pubertal growth spurt corresponds to a peak in circulating GH levels. Total secretion varies from about 2 mg day^{-1} during puberty to about 1/100th of that, 0.02 mg day^{-1}, in elderly or obese adults. The increased secretion during puberty is due to increased secretion at each pulse, rather than a change in the frequency of pulses.

THE COMPLICATED GH SECRETION PATTERN IS PRODUCED BY COMPLICATED NEURONAL CIRCUITS

Pulsatile GH secretion that varies with the time of day and with development requires multiple inputs and complicated circuitry. These secretion patterns largely reflect the interplay between two hypothalamic controls of GH: **GHRH**, **growth hormone releasing hormone**, secreted by cells in the arcuate nucleus, and **somatostatin** (**SST**) secreted by cells in the periventricular nucleus. SST is also referred to as **somatotropin release inhibiting factor** (**SRIF**). Although a lot of the "wiring" has been worked out, it is unclear how much more remains undescribed (see Figure 9.2.9).

The somatotroph cells that secrete GH respond to multiple signals, including:

- **GHRH**, the main stimulator of GH synthesis and release;
- **SST**, the major inhibitor of GH synthesis and release;
- **GH**, which forms a negative feedback inhibition of its own secretion;
- **IGF** (**insulin-like growth factor**, formerly called **somatomedin**);
- **Ghrelin**, a polypeptide made by the stomach that promotes GH secretion.

GHRH TRAVELS TO SOMATOTROPHS THROUGH THE HYPOPHYSEAL PORTAL CIRCULATION

Cells in the arcuate nucleus in the hypothalamus produce GHRH and release it into the hypophyseal portal circulation. These hypothalamic cells receive a variety of inputs, as shown in Figure 9.2.9. Physiological stimuli for GHRH secretion include:

- Episodic, spontaneous release (neuronal patterns)
- Exercise
- Stress (physical or psychological)
- Slow wave sleep
- Fasting
- Postprandial glucose decline
- Gonadal steroids.

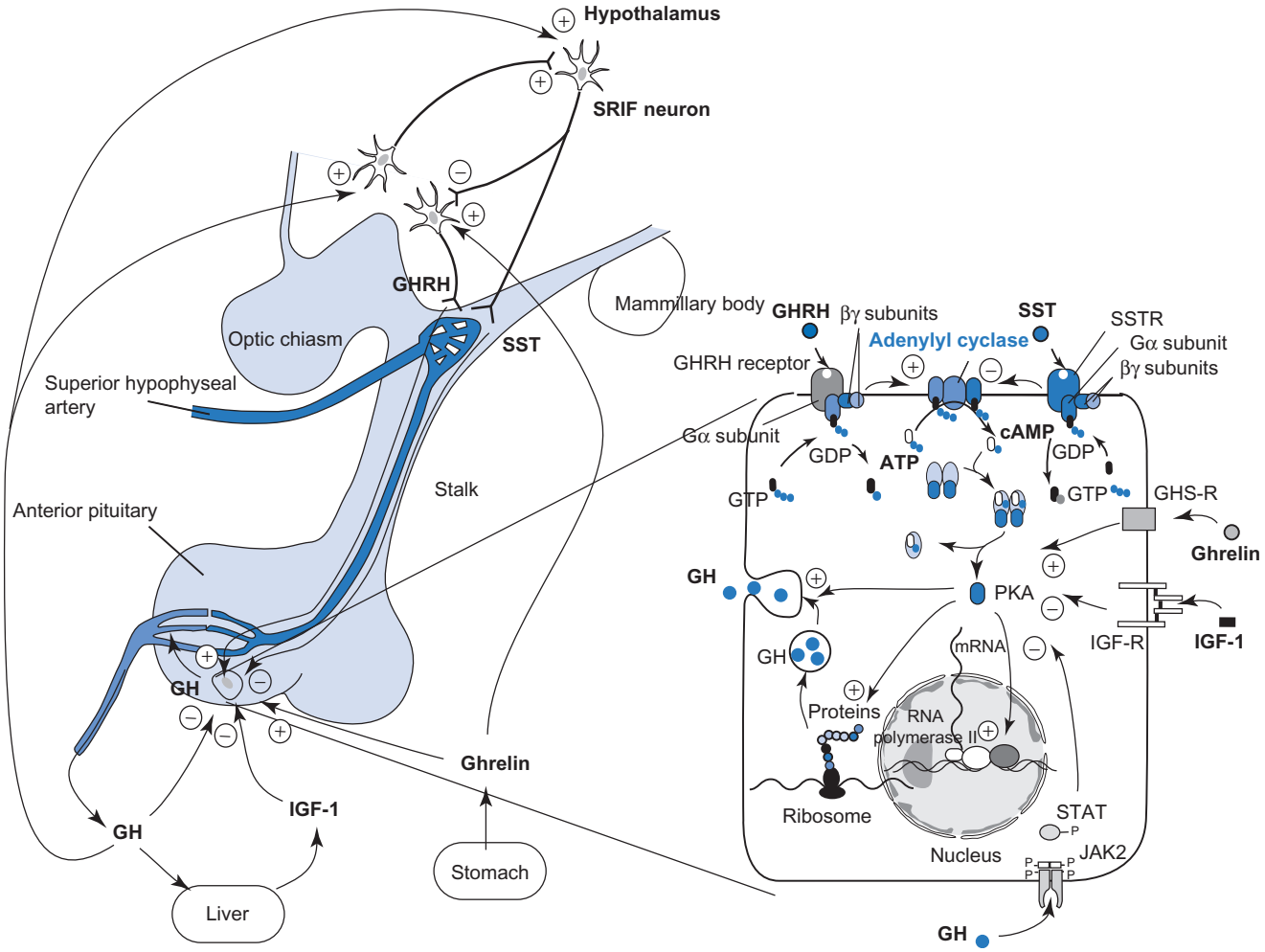

FIGURE 9.2.9 Control of GH secretion. GHRH secreted by cells in the hypothalamus is released into the portal circulation and stimulates GH synthesis and secretion by somatotrophs in the anterior pituitary. SST, also secreted by cells in the hypothalamus, inhibits GH secretion. Ghrelin is secreted by the stomach and promotes GH secretion by direct action in the anterior pituitary and by increasing GHRH secretion from the hypothalamus. GH causes negative feedback inhibition of GH secretion both by itself and through its stimulation of IGF-I and IGF-II secretion into the blood by the liver. All five of these stimuli appear to work through separate receptors on the surface of the somatotroph. GHRH secretion is inhibited by SST and activated by ghrelin and other inputs. Stimulation of SRIF neurons by GH increases SST secretion, which inhibits GH secretion.

GHRH binds to receptors on the somatotrophs' plasma membrane that is coupled to a G_s protein. This stimulates adenylyl cyclase activity and increases cytoplasmic cAMP levels, and activates **protein kinase A (PKA)** that phosphorylates target proteins, causing release of preformed GH, increased GH mRNA transcription, and increased GH synthesis.

SST INHIBITS GH RELEASE

SRIF cells in the periventricular nucleus secrete SST into the hypophyseal portal circulation. SST was found unexpectedly in early efforts to isolate GHRH from pituitary extracts, and the term "SST" was originally applied to a 14 amino acid peptide, now referred to as SST-14. SST-14 is a fragment of SST-28. There are five SST receptors identified so far, and all are present in brain, stomach, and the islets of Langerhans in the pancreas. In somatotrophs, SST is coupled to a G_i protein that inhibits GH synthesis and release.

GH FORMS A SHORT NEGATIVE FEEDBACK LOOP ON GH SECRETION

Somatotrophs have receptors for GH itself. Thus GH released by the somatotrophs feeds back directly on the secretory cells, inhibiting further GH secretion. This forms a short negative feedback loop, so-called because there are no intermediate steps in the loop. The overall control of GH secretion is shown diagrammatically in Figure 9.2.10.

IGF-I INHIBITS GH SECRETION

IGF stands for **i**nsulin-like **g**rowth **f**actor. There are two major types, IGF-I and IGF-II. IGF-I contains 70 amino acids, whereas IGF-II has 67, but the two are separate gene products. These were originally called **somatomedins**, whose properties include:

- serum concentration dependent on GH;
- insulin-like activity;
- stimulation of DNA synthesis and cell multiplication;
- stimulation of sulfate incorporation into cartilage.

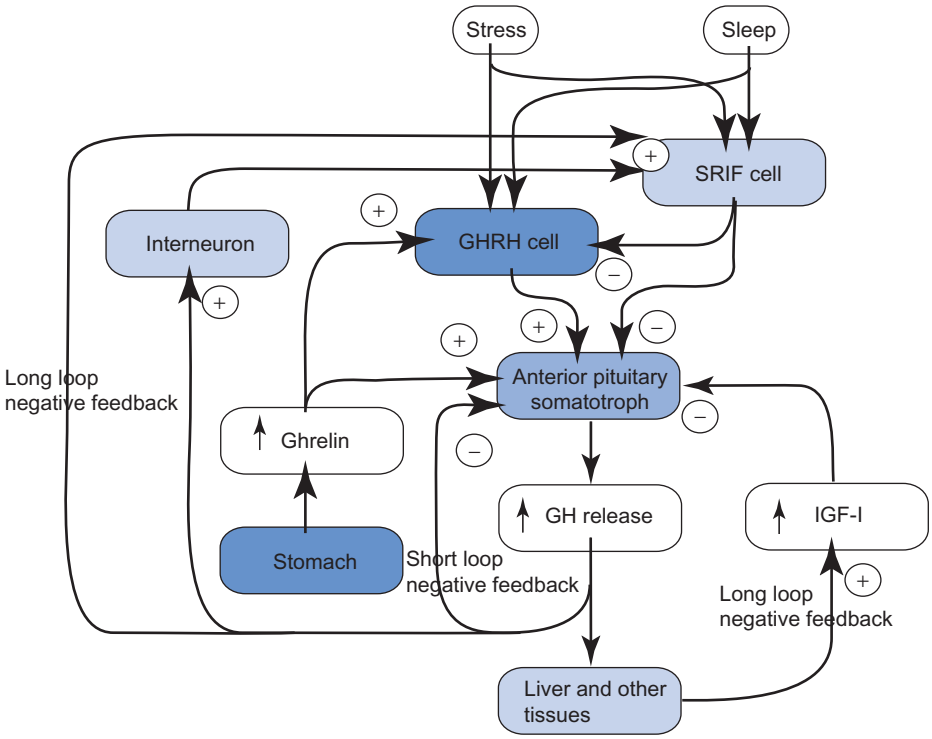

FIGURE 9.2.10 Overall control of GH secretion. The ultimate effect of any pathway can be determined by multiplying the signs of their effects: negative signs denote a decrease or inhibition, and positive signs denote stimulation or increase. Thus GH causes a negative feedback inhibition on its own secretion in a variety of ways: by direct feedback in a short loop ($- = -$); by a long loop through the SRIF cell ($+ \times - = -$); and by a long loop through hypothalamic interneurons ($+ \times + \times - = -$). Light blue boxes denote sources of inhibition of GH secretion, dark blue boxes denote sources of stimulation. The carriers of the signals are in white boxes.

Because of their structural similarity to proinsulin, the somatomedins were renamed as IGF in 1978. GH stimulates IGF-I production by the liver and other tissues. The somatotrophs have receptors for IGF-I and IGF-II, and their occupancy inhibits GH secretion, forming a **long negative feedback loop**.

GHRELIN STIMULATES GH SECRETION

Ghrelin is a 28 amino acid polypeptide secreted by endocrine cells of the stomach, in response to fasting. Somatotrophs have another receptor, called GHS receptor, for **g**rowth **h**ormone **s**ecretagogue. Ghrelin binds to this receptor in both the pituitary and in the hypothalamus.

GH MEDIATES SOME OF ITS EFFECTS THROUGH INCREASED IGF-I

Many of the effects of GH are mediated through somatomedin, or IGF, IGF-I, and IGF-II. IGF-I and II are about the same size but are produced by entirely different genes. GH is the primary regulator of IGF-I gene expression through the JAK-STAT pathway. Binding of one GH molecule to two of its receptors activates JAK2 (Janus kinase). The activated tyrosine kinase activity then phosphorylates a number of signaling molecules including STAT1, STAT3, and STAT5 (STAT refers to **s**ignal **t**ransduction and **a**ctivators of **t**ranscription). The phosphorylated STATs travel to the nucleus where they bind to DNA and elicit specific gene transcription.

Binding of GH to its receptor also activates the MAP/ERK pathway and the mTOR pathway in some tissues. These pathways are shown in Figure 9.2.11.

The somatomedin hypothesis posits that *all* effects of GH are mediated by IGFs. However, IGF administration cannot duplicate all of the effects of GH, and some effects of GH, such as raising blood glucose, are opposite to the effects of IGF. Thus it appears that some effects of GH are independent of IGF.

The overall physiological effects of GH are listed in Table 9.2.2.

SKELETAL GROWTH OCCURS MAINLY AT THE GROWTH PLATES

Most bones are formed by a process called endochondral ossification. This is a highly regulated process shown in Figure 9.2.12. It begins with condensation of mesenchymal cells that differentiate into chrondrocytes. These undergo a regular pattern of proliferation, hypertrophy and calcification and cell death (see Figure 9.2.13) that leaves a mineralized cartilage that is destroyed and replaced with bone tissue by osteogenesis. A large number of signals regulate this process, including insulin-like growth factor (IGF), fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs), and vascular endothelial growth factors (VEGFs). Linear growth of the long bones, which largely determine the height of a person, occurs by proliferation of cells at the epiphyseal plate or the **growth plate**. This is influenced by a number of hormones including GH, IGF-1, thyroid hormone, glucocorticoids, androgens, and estrogens. When the cartilage cells stop proliferation and all become calcified, the growth plate closes and no more linear growth is possible. This is referred

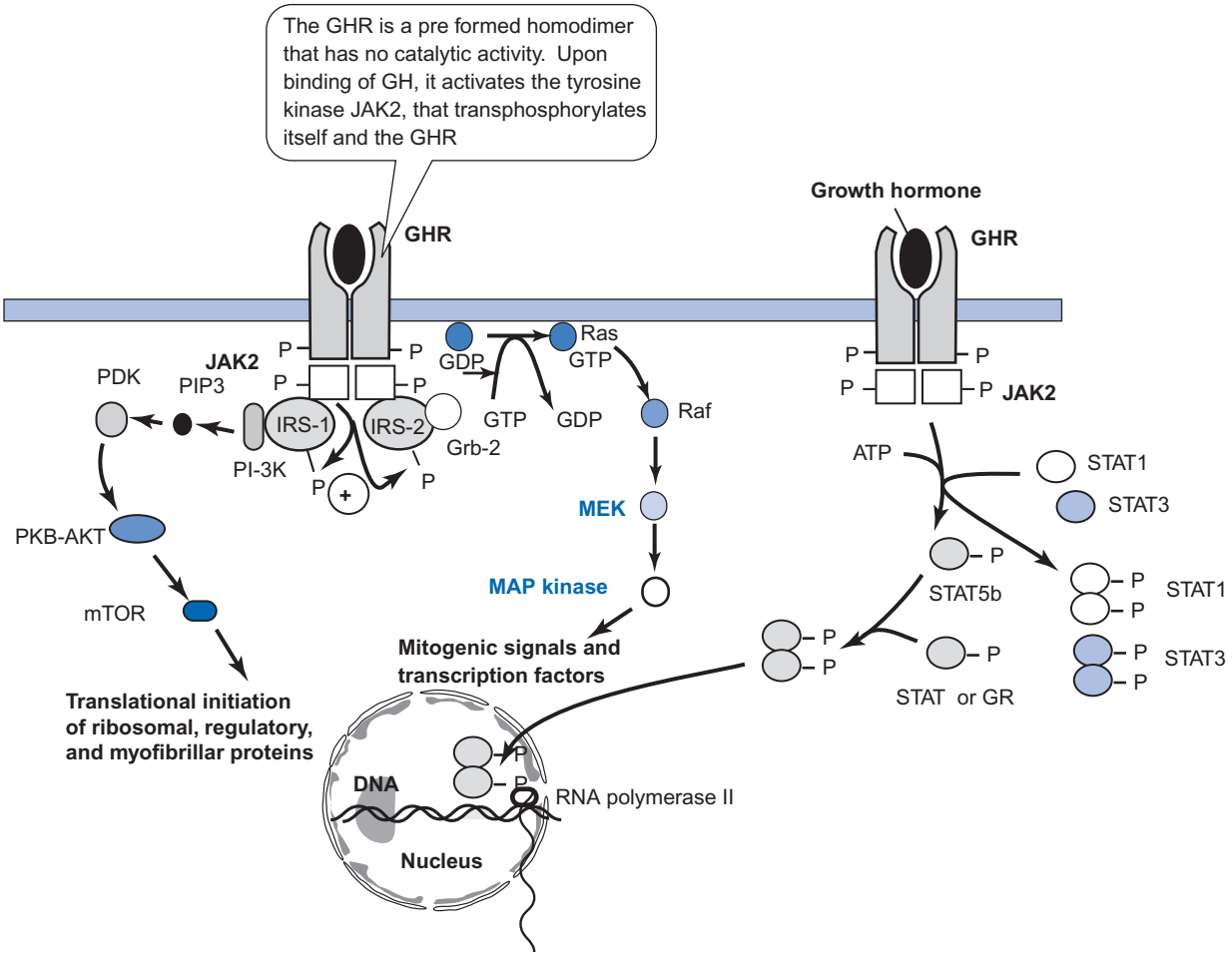

FIGURE 9.2.11 Mechanisms of action of growth hormone, GH. GH binding activates a receptor-associated tyrosine kinase. The GHR already is present in target tissues as a homodimer. Binding of GH activates Janus Kinase (JAK2) that phosphorylates the GHR and itself and phosphorylates interesting proteins including STAT 1, 3, 5a and 5b for **s**ignal **t**ransduction and **a**ctivation of **t**ranscription. These then dimerize and modulate gene expression in the target cell. Most of the effect is mediated by STAT 5b. The GHR-associated tyrosine kinase also phosphorylates IRS (insulin receptor substrates) that activates PI-3K (phosphatidylinositol 3kinase) that produces PIP3, phosphatidylinositol tri phosphate, that activates PDK (protein kinase D) that activates PKB, also known as AKT (activin), which further activates mTOR (mammalian target of rapamycin). mTOR turns on particular genes. In yet a third pathway, MAP kinase (mitogen activated protein kinase) is turned on through a cascade of events.

TABLE 9.2.2 Overview of the Physiological Actions of Growth Hormone

1. **The skeleton**
   - 1.1. Increases formation of cartilage and extracellular matrix
   - 1.2. Increases sulfate incorporation into cartilage (chondroitin sulfate)
   - 1.3. Increases thickness of epiphyseal cartilage of long bones
   - 1.4. Stimulates epiphyseal growth so that long bones are longer
   - 1.5. Stimulates osteoclast differentiation and osteoblast activity, and thereby increases bone mass
2. **Cell proliferation and size**
   - 2.1. Increases the number of cells in most organs of the body
   - 2.2. Increases the size of cells in most organs of the body
3. **Protein metabolism**
   - 3.1. Increases uptake of amino acids into muscle, heart, liver
   - 3.2. Increases total body nitrogen retention
   - 3.3. Increases lean body mass
   - 3.4. Stimulates protein synthesis
4. **Carbohydrate metabolism**
   - 4.1. Increases plasma glucose (the "diabetogenic" effect of GH)
   - 4.2. Mobilizes liver glycogen and increases liver gluconeogenesis
   - 4.3. Increases insulin release
   - 4.4. Inhibits glucose uptake by muscle and adipose tissue
5. **Fat metabolism**
   - 5.1. Increases breakdown of triglycerides to glycerol and fatty acids (lipolysis)
   - 5.2. Increases plasma free fatty acids
   - 5.3. Decreases glucose uptake into adipose tissue
   - 5.4. Decreases body fat
6. **Synergistic actions with other hormones**
   - 6.1. Many hormones (ACTH, TSH, FSH, LH) are more effective with GH present
   - 6.2. Full response to GH requires T3, insulin, sex steroids

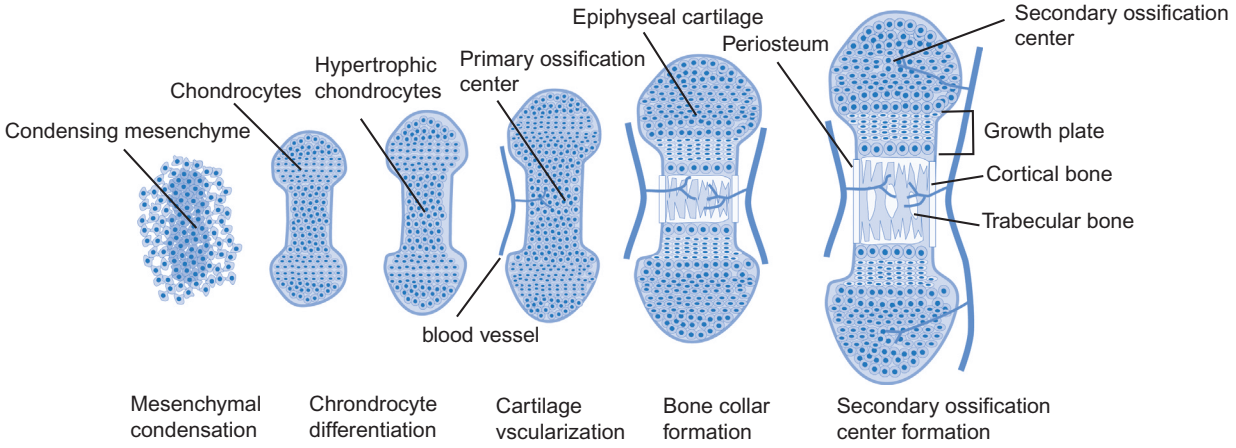

FIGURE 9.2.12 Endochondral bone formation. Endochondral bone formation begins with condensation of mesenchymal cells that then differentiate into chondrocytes that form the extracellular matrix of cartilage. The cells undergo defined steps of proliferation, hypertrophy, and calcification. The primary ossification center begins in the center of the long bones and migrates to each side of the long bones at the epiphyseal growth plates. Here proliferation of chondrocytes continues until closure of the growth plate during early adulthood. The process is regulated by a number of endocrine and paracrine secretions. *Adapted from Y. Xie, S. Zhou, H. Chen, X. Du and L. Chen, Recent research on the growth plate. Advances in fibroblast growth factor signaling in growth plate development and disorders.* J. Mol. Endocrinol. ***53****: T11-34, 2014.*

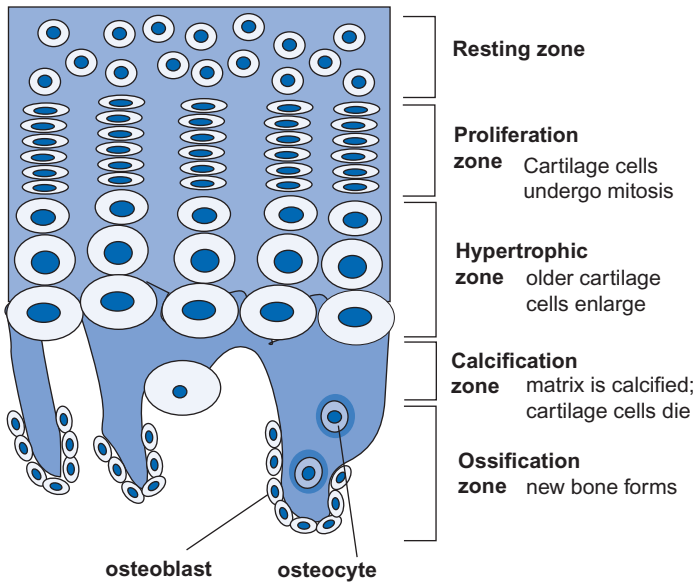

FIGURE 9.2.13 Cartoon of chondrocyte involvement in the formation of bone. Chondrocyte shows distinct stages that are reflected in spatial zones within the growth plate. The resting zone has small round cells that are adjacent to the articular surface. These cells undergo mitosis to form flat chondrocytes that are arranged in proliferative columns. Resting cells and proliferative chondrocytes secrete collagen II, aggrecan, and other matrix proteins to form the cartilage matrix. The proliferative chondrocytes form prehypertrophic and then hypertrophic condrocytes that secrete collagen X. These hypertrophic chondrocytes remodel the cartilage and then die. The matrix is calcified in the calcification zone. The calcified matrix is then ossified by resorption of the mineralized cartilage, vascularization, and formation of bone through osteoblasts. A mnemonic for these zones is "Real People Have Career Options", for Resting, Proliferation, Hypertrophy, Calcification and Ossification.

to as closure of the growth plate. Thus the adult height is determined by the regulation of proliferation and its final ending at the growth plate, and this process is controlled by multiple genes.

BOTH STARVATION AND ESTROGEN REDUCE ADULT HEIGHT

Children who suffer from protein-calorie malnutrition exhibit stunted growth. It is possible that this effect is mediated by **fibroblast growth factor 21 (FGF21)**. In rodents, FGF21 is secreted by mainly by liver and adipose tissue in response to energy deprivation, mediated by PPARα (peroxisome proliferator-activated receptor) which is in turn activated by increased free fatty acids in plasma that occur following lipolysis stimulated by starvation. FGF21 binds to its receptor, β-Klotho, and initiates signals that interferes with JAK/STAT signaling by GH. FGF21 acts on both the liver and the chondrocytes in the growth plate to inhibit GH actions. Osteoblasts secrete IGF-1 in response to GH. This IGF-1 acts as a paracrine hormone, and its effects are attenuated by FGF21. This effect is shown schematically in Figure 9.2.14. Whether this explains growth inhibition in malnourished children is less clear, as FGF21 in humans is less responsive to fasting, and circulating FGF21 level is elevated in obese humans.

Other hormones, such as estrogen, have biphasic effects on growth. At low doses, estradiol stimulates GH effects on the liver, apparently explaining the stimulation of growth in early puberty. High doses of estradiol inhibit longitudinal growth, explaining the reduced stature of women. In the liver, estrogen attenuates GH effects by stimulating SOCS2 (suppressor of cytokine signaling 2).

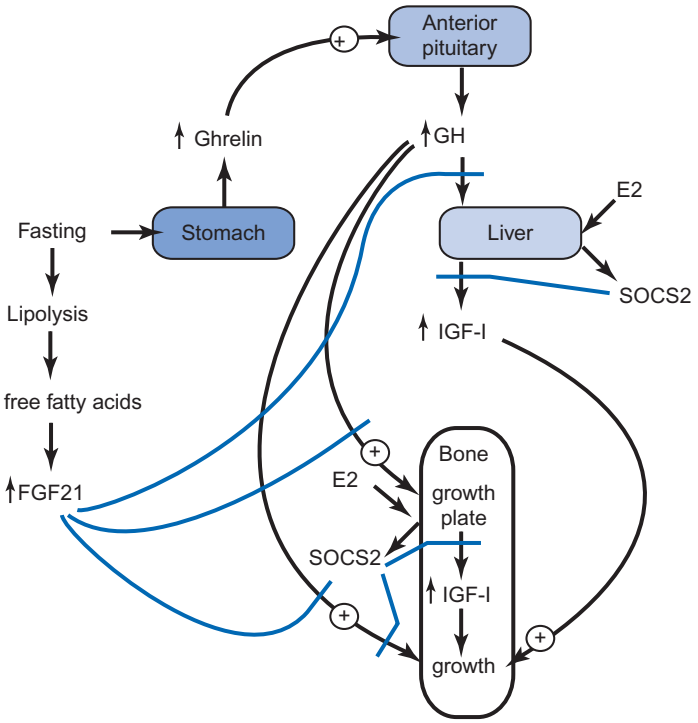

FIGURE 9.2.14 Interactions of growth hormone with other modulators. The major effects of GH are mediated by IGF-1 released by the liver systemically and by IGF-1 released within the tissues as a paracrine messenger. Some effects of GH are independent of IGF-1. The effects of GH are inhibited by fibroblast growth factor 21 (FGF21) that is released mostly by liver and adipose tissue in response to fasting. FGF21 interferes with GH signaling in liver and bone, thereby inhibiting linear growth during energy deprivation. Estadiol (E2) at low levels stimulates growth and in higher levels inhibits growth. Inhibition likely occurs by increased expression of SOCS2 (suppressor of cytokine signaling 2).

The family of SOCS proteins use a variety of mechanisms to disrupt signaling including masking of binding sites on the GHR/JAK2 complex, inhibition of JAK2 activity, and stimulation of the ubiquitinylation of the GHR, leading to its degradation. It is likely that this is part of the inhibition of growth by estrogen that is responsible for the shorter height of human females, as the estrogen produced later on during puberty leads to an earlier closure of the growth plate, and therefore less linear growth.

SUMMARY

The pituitary gland consists of two major components: the adenohypophysis and the neurohypophysis. Part of the adenohypophysis is the pars distalis, also referred to as the anterior lobe. The infundibular process of the neurohypophysis forms the posterior pituitary. The gland sits below the hypothalamus and is connected to it by the hypophyseal stalk. This stalk contains neuronal processes and blood vessels that collect neurotransmitters released by nerve cells in the hypothalamus. In this way, the endocrine system is connected to and controlled by the nervous system.

The hormones released by the posterior pituitary include ADH and oxytocin. These are synthesized by cells in the paraventricular and supraoptic nucleus of the hypothalamus and are transported down into the posterior pituitary by axoplasmic transport, bound within vesicles to neurophysin. Stimulation of the cells in the hypothalamus causes fusion of the vesicles and release of the hormones into the blood. Both ADH and oxytocin contain nine amino acids and show structural similarity. ADH release is increased by increased plasma osmolarity and decreased blood volume. The actions of ADH are twofold: it increases the water and urea permeability of the distal nephron and thereby causes the kidneys to excrete a low volume of highly concentrated urine. This effect on water and urea permeability is due to cAMP and PKA-mediated phosphorylation of aquaporin channels which are then inserted into the apical membrane of kidney tubule cells. The second action of ADH is vasoconstriction, from which ADH derives its other name: vasopressin.

Stimulation of oxytocin is provided by stretch of the uterus and suckling or associated psychosocial cues. The hormone causes uterine contraction and is essential in parturition. It also causes the milk "let-down" reflex or the milk ejection reflex: it stimulates contraction of myoepithelial cells in the breast and milk secretion by the breast.

The anterior pituitary releases a number of "master hormones" including TSH, LH, FSH, PRL, GH, and ACTH. These are released from specific cells in the anterior pituitary in response to releasing factors produced by neurons in the hypothalamus. These neurons package the releasing factors in neurotransmitter vesicles that dump their contents into the hypophyseal portal circulation that carries the factors to the anterior pituitary without dilution.

GH is synthesized and released by specific cells called somatotrophs in the anterior pituitary. These cells integrate at least five separate signals: GHRH, SST, ghrelin, IGF-1, and GH itself. GHRH is released from cells in the arcuate nucleus of the hypothalamus and stimulates GH release by somatotrophs by a G_s mechanism. SST is released from cells in the periventricular nucleus and inhibits GH release by a G_i mechanism. Ghrelin is released from the stomach during fasting and stimulates somatotrophs directly and also stimulates release of GHRH by hypothalamic cells. GH negatively feeds back onto somatotrophs to reduce GH secretion.

Clinical Applications: GH Excess or Deficiency

Excess GH secretion from childhood is **gigantism** and results in abnormally tall persons. Probably the documented record for the tallest human being was Robert Wadlow (February 22, 1918—July 15, 1940) who reached the height of 8′11″ (2.72 m) but had not stopped growing at the time of his death at the age of 22. The average height in the United States for men is 5′10″ or 1.72 m. His weight at the time of death was 485 lb (220 kg) with size 37AA shoes. Wadlow is sometimes known as the Alton Giant, named for his home town of Alton, Illinois (see Figure 9.2.15).

Excess GH has its consequences. Wadlow suffered from muscle weakness and tendency toward infections. He required braces to walk, and one of these irritated his ankle, causing a blister and subsequent infection. This probably progressed to septicemia and he died in his sleep at age 22.

Excess GH secretion in the adult causes **acromegaly**, first described by Pierre Marie in 1886 as disordered somatic growth and proportion. Pituitary adenomas cause 95% of the cases of acromegaly. The adenomas typically are slow-growing tumors that appear in the third to fifth decade of life. The symptoms of acromegaly include glucose intolerance, widening of bones leading to coarser facial features and enlarged hands and feet, enlarged heart, liver, and kidneys, and thickened skin and enlarged muscles.

GH deficiency in childhood produces short adults with a general tendency toward obesity. Any malfunction in the cascade from GHRH secretion to target cell responsiveness could account for dwarfism. These people have delayed skeletal growth and sexual maturation, but they are otherwise healthy with normal mental capacity. However, persons with GH deficiency have reduced life expectancy due to cardiovascular and cerebrovascular diseases. Because the window of opportunity closes early in life, diagnosis of GH deficiency must be made early. Children 3 standard deviations (SD) below average or with growth deceleration (2 SD below average for 1 year), or with combinations of these, should be evaluated for the cause of poor growth. A variety of conditions can cause secondary growth disorders: malnutrition, chronic diseases such as malabsorption and GI diseases, chronic liver disease, cardiovascular disease, or renal disease. Primary causes of GH deficiency lie in pituitary or hypothalamic dysfunction, and IGF deficiency due to GH insensitivity.

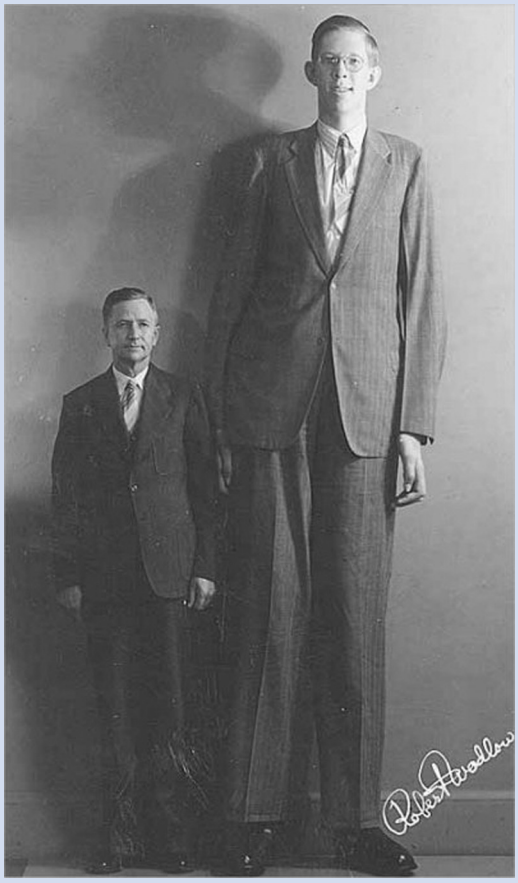

FIGURE 9.2.15 Robert Wadlow compared to his father, Franklin Wadlow, at 5′11″.

Probably the most famous dwarf was Charles Stratton (January 4, 1838—July 15, 1883) who achieved fame through association with P.T. Barnum. He was born in Bridgeport, CT, weighing 4.3 kg at birth. He stopped growing at 6 months of age and 25″ (64 cm). At 9 years of age he began to grow again, reaching 82.6 cm at age 18. He toured the United States and Europe as an entertainer, with the stage name General Tom Thumb, earning a fortune. He died in 1883 from a stroke at the age of 45.

The hypothalamic cells respond to a variety of stimuli. The final GH release is episodic and pulsatile.

GH has multiple effects on multiple systems. Excess produces gigantism in youth and acromegaly in adults. Deficits in childhood cause dwarfism. It increases the growth of long bones and increases the uptake of amino acids, increases blood glucose and mobilizes glycogen, and increases lipolysis. Linear growth stops upon closure of the epiphyseal growth plate in the long bones. Effect of GH on the growth plates is inhibited by fasting through elevation of fibroblast growth factor 21 (FGF21) and by high levels of estradiol, probably mediated by increased expression of suppressor of cytokine signaling 2 (SOCS2).

REVIEW QUESTIONS

1. Where is the pituitary gland? What is the adenohypophysis? What is the neurohypophysis?
2. What hormones are secreted by the posterior pituitary? What are their chemical natures?
3. What stimulates ADH release? What are the main effects of ADH? What signaling mechanism is involved in the renal effects of ADH? What signaling mechanism is involved in the vascular effects of ADH?
4. What stimulates oxytocin release? What are the main effects of oxytocin?

5. What hormones are secreted by the anterior pituitary? What controls their release?
6. What cells secrete GH? What hypothalamic factors increase secretion? What hypothalamic factors decrease secretion?
7. Describe the anatomic relationship between hypothalamic cells and control of GH release.
8. What other factors control GH release?
9. What signaling mechanism does GH use? What does GH do directly? List the effects of GH.
10. What happens when GH is present in excess in youth? In adulthood? What happens when it is deficient?