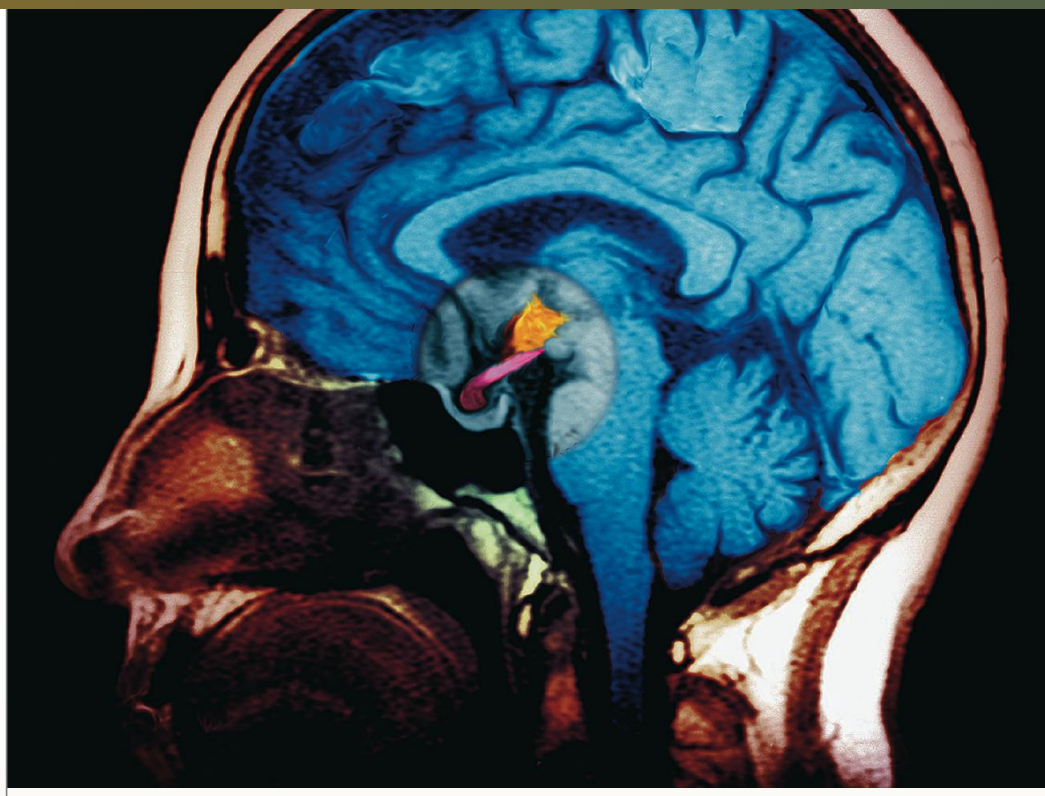
The Endocrine System

CHAPTER 11



MRI of a human brain showing the connection between the hypothalamus (orange) and the pituitary gland (red).

In Chapters 6–8 and 10, you learned that the nervous system is one of the two major control systems of the body, and now we turn our attention to the other—the endocrine system. The **endocrine system** consists of all those ductless glands called **endocrine glands** that secrete hormones, as well as hormone-secreting cells located in various organs such as the brain, heart, kidneys, liver, and stomach. You will learn about exocrine (ducted) glands in Chapter 15. **Hormones** are chemical messengers that enter the blood, which carries them from their site of secretion to the cells upon which they act. The cells a particular hormone influences that express the receptor for the hormone are known as the target cells for that hormone. The aim of this chapter is to first present a detailed overview of endocrinology—that is, a structural and functional analysis of general features of hormones—followed by a more detailed analysis of several important hormonal systems. Before continuing, you should review the principles of ligand-receptor interactions and cell signaling that were described in Chapter 3 (Section C) and Chapter 5, because they pertain to the mechanisms by which hormones exert their actions.

Hormones functionally link various organ systems together. As such, several of the general principles of physiology first introduced in Chapter 1 apply to the study of the endocrine system, including the principle that the functions of organ systems are coordinated with each other. This coordination is key to the maintenance of homeostasis, which is important for health and survival, another important general principle of physiology that will be covered in Sections C, D, and F. In many cases, the actions of one hormone can be potentiated, inhibited, or counterbalanced by the actions of another. This illustrates the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition, which it will be especially relevant in the sections on the endocrine control of metabolism and the control of pituitary gland function. The binding of hormones to their carrier proteins and receptors illustrates the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The anatomy of the connection of the hypothalamus and anterior pituitary demonstrates that structure is a determinant of—and has coevolved with—function (hypothalamic control of anterior pituitary function). The regulated uptake of iodine into the cells of the thyroid gland that synthesize thyroid hormones demonstrates the general principle of physiology that controlled exchange of materials occurs between compartments and across cellular membranes. Finally, this chapter exemplifies the general principle of physiology that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes. ■

SECTION A

General Characteristics of Hormones and Hormonal Control Systems

11.1 Hormones and Endocrine Glands

Endocrine glands are distinguished from another type of gland in the body called exocrine glands. Exocrine glands secrete their products into a duct, from where the secretions either exit the body (as in sweat) or enter the lumen of another organ, such as the intestines. By contrast, endocrine glands are ductless and release hormones into the blood (**Figure 11.1**). Hormones are actually released first into interstitial fluid, from where they diffuse into the blood, but for simplicity we will often omit the interstitial fluid step in our discussion.

Table 11.1 summarizes most of the endocrine glands and other hormone-secreting organs, the hormones they secrete, and some of the major functions the hormones control. The endocrine system differs from most of the other organ systems of the body in that the various components are not anatomically connected; however, they do form a system in the functional sense. You may be puzzled to see some organs—the heart, for instance—that clearly have other functions yet are listed as part of the endocrine system. The explanation is that, in addition to the cells that carry out other functions, the organ also contains cells that secrete hormones.

Note also in Table 11.1 that the hypothalamus, a part of the brain, is considered part of the endocrine system. This is because the chemical messengers released by certain axon terminals in both the hypothalamus and its extension, the posterior pituitary, do not function as neurotransmitters affecting adjacent cells but, rather, enter the blood as hormones. The blood then carries these hormones to their sites of action.

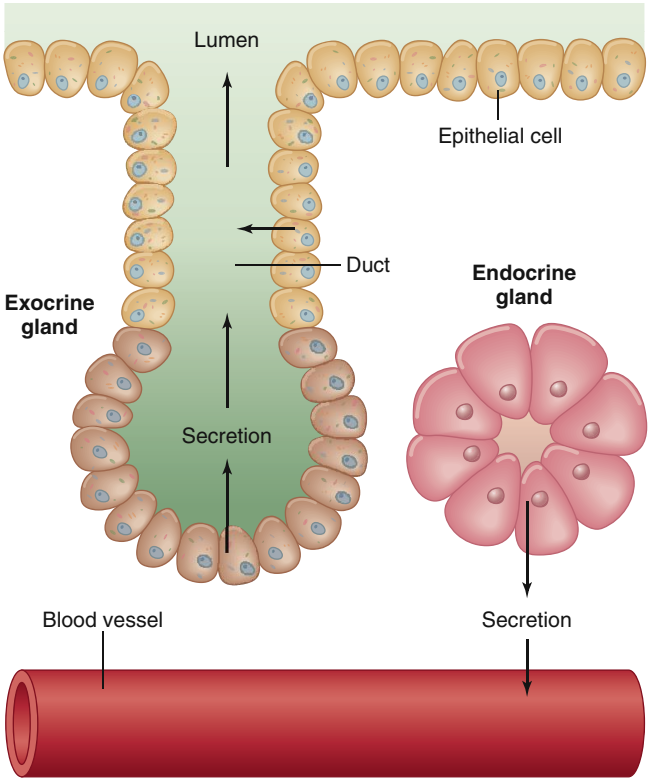
Table 11.1 demonstrates that there are a large number of endocrine glands and hormones. This chapter is not all inclusive. Some of the hormones listed in Table 11.1 are best considered in the context of the control systems in which they participate. For example, the pancreatic hormones (insulin and glucagon) are described in Chapter 16 in the context of organic metabolism, and the reproductive hormones are extensively covered in Chapter 17.

Also evident from Table 11.1 is that a single gland may secrete multiple hormones. The usual pattern in such cases is that a single cell type secretes only one hormone, so that multiple-hormone secretion reflects the presence of different types of endocrine cells in the same gland. In a few cases, however, a single cell may secrete more than one hormone or different forms of the same hormone.

Finally, in some cases, a hormone secreted by an endocrine-gland cell may also be secreted by other cell types and serves in these other locations as a neurotransmitter or paracrine or autocrine substance. For example, somatostatin, a hormone produced by neurons in the hypothalamus, is also secreted by cells of the stomach and pancreas, where it has local paracrine actions.

11.2 Hormone Structures and Synthesis

Hormones fall into three major structural classes: (1) amines, (2) peptides and proteins, and (3) steroids.



AP|R **Figure 11.1** Exocrine-gland secretions enter ducts from where their secretions either exit the body or, as shown here, connect to the lumen of a structure such as the intestines or to the surface of the skin. By contrast, endocrine glands secrete hormones that enter the interstitial fluid and diffuse into the blood, from where they can reach distant target cells.

Amine Hormones

The **amine hormones** are derivatives of the amino acid tyrosine. They include the **thyroid hormones** (produced by the thyroid gland) and the catecholamines **epinephrine** and **norepinephrine** (produced by the adrenal medulla) and **dopamine** (produced by the hypothalamus). The structure and synthesis of the iodine-containing thyroid hormones will be described in detail in Section C of this chapter. For now, their structures are included in **Figure 11.2**. Chapter 6 described the structures of catecholamines and the steps of their synthesis; the structures are reproduced here in Figure 11.2.

There are two adrenal glands, one above each kidney. Each **adrenal gland** is composed of an inner **adrenal medulla,** which secretes catecholamines, and a surrounding **adrenal cortex,** which secretes steroid hormones. The adrenal medulla is really a modified sympathetic ganglion whose cell bodies do not have axons. Instead, they release their secretions into the blood, thereby fulfilling a criterion for an endocrine gland.

The adrenal medulla secretes mainly two catecholamines, epinephrine and norepinephrine. In humans, the adrenal medulla secretes approximately four times more epinephrine than norepinephrine. This is because the adrenal medulla expresses high amounts of an enzyme called phenylethanolamine-N-methyltransferase (PNMT), which catalyzes the reaction that converts norepinephrine to epinephrine. Epinephrine and norepinephrine exert actions similar to those of the sympathetic nerves, which, because they do not express PNMT, make only

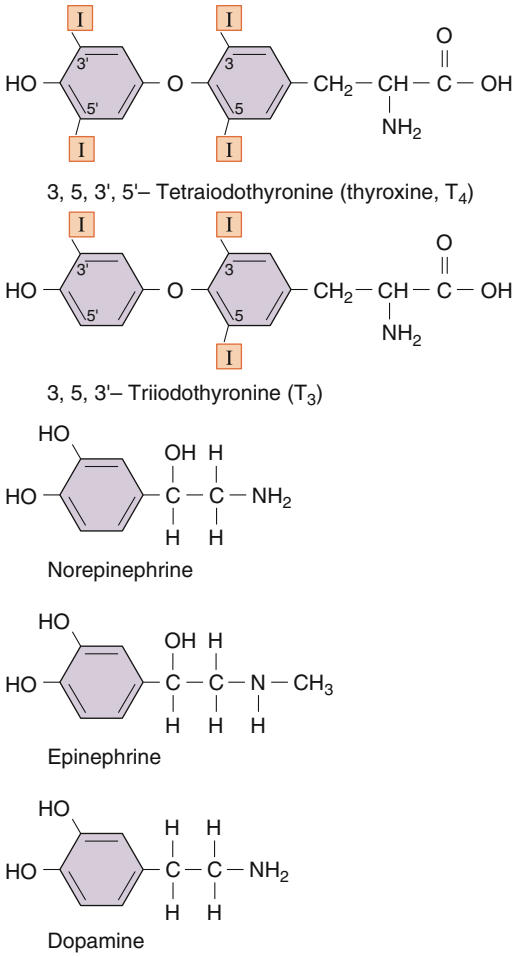


Figure 11.2 Chemical structures of the amine hormones: thyroxine and triiodothyronine (thyroid hormones), and norepinephrine, epinephrine, and dopamine (catecholamines). The two thyroid hormones differ by only one iodine atom, a difference noted in the abbreviations T_3 and T_4. The position of the carbon atoms in the two rings of T_3 and T_4 are numbered; this provides the basis for the complete names of T_3 and T_4 as shown in the figure. T_4 is the primary secretory product of the thyroid gland, but is activated to the much more potent T_3 in target tissue.

norepinephrine. These actions are described in various chapters and summarized in Section B of this chapter.

The other catecholamine hormone, dopamine, is synthesized by neurons in the hypothalamus. Dopamine is released into a special circulatory system called a portal system (see Section B), which carries the hormone to the pituitary gland; there, it acts to inhibit the activity of certain endocrine cells.

Peptide and Protein Hormones

Most hormones are polypeptides. Recall from Chapter 2 that short polypeptides with a known function are often referred to simply as peptides; longer polypeptides with tertiary structure and a known function are called proteins. Hormones in this class range in size from small peptides having only three amino acids to proteins, some of which contain carbohydrate and thus are glycoproteins. For convenience, we will simply refer to all these hormones as **peptide hormones.**

In many cases, peptide hormones are initially synthesized on the ribosomes of endocrine cells as larger molecules known

TABLE 11.1 Summary of Some Important Hormones

Site Produced	Hormone	Major Function* Is Control Of:
Adipose tissue cells	Leptin, several others	Appetite; metabolic rate; reproduction
Adrenal glands:		
Adrenal cortex	Cortisol	Organic metabolism; response to stress; immune system; development
	Androgens	Sex drive in women; adrenarche
	Aldosterone	Na^+ and K^+ excretion by kidneys; extracellular water balance
Adrenal medulla	Epinephrine and norepinephrine	Organic metabolism; cardiovascular function; response to stress ("fight-or-flight")
Gastrointestinal tract	Gastrin	Gastrointestinal tract motility and acid secretion
	Ghrelin	Appetite
	Secretin	Exocrine and endocrine secretions from pancreas
	Cholecystokinin (CCK)†	Secretion of bile from gallbladder
	Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)	Insulin secretion
	Motilin	Gastrointestinal tract motility
Gonads:		
Ovaries: female	Estrogen (estradiol in humans)	Reproductive system; secondary sex characteristics; growth and development; development of ovarian follicles
	Progesterone	Endometrium and pregnancy
	Inhibin	Follicle-stimulating hormone (FSH) secretion
	Relaxin	Cardiovascular adaptations during pregnancy
Testes: male	Androgen (testosterone and dihydrotestosterone)	Reproductive system; secondary sex characteristics; growth and development; sex drive; gamete development
	Inhibin	FSH secretion
	Anti-mullerian hormone (AMH)	Regression of Müllerian ducts
Heart	Atrial natriuretic peptide (ANP)	Na^+ excretion by kidneys; blood pressure
Hypothalamus	Hypophysiotropic hormones:	Secretion of hormones by the anterior pituitary gland
	Corticotropin-releasing hormone (CRH)	Secretion of adrenocorticotropic hormone (ACTH)
	Thyrotropin-releasing hormone (TRH)	Secretion of thyroid-stimulating hormone (TSH)
	Growth hormone–releasing hormone (GHRH)	Secretion of growth hormone (GH)
	Somatostatin (SST)	Secretion of growth hormone
	Gonadotropin-releasing hormone (GnRH)	Secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
	Dopamine (DA)	Secretion of prolactin (PRL)
Kidneys	Erythropoietin (EPO; also made in liver)	Erythrocyte production in bone marrow
	1,25-dihydroxyvitamin D	Ca^{2+} absorption in GI tract
Liver	Insulin-like growth factor 1 (IGF-1)	Cell division and growth of bone and other tissues
Pancreas	Insulin	Plasma glucose, amino acids, and fatty acids
	Glucagon	Plasma glucose
Parathyroid glands	Parathyroid hormone (PTH, parathormone)	Plasma Ca^{2+} and phosphate ion; synthesis of 1,25-dihydroxyvitamin D
Pineal	Melatonin	Possible role in circadian sleep-wake cycles

(continued)

TABLE 11.1 Summary of Some Important Hormones *(Continued)*

Site Produced	Hormone	Major Function* Is Control Of:
Pituitary gland:		
Anterior pituitary gland	Growth hormone (somatotropin)	Growth, mainly via local production of IGF-1; protein, carbohydrate, and lipid metabolism
	Thyroid-stimulating hormone (thyrotropin)	Thyroid gland activity and growth
	Adrenocorticotropic hormone (corticotropin)	Adrenal cortex activity and growth
	Prolactin	Milk production in breast
	Gonadotropic hormones:	
	Follicle-stimulating hormone	
	Males	Gamete production
	Females	Ovarian follicle growth
	Luteinizing hormone:	
	Males	Testicular production of testosterone
	Females	Ovarian production of estradiol; ovulation
	β-lipotropin and β-endorphin	Possibly fat mobilization and analgesia during stress
Posterior pituitary‡	Oxytocin	Milk secretion; uterine motility
	Vasopressin (antidiuretic hormone, ADH)	Blood pressure; water excretion by the kidneys
Placenta	Human chorionic gonadotropin (hCG)	Secretion of progesterone and estrogen by corpus luteum
	Estrogens	See Gonads: ovaries
	Progesterone	See Gonads: ovaries
	Human placental lactogen (hPL)	Breast development; organic metabolism
Thymus	Thymopoietin	T-lymphocyte function
Thyroid	Thyroxine (T_4) and triiodothyronine (T_3)	Metabolic rate; growth; brain development and function
	Calcitonin	Plasma Ca^{2+} in some vertebrates (role unclear in humans)
Other (produced in blood)	Angiotensin II	Blood pressure; production of aldosterone from adrenal cortex

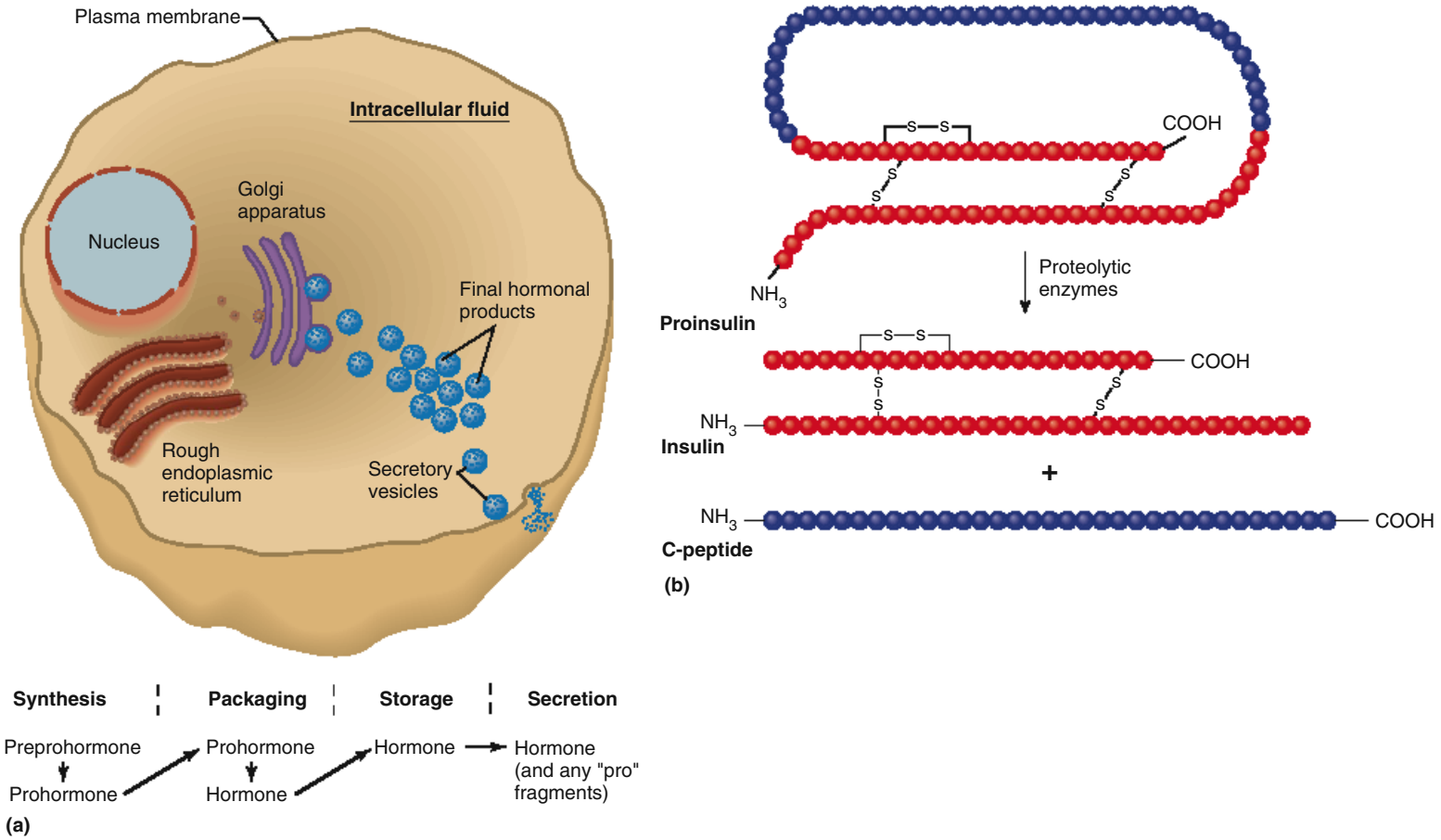
*This table does not list all functions of all hormones.
†The names and abbreviations in parentheses are synonyms.
‡The posterior pituitary stores and secretes these hormones; they are synthesized in the hypothalamus.

as preprohormones, which are then cleaved to **prohormones** by proteolytic enzymes in the rough endoplasmic reticulum (**Figure 11.3a**). The prohormone is then packaged into secretory vesicles by the Golgi apparatus. In this process (called post-translational processing), the prohormone is cleaved to yield the active hormone and other peptide chains found in the prohormone. Consequently, when the cell is stimulated to release the contents of the secretory vesicles by exocytosis, the other peptides are secreted along with the hormone. In certain cases, these other peptides may also exert hormonal effects. In other words, instead of just one peptide hormone, the cell may secrete multiple peptide hormones—derived from the same prohormone—each of which differs in its effects on target cells. One well-studied example of this is the synthesis of insulin in the pancreas (**Figure 11.3b**). Insulin is synthesized as a polypeptide preprohormone, then processed to the prohormone. Enzymes clip off a portion of the prohormone resulting in insulin and another product called C-peptide. Both insulin and C-peptide are secreted into the circulation in roughly equimolar amounts. Insulin is a key regulator of metabolism, while C-peptide may have several actions on a variety of cell types.

Steroid Hormones

Steroid hormones make up the third family of hormones. **Figure 11.4** shows some examples of steroid hormones; their ring-like structure was described in Chapter 2. Steroid hormones are primarily produced by the adrenal cortex and the **gonads** (testes and ovaries), as well as by the placenta during pregnancy. In addition, vitamin D is enzymatically converted by two hydroxylation reactions into the biologically active steroid hormone called **1,25-dihydroxyvitamin D** (also called 1,25-dihydroxycalciferol or calcitriol and abbreviated **1,25-$(OH)_2$D**). These reactions occur in the liver and kidneys.

The general process of steroid hormone synthesis is illustrated in **Figure 11.5a**. In both the gonads and the adrenal cortex, the hormone-producing cells are stimulated by the binding of an anterior pituitary gland hormone to its plasma membrane receptor. These receptors are linked to G_s proteins (refer back to Figure 5.6), which activate adenylyl cyclase and cAMP production. The subsequent activation of protein kinase A by cAMP results in phosphorylation of numerous intracellular proteins, which facilitate the subsequent steps in the process.



AP|R **Figure 11.3** Typical synthesis and secretion of peptide hormones. (a) Peptide hormones typically are processed by enzymes from preprohormones containing a signal peptide, to prohormones; further processing results in one or more active hormones that are stored in secretory vesicles. Secretion of stored secretory vesicles occurs by the process of exocytosis. (b) An example of peptide hormone synthesis. Insulin is synthesized as a preprohormone (not shown) that is cleaved to the prohormone shown here. Each bead represents an amino acid. The action of proteolytic enzymes cleaves the prohormone into insulin and C-peptide. Note that this cleavage results in two chains of insulin, which are connected by disulfide bridges.

PHYSIOLOGICAL INQUIRY

- What is the advantage of packaging peptide hormones in secretory vesicles?

Answer can be found at end of chapter.

All of the steroid hormones are derived from cholesterol, which is either taken up from the extracellular fluid by the cells or synthesized by intracellular enzymes. The final steroid hormone product depends upon the cell type and the types and amounts of the enzymes it expresses. Cells in the ovary, for example, express large amounts of the enzyme needed to convert testosterone to estradiol, whereas cells in the testes do not express significant amounts of this enzyme and therefore make primarily testosterone.

Once formed, the steroid hormones are not stored in the cytosol in membrane-bound vesicles, because the lipophilic nature of the steroids allows them to freely diffuse across lipid bilayers. As a result, once they are synthesized, steroid hormones diffuse across the plasma membrane into the circulation. Because of their lipid nature, steroid hormones are not highly soluble in blood. The majority of steroid hormones are reversibly bound in plasma to carrier proteins such as albumin and various other specific proteins.

The next sections describe the pathways for steroid synthesis in the adrenal cortex and gonads. Those for the placenta are somewhat unusual and are briefly discussed in Chapter 17.

Hormones of the Adrenal Cortex

The five major hormones secreted by the adrenal cortex are aldosterone, cortisol, corticosterone, dehydroepiandrosterone (DHEA), and androstenedione (**Figure 11.5b**). **Aldosterone** is known as a **mineralocorticoid** because its effects are on salt (mineral) balance, mainly on the kidneys' handling of sodium, potassium, and hydrogen ions. Its actions are described in detail in Chapter 14. Briefly, production of aldosterone is under the control of another hormone called **angiotensin II,** which binds to plasma membrane receptors in the adrenal cortex to activate the inositol trisphosphate second-messenger pathway (see Chapter 5). This is different from the more common cAMP-mediated mechanism by which most steroid hormones are produced, as previously described. Once synthesized, aldosterone enters the circulation and acts on cells of the kidneys to stimulate Na^+ and H_2O retention, and K^+ and H^+ excretion in the urine.

Cortisol and corticosterone are called **glucocorticoids** because they have important effects on the metabolism of glucose and other organic nutrients. Cortisol is the predominant

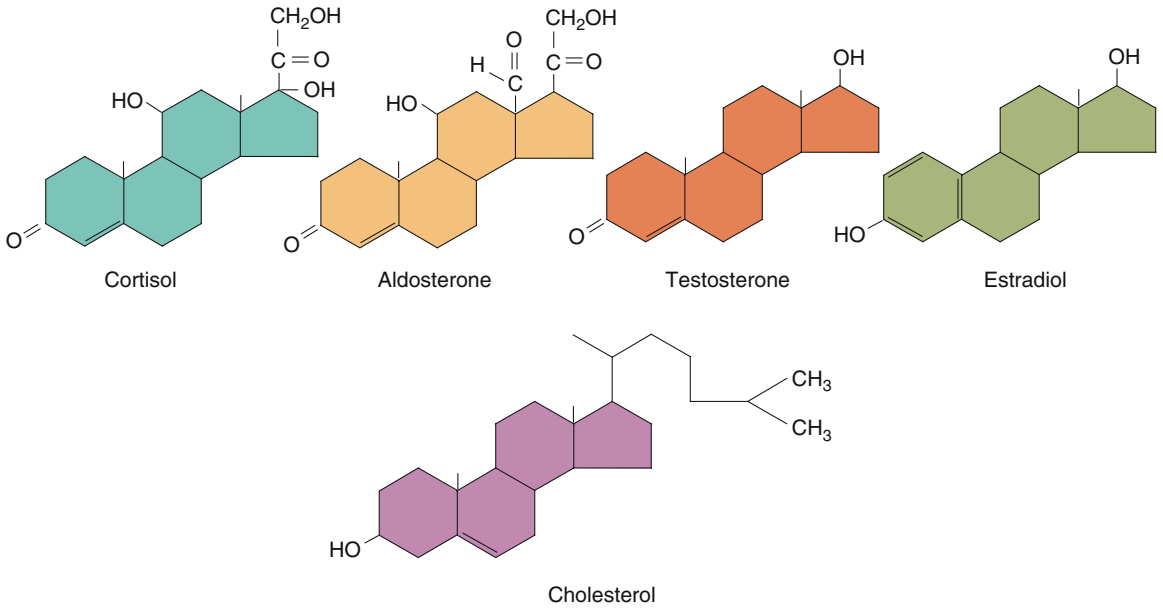


Figure 11.4 Structures of representative steroid hormones and their structural relationship to cholesterol.

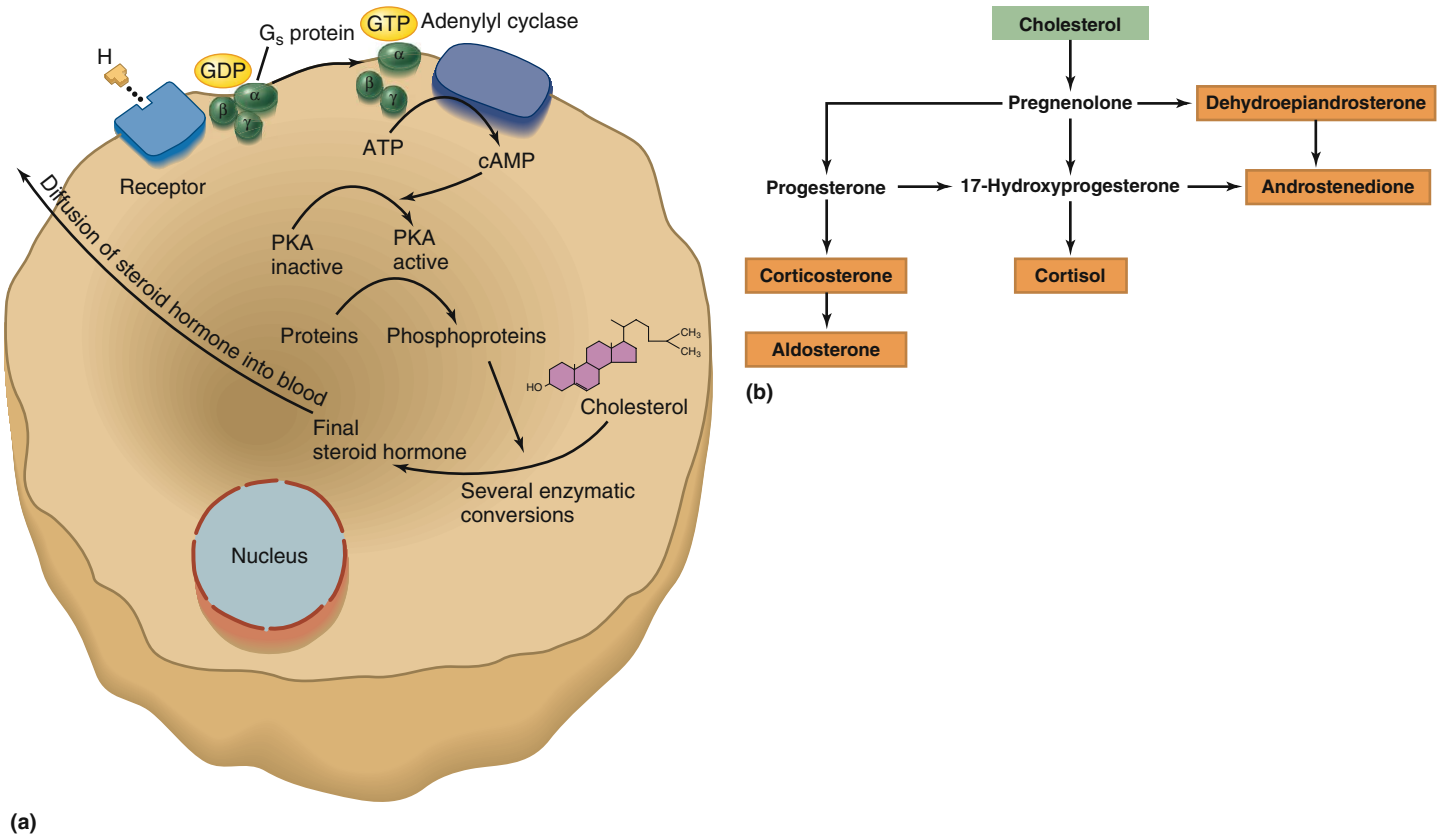


Figure 11.5 (a) Schematic overview of steps involved in steroid synthesis. (b) The five hormones shown in boxes are the major hormones secreted from the adrenal cortex. Dehydroepiandrosterone (DHEA) and androstenedione are androgens—that is, testosterone-like hormones. Cortisol and corticosterone are glucocorticoids, and aldosterone is a mineralocorticoid that is only produced by one part of the adrenal cortex. *Note:* For simplicity, not all enzymatic steps are indicated.

PHYSIOLOGICAL INQUIRY

- Why are steroid hormones not packaged into secretory vesicles, such as those depicted in Figure 11.3?

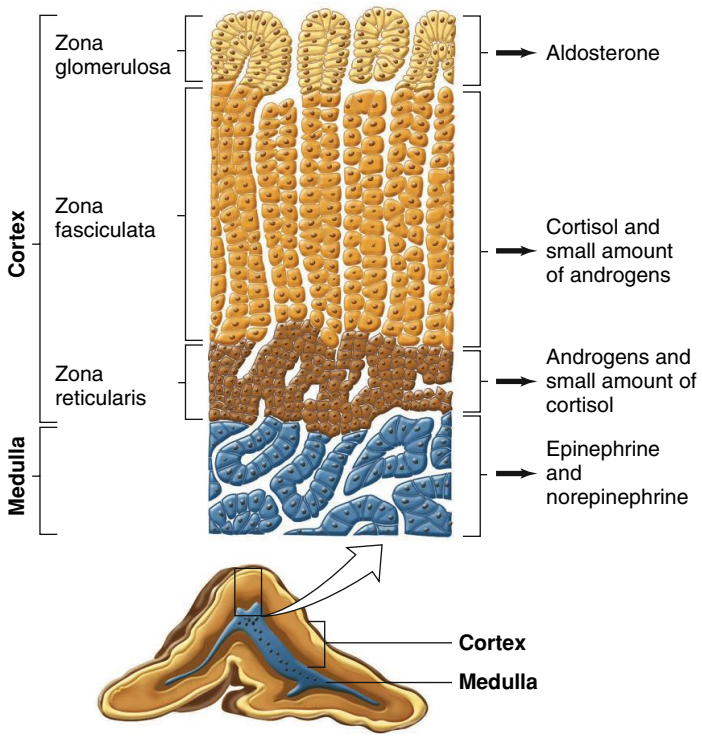
Answer can be found at end of chapter.

glucocorticoid in humans and is the only one we will discuss. In addition to its effects on organic metabolism, cortisol exerts many other effects, including facilitation of the body's responses to stress and regulation of the immune system (see Section D).

Dehydroepiandrosterone (DHEA) and androstenedione belong to the class of steroid hormones known as **androgens;** this class also includes the major male sex steroid **testosterone,** produced by the testes. The adrenal androgens are much less potent than testosterone, and they are usually of little physiological significance in the adult male. They do, however, have functions in the adult female and in both sexes in the fetus and at puberty, as described in Chapter 17.

The adrenal cortex is composed of three distinct layers (**Figure 11.6**). The cells of the outer layer—the zona glomerulosa—express the enzymes required to synthesize corticosterone and then convert it to aldosterone (see Figure 11.5b) but do *not* express the genes that code for the enzymes required for the formation of cortisol and androgens. Therefore, this layer synthesizes and secretes aldosterone but not the other major adrenocortical hormones. In contrast, the zona fasciculata and zona reticularis have the opposite enzyme profile. They secrete no aldosterone but do secrete cortisol and androgens. In humans, the zona fasciculata primarily produces cortisol and the zona reticularis primarily produces androgens, but both zones produce both types of steroid.

In certain diseases, the adrenal cortex may secrete decreased or increased amounts of various steroids. For example, the absence of an enzyme required for the formation of cortisol by the adrenal cortex can result in the shunting of the cortisol precursors into the androgen pathway. (Look at Figure 11.5b to imagine how this might happen.) One example of an inherited disease of this type is ***congenital adrenal hyperplasia*** (***CAH***) (see Chapter 17 for more details). In CAH, the excess adrenal androgen production results in virilization of the genitalia of female fetuses; at birth, it may not be obvious whether the baby is phenotypically male or female. Fortunately, the most common form of this disease is routinely screened for at birth in many countries and appropriate therapeutic measures can be initiated immediately.



AP|R **Figure 11.6** Section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete.

Hormones of the Gonads

Compared to the adrenal cortex, the gonads have very different concentrations of key enzymes in their steroid pathways. Endocrine cells in both the testes and the ovaries do not express the enzymes required to produce aldosterone and cortisol. They possess high concentrations of enzymes in the androgen pathways leading to androstenedione, as in the adrenal cortex. In addition, the endocrine cells in the testes contain a high concentration of the enzyme that converts androstenedione to testosterone, which is the major androgen secreted by the testes (**Figure 11.7**). The ovarian endocrine cells synthesize the female sex hormones, which are collectively known as **estrogens** (primarily estradiol and estrone). **Estradiol** is the predominant estrogen present during a woman's lifetime. The ovarian endocrine cells have a high concentration of the enzyme aromatase, which catalyzes the conversion of androgens to estrogens (see Figure 11.7). Consequently, estradiol—rather than testosterone—is the major steroid hormone secreted by the ovaries.

Very small amounts of testosterone do diffuse out of ovarian endocrine cells, however, and very small amounts of estradiol are produced from testosterone in the testes. Moreover, following their release into the blood by the gonads and the adrenal cortex, steroid hormones may undergo further conversion in other organs. For example, testosterone is converted to estradiol in some of its target cells. Consequently, the major male and female sex hormones—testosterone and estradiol, respectively—are not unique to males and females. The ratio of the concentrations of the hormones, however, is very different in the two sexes.

Finally, endocrine cells of the corpus luteum, an ovarian structure that arises following each ovulation, secrete another major steroid hormone, **progesterone.** This steroid is critically important for uterine maturation during the menstrual cycle and for maintaining a pregnancy (see Chapter 17). Progesterone is also synthesized in other parts of the body—notably, the placenta in pregnant women and the adrenal cortex in both males and females.

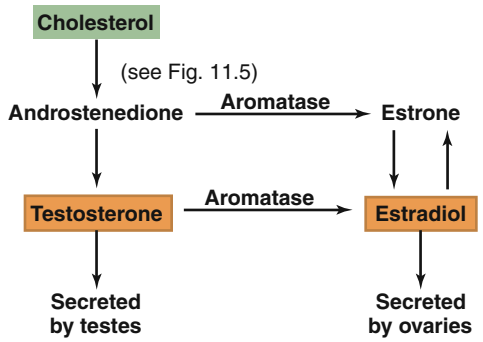


Figure 11.7 Gonadal production of steroids. Only the ovaries have high concentrations of the enzyme (aromatase) required to produce the estrogens estrone and estradiol.

11.3 Hormone Transport in the Blood

Most peptide and all catecholamine hormones are water-soluble. Therefore, with the exception of a few peptides, these hormones are transported simply dissolved in plasma (**Table 11.2**). In contrast, the poorly soluble steroid hormones and thyroid hormones circulate in the blood largely bound to plasma proteins. Even though the steroid and thyroid hormones exist in plasma mainly bound to large proteins, small concentrations of these hormones do exist dissolved in the plasma. The dissolved, or free, hormone is in equilibrium with the bound hormone:

$$\text{Free hormone} + \text{Binding protein} \rightleftharpoons \text{Hormone–protein complex}$$

This reaction is an excellent example of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The balance of this equilibrium will shift to the right as the endocrine gland secretes more free hormone and to the left in the target gland as hormone dissociates from its binding protein in plasma and diffuses into the target gland cell. The total hormone concentration in plasma is the sum of the free and bound hormones. However, only the *free* hormone can diffuse out of capillaries and encounter its target cells. Therefore, the concentration of the free hormone is what is biologically important rather than the concentration of the total hormone, most of which is bound. As we will see next, the degree of protein binding also influences the rate of metabolism and the excretion of the hormone.

11.4 Hormone Metabolism and Excretion

Once a hormone has been synthesized and secreted into the blood, has acted on a target tissue, and its increased activity is no longer required, the concentration of the hormone in the blood usually returns to normal. This is necessary to prevent excessive, possibly harmful effects from the prolonged exposure of target cells to hormones. A hormone's concentration in the plasma depends upon (1) its rate of secretion by the endocrine gland and (2) its rate of removal from the blood. Removal, or "clearance," of the hormone occurs either by excretion or by metabolic transformation. The liver and the kidneys are the major organs that metabolize or excrete hormones. A more detailed explanation of clearance can be found in Chapter 14, Section 14.4.

The liver and kidneys, however, are not the only routes for eliminating hormones. Sometimes a hormone is metabolized by the cells upon which it acts. In the case of some peptide hormones, for example, endocytosis of hormone–receptor complexes on plasma membranes enables cells to remove the hormones rapidly from their surfaces and catabolize them intracellularly. The receptors are then often recycled to the plasma membrane.

In addition, enzymes in the blood and tissues rapidly break down catecholamine and peptide hormones. These hormones therefore tend to remain in the bloodstream for only brief periods—minutes to an hour. In contrast, protein-bound hormones are protected from excretion or metabolism by enzymes as long as they remain bound. Therefore, removal of the circulating steroid and thyroid hormones generally takes longer, often several hours to days.

In some cases, metabolism of a hormone *activates* the hormone rather than inactivates it. In other words, the secreted hormone may be relatively inactive until metabolism transforms it. One example is thyroxine produced by the thyroid gland, which is converted to a more active hormone inside the target cell.

Figure 11.8 summarizes the possible fates of hormones after their secretion.

11.5 Mechanisms of Hormone Action

Hormone Receptors

Because hormones are transported in the blood, they can reach all tissues. Yet, the response to a hormone is highly specific, involving only the target cells for that hormone. The ability to respond depends upon the presence of specific receptors for those hormones on or in the target cells.

As emphasized in Chapter 5, the response of a target cell to a chemical messenger is the final event in a sequence that begins when the messenger binds to specific cell receptors. As that chapter described, the receptors for water-soluble chemical messengers like peptide hormones and catecholamines are proteins located in the plasma membranes of the target cells. In contrast, the receptors for lipid-soluble chemical messengers like steroid and thyroid hormones are proteins located mainly *inside* the target cells.

Hormones can influence the response of target cells by regulating hormone receptors. Again, Chapter 5 described basic concepts of receptor modulation such as up-regulation and down-regulation. In the context of hormones, **up-regulation** is an

TABLE 11.2 Categories of Hormones

Chemical Class	Major Form in Plasma	Location of Receptors	Most Common Signaling Mechanisms*	Rate of Excretion/Metabolism
Peptides and catecholamines	Free (unbound)	Plasma membrane	1. Second messengers (e.g., cAMP, Ca^{2+}, IP_3) 2. Enzyme activation by receptor (e.g., JAK) 3. Intrinsic enzymatic activity of receptor (e.g., tyrosine autophosphorylation)	Fast (minutes)
Steroids and thyroid hormone	Protein-bound	Intracellular	Intracellular receptors directly alter gene transcription	Slow (hours to days)

*The diverse mechanisms of action of chemical messengers such as hormones were discussed in detail in Chapter 5.

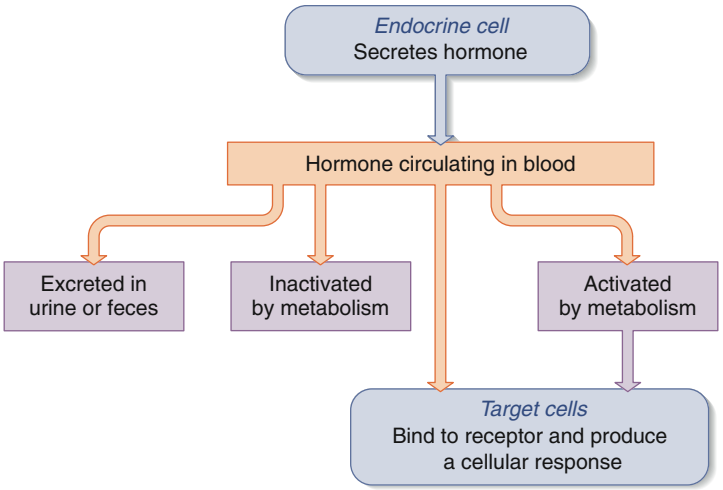


Figure 11.8 Possible fates and actions of a hormone following its secretion by an endocrine cell. Not all paths apply to all hormones. Many hormones are activated by metabolism inside target cells.

increase in the number of a hormone's receptors in a cell, often resulting from a prolonged exposure to a low concentration of the hormone. This has the effect of increasing target-cell responsiveness to the hormone. **Down-regulation** is a decrease in receptor number, often from exposure to high concentrations of the hormone. This temporarily decreases target-cell responsiveness to the hormone, thereby preventing overstimulation.

In some cases, hormones can down-regulate or up-regulate not only their own receptors but the receptors for other hormones as well. If one hormone induces down-regulation of a second hormone's receptors, the result will be a reduction of the second hormone's effectiveness. On the other hand, a hormone may induce an increase in the number of receptors for a second hormone. In this case, the effectiveness of the second hormone is increased. This latter phenomenon, in some cases, underlies the important hormone–hormone interaction known as permissiveness. In general terms, **permissiveness** means that hormone A must be present in order for hormone B to exert its full effect. A low concentration of hormone A is usually all that is needed for this permissive effect, which may be due to A's ability to up-regulate B's receptors. For example, epinephrine causes a large release of fatty acids from adipose tissue, but only in the presence of permissive amounts of thyroid hormones (**Figure 11.9**). One reason is that thyroid hormones stimulate the synthesis of beta-adrenergic receptors for epinephrine in adipose tissue; as a result, the tissue becomes much more sensitive to epinephrine. However, receptor up-regulation does not explain all cases of permissiveness. Sometimes, the effect may be due to changes in the signaling pathway that mediates the actions of a given hormone.

Events Elicited by Hormone–Receptor Binding

The events initiated when a hormone binds to its receptor—that is, the mechanisms by which the hormone elicits a cellular response—are one or more of the signal transduction pathways that apply to all chemical messengers, as described in Chapter 5. In other words, there is nothing unique about the mechanisms that hormones initiate as compared to those used by neurotransmitters and paracrine or autocrine substances, and so we will only briefly review them here (see Table 11.2).

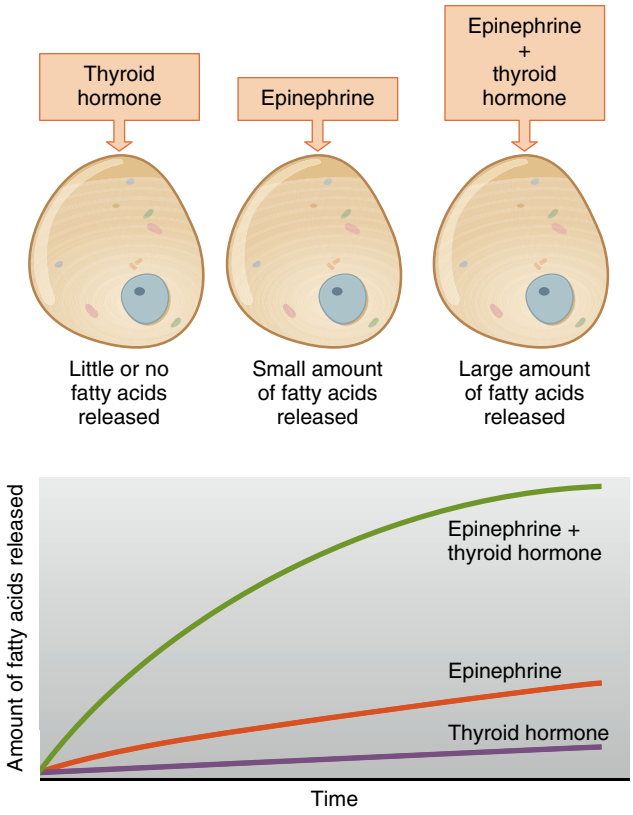


Figure 11.9 The ability of thyroid hormone to "permit" epinephrine-induced release of fatty acids from adipose tissue cells. Thyroid hormone exerts this effect by causing an increased number of beta-adrenergic receptors on the cell. Thyroid hormone by itself stimulates only a small amount of fatty acid release.

PHYSIOLOGICAL INQUIRY

- A patient is observed to have symptoms that are consistent with increased concentrations of epinephrine in the blood, including a rapid heart rate, anxiety, and elevated fatty acid concentrations. However, the circulating epinephrine concentrations are measured and found to be in the normal range. What might explain this?

Answer can be found at end of chapter.

Effects of Peptide Hormones and Catecholamines

As stated previously, the receptors for peptide hormones and catecholamines are located on the extracellular surface of the target cell's plasma membrane. This location is important because these hormones are too hydrophilic to diffuse through the plasma membrane. When activated by hormone binding, the receptors trigger one or more of the signal transduction pathways for plasma membrane receptors described in Chapter 5. That is, the activated receptors directly influence (1) enzyme activity that is part of the receptor, (2) activity of cytoplasmic janus kinases associated with the receptor, or (3) G proteins coupled in the plasma membrane to effector proteins—ion channels and enzymes—that generate second messengers such as cAMP and Ca^{2+} (see Figure 11.5a as an example). The opening or closing of ion channels changes the electrical potential across the membrane. When a Ca^{2+} channel is involved, the cytosolic concentration of this important ionic second messenger changes. The changes in enzyme activity are

usually very rapid (e.g., due to phosphorylation) and produce changes in the activity of various cellular proteins. In some cases, the signal transduction pathways also lead to activation or inhibition of particular genes, causing a change in the synthesis rate of the proteins coded for by these genes. Thus, peptide hormones and catecholamines may exert both rapid (nongenomic) and slower (gene transcription) actions on the same target cell.

Effects of Steroid and Thyroid Hormone The steroid hormones and thyroid hormone are lipophilic, and their receptors, which are intracellular, are members of the nuclear receptor superfamily. As described for lipid-soluble messengers in Chapter 5, the binding of hormone to its receptor leads to the activation (or in some cases, inhibition) of the transcription of particular genes, causing a change in the synthesis rate of the proteins coded for by those genes. The ultimate result of changes in the concentrations of these proteins is an enhancement or inhibition of particular processes the cell carries out or a change in the cell's rate of protein secretion. Evidence exists for plasma membrane receptors for these hormones, but their physiological significance in humans is not established.

Pharmacological Effects of Hormones

The administration of very large quantities of a hormone for medical purposes may have effects on an individual that are not usually observed at physiological concentrations. These ***pharmacological effects*** can also occur in diseases involving the secretion of excessive amounts of hormones. Pharmacological effects are of great importance in medicine because hormones are often used in large doses as therapeutic agents. Perhaps the most common example is that of very potent synthetic forms of cortisol, such as prednisone, which is administered to suppress allergic and inflammatory reactions. In such situations, a host of unwanted effects may be observed (as described in Section D).

11.6 Inputs That Control Hormone Secretion

Hormone secretion is mainly under the control of three types of inputs to endocrine cells (**Figure 11.10**): (1) changes in the plasma concentrations of mineral ions or organic nutrients, (2) neurotransmitters released from neurons ending on the endocrine cell, and (3) another hormone (or, in some cases, a paracrine substance) acting on the endocrine cell.

Before we look more closely at each category, we must stress that more than one input may influence hormone secretion. For example, insulin secretion is stimulated by the extracellular concentrations of glucose and other nutrients, and is either stimulated or inhibited by the different branches of the autonomic nervous system. Thus, the control of endocrine cells illustrates the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition. The resulting output—the rate of hormone secretion—depends upon the relative amounts of stimulatory and inhibitory inputs.

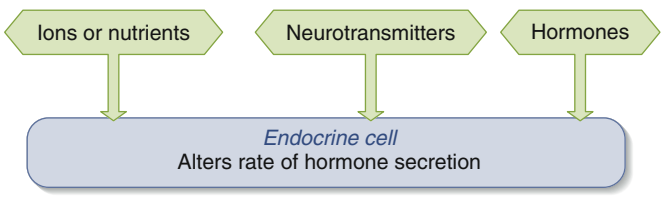


Figure 11.10 Inputs that act directly on endocrine gland cells to stimulate or inhibit hormone secretion.

The term *secretion* applied to a hormone denotes its release by exocytosis from the cell. In some cases, hormones such as steroid hormones are not secreted, per se, but instead diffuse through the cell's plasma membrane into the extracellular space. Secretion or release by diffusion is sometimes accompanied by increased synthesis of the hormone. For simplicity in this chapter and the rest of the book, we will usually not distinguish between these possibilities when we refer to stimulation or inhibition of hormone "secretion."

Control by Plasma Concentrations of Mineral Ions or Organic Nutrients

The secretion of several hormones is directly controlled—at least in part—by the plasma concentrations of specific mineral ions or organic nutrients. In each case, a major function of the hormone is to regulate through negative feedback (see Chapter 1, Section 1.5) the plasma concentration of the ion or nutrient controlling its secretion. For example, insulin secretion is stimulated by an increase in plasma glucose concentration. Insulin, in turn, acts on skeletal muscle and adipose tissue to promote facilitated diffusion of glucose across the plasma membranes into the cytosol. The effect of insulin, therefore, is to restore plasma glucose concentration to normal (**Figure 11.11**). Another example is the regulation of calcium ion homeostasis by parathyroid hormone (PTH), as described in detail in Section F. This hormone is produced by cells of the parathyroid glands, which, as their name implies, are located in close proximity to the thyroid gland. A decrease in the plasma Ca^{2+} concentration directly stimulates PTH secretion. PTH then exerts several actions on bone and other tissue that increase calcium release into the blood thereby restoring plasma Ca^{2+} to normal.

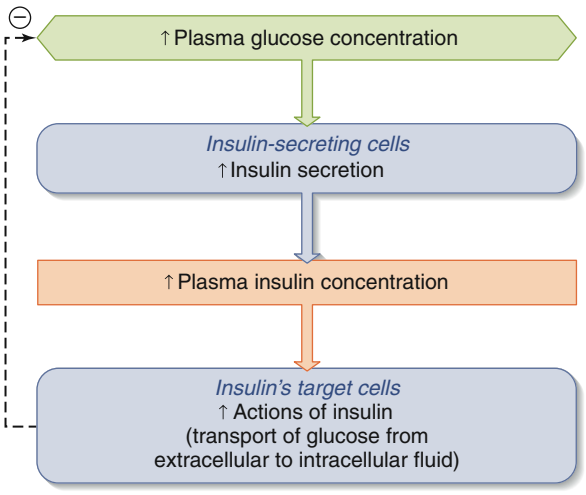


Figure 11.11 Example of how the direct control of hormone secretion by the plasma concentration of a substance—in this case, an organic nutrient—results in negative feedback control of the substance's plasma concentration. In other cases, the regulated plasma substance may be a mineral, such as Ca^{2+}.

Control by Neurons

As stated earlier, the adrenal medulla is a modified sympathetic ganglion and thus is stimulated by sympathetic preganglionic fibers (refer back to Chapter 6 for a discussion of the autonomic nervous system). In addition to controlling the adrenal medulla, the autonomic nervous system influences other endocrine glands (**Figure 11.12**). Both parasympathetic and sympathetic inputs to these other glands may occur, some inhibitory and some stimulatory. Examples are the secretions of insulin and the gastrointestinal hormones, which are stimulated by neurons of the parasympathetic nervous system and inhibited by sympathetic neurons.

One large group of hormones—those secreted by the hypothalamus and the posterior pituitary—is under the direct control of neurons in the brain itself (see Figure 11.12). This category will be described in detail in Section B.

Control by Other Hormones

In many cases, the secretion of a particular hormone is directly controlled by the blood concentration of another hormone. Often, the only function of the first hormone in a sequence is to stimulate the secretion of the next. A hormone that stimulates the secretion of another hormone is often referred to as a **tropic hormone.** The tropic hormones usually stimulate not only secretion but also the growth of the stimulated gland. (When specifically referring to growth-promoting actions, the term *trophic* is often used, but for simplicity we will usually use only the general term *tropic*.) These types of hormonal sequences are covered in detail in Section B. In addition to stimulatory actions, however, some hormones such as those in a multihormone sequence inhibit secretion of other hormones.

11.7 Types of Endocrine Disorders

Because there is such a wide variety of hormones and endocrine glands, the features of disorders of the endocrine system may vary considerably. For example, endocrine disease may manifest as an imbalance in metabolism, leading to weight gain or loss; as a failure to grow or develop normally in early life; as an abnormally high or low blood pressure; as a loss of reproductive fertility; or as mental and emotional changes, to name a few. Despite these varied features, which depend upon the particular hormone affected, essentially all endocrine diseases can be categorized in one of four ways. These include (1) too little hormone (***hyposecretion***), (2) too much hormone (***hypersecretion***), (3) decreased responsiveness of the target cells to hormone (***hyporesponsiveness***), and (4) increased responsiveness of the target cells to hormone (***hyperresponsiveness***).

Hyposecretion

An endocrine gland may be secreting too little hormone because the gland is not functioning normally, a condition termed ***primary hyposecretion.*** Examples include (1) partial destruction of a

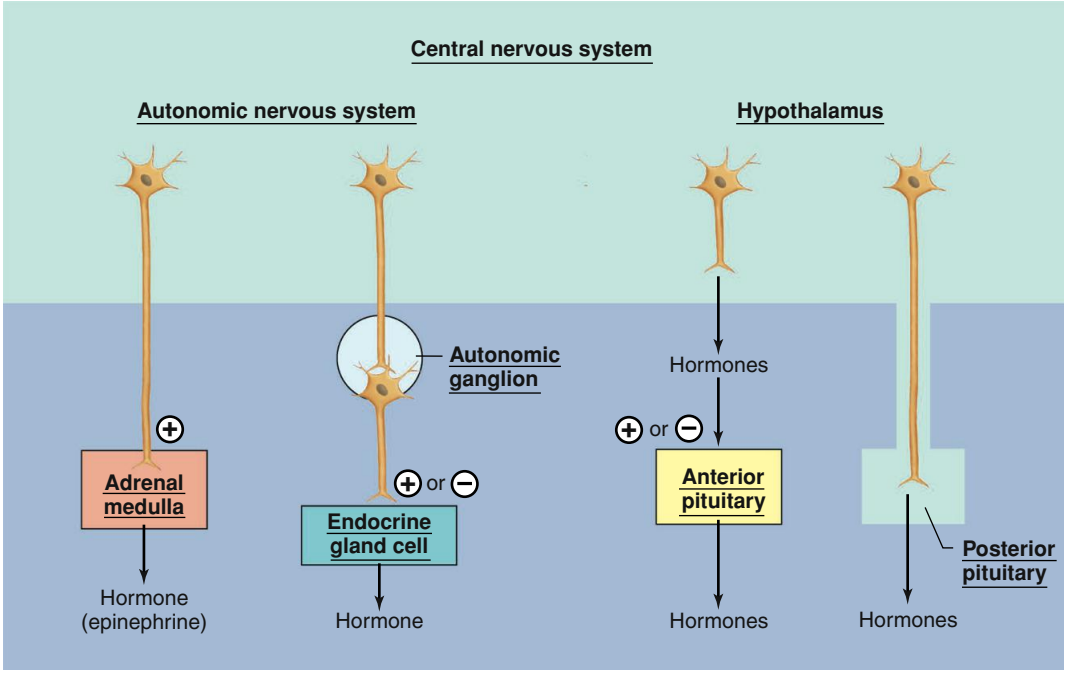


Figure 11.12 Pathways by which the nervous system influences hormone secretion. The autonomic nervous system controls hormone secretion by the adrenal medulla and many other endocrine glands. Certain neurons in the hypothalamus, some of which terminate in the posterior pituitary, secrete hormones. The secretion of hypothalamic hormones from the posterior pituitary and the effects of other hypothalamic hormones on the anterior pituitary gland are described later in this chapter. The ⊕ and ⊖ symbols indicate stimulatory and inhibitory actions, respectively.

PHYSIOLOGICAL INQUIRY

- List the several ways this figure illustrates the general principle of physiology described in Chapter 1 that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes.

Answer can be found at end of chapter.

gland, leading to decreased hormone secretion; (2) an enzyme deficiency resulting in decreased synthesis of the hormone; and (3) dietary deficiency of iodine, specifically leading to decreased secretion of thyroid hormones. Many other causes, such as infections and exposure to toxic chemicals, have the common denominator of damaging the endocrine gland or reducing its ability to synthesize or secrete the hormone.

The other major cause of hyposecretion is ***secondary hyposecretion.*** In this case, the endocrine gland is not damaged (at least at first) but is receiving too little stimulation by its tropic hormone. In the long term, lack of the trophic action of the tropic hormones invariably leads to atrophy of the target gland that can be reversed if the tropic hormone increases.

To distinguish between primary and secondary hyposecretion, one measures the concentration of the tropic hormone in the blood. If increased, the cause is primary; if not increased or lower than normal, the cause is secondary.

The most common means of treating hormone hyposecretion is to administer the missing hormone or a synthetic analog of the hormone. This is normally done by oral (pill), topical (cream applied to skin), or nasal (spray) administration, or by injection. The route of administration typically depends upon the chemical nature of the hormone being replaced. For example, individuals with low thyroid hormone take a daily pill to restore normal hormone concentrations, because thyroid hormones are readily absorbed from the intestines. By contrast, people with diabetes mellitus who require insulin typically obtain it via injection; insulin is a peptide that would be digested by the enzymes of the gastrointestinal tract if it were ingested.

Hypersecretion

A hormone can also undergo either ***primary hypersecretion*** (the gland is secreting too much of the hormone on its own) or ***secondary hypersecretion*** (excessive stimulation of the gland by its tropic hormone). One cause of primary or secondary hypersecretion is the presence of a hormone-secreting, endocrine-cell tumor. These tumors tend to produce their hormones continually at a high rate, even in the absence of stimulation or in the presence of increased negative feedback.

When an endocrine tumor causes hypersecretion, the tumor can often be removed surgically or destroyed with radiation if it is confined to a small area. These procedures are also useful in certain cases where an endocrine gland is hypersecreting for reasons unrelated to the presence of a tumor. Both of these procedures can be used, for example, in treating hypersecretion from an overactive thyroid gland (see Section C). In many cases, drugs that inhibit a hormone's synthesis can block hypersecretion. Alternatively, the situation can be treated with drugs that do not alter the hormone's secretion but instead block the hormone's actions on its target cells (receptor antagonists).

Hyporesponsiveness and Hyperresponsiveness

In some cases, a component of the endocrine system may not be functioning normally, even though there is nothing wrong with hormone secretion. The problem is that the target cells do not respond normally to the hormone, a condition termed hyporesponsiveness, or hormone resistance. An important example of a disease resulting from hyporesponsiveness is the most common form of diabetes mellitus (called ***type 2 diabetes mellitus***), in which the target cells of the hormone insulin are hyporesponsive to this hormone.

Hyporesponsiveness can result from deficiency or loss of function of receptors for the hormone. For example, some individuals who are genetically male have a defect manifested by the absence of receptors for androgens. Consequently, their target cells are unable to bind androgens, and the result is lack of development of certain male characteristics, as though the hormones were not being produced (see Chapter 17 for additional details).

In a second type of hyporesponsiveness, the receptors for a hormone may be normal but some signaling event that occurs within the cell after the hormone binds to its receptors may be defective. For example, the activated receptor may be unable to stimulate formation of cyclic AMP or another component of the signaling pathway for that hormone.

A third cause of hyporesponsiveness applies to hormones that require metabolic activation by some other tissue after secretion. There may be a deficiency of the enzymes that catalyze the activation. For example, some men secrete testosterone (the major circulating androgen) normally and have normal receptors for androgens. However, these men are missing the intracellular enzyme that converts testosterone to dihydrotestosterone, a potent metabolite of testosterone that binds to androgen receptors and mediates some of the actions of testosterone on secondary sex characteristics such as the growth of facial and body hair.

By contrast, hyperresponsiveness to a hormone can also occur and cause problems. For example, thyroid hormone causes an up-regulation of beta-adrenergic receptors for epinephrine; therefore, hypersecretion of thyroid hormone causes, in turn, a hyperresponsiveness to epinephrine. One result of this is the increased heart rate typical of people with increased concentrations of thyroid hormone.

SECTION A SUMMARY

Hormones and Endocrine Glands

I. The endocrine system is one of the body's two major communications systems. It consists of all the glands and organs that secrete hormones, which are chemical messengers carried by the blood to target cells elsewhere in the body.
II. Endocrine glands differ from exocrine glands in that the latter secrete their products into a duct that connects with another structure, such as the intestines, or with the outside of the body.
III. A single gland may, in some cases, secrete multiple hormones.

Hormone Structures and Synthesis

I. The amine hormones are the iodine-containing thyroid hormones and the catecholamines secreted by the adrenal medulla and the hypothalamus.
II. The majority of hormones are peptides, many of which are synthesized as larger (inactive) molecules, which are then cleaved into active fragments.
III. Steroid hormones are produced from cholesterol by the adrenal cortex and the gonads and from steroid precursors by the placenta during pregnancy.
    a. The predominant steroid hormones produced by the adrenal cortex are the mineralocorticoid aldosterone; the glucocorticoid cortisol; and two androgens, DHEA and androstenedione.
    b. The ovaries produce mainly estradiol and progesterone, and the testes produce mainly testosterone.

Hormone Transport in the Blood

I. Peptide hormones and catecholamines circulate dissolved in the plasma, but steroid and thyroid hormones circulate mainly bound to plasma proteins.

Hormone Metabolism and Excretion

I. The liver and kidneys are the major organs that remove hormones from the plasma by metabolizing or excreting them.
II. The peptide hormones and catecholamines are rapidly removed from the blood, whereas the steroid and thyroid hormones are removed more slowly, mainly because they circulate bound to plasma proteins.
III. After their secretion, some hormones are metabolized to more active molecules in their target cells or other organs.

Mechanisms of Hormone Action

I. The majority of receptors for steroid and thyroid hormones are inside the target cells; those for the peptide hormones and catecholamines are on the plasma membrane.
II. Hormones can cause up-regulation and down-regulation of their own receptors and those of other hormones. The induction of one hormone's receptors by another hormone increases the first hormone's effectiveness and may be essential to permit the first hormone to exert its effects.
III. Receptors activated by peptide hormones and catecholamines utilize one or more of the signal transduction pathways linked to plasma membrane receptors; the result is altered membrane potential or protein activity in the cell.
IV. Intracellular receptors activated by steroid and thyroid hormones typically function as transcription factors; the result is increased synthesis of specific proteins.
V. In pharmacological doses, hormones can have effects not seen under ordinary circumstances, some of which may be deleterious.

Inputs That Control Hormone Secretion

I. The secretion of a hormone may be controlled by the plasma concentration of an ion or nutrient that the hormone regulates, by neural input to the endocrine cells, and by one or more hormones.
II. Neural input from the autonomic nervous system controls the secretion of many hormones. Neuron endings from the sympathetic and parasympathetic nervous systems terminate directly on cells within some endocrine glands, thereby regulating hormone secretion.

Types of Endocrine Disorders

I. Endocrine disorders may be classified as hyposecretion, hypersecretion, and target-cell hyporesponsiveness or hyperresponsiveness.
   a. Primary disorders are those in which the defect is in the cells that secrete the hormone.
   b. Secondary disorders are those in which there is too much or too little tropic hormone.
   c. Hyporesponsiveness is due to an alteration in the receptors for the hormone, to disordered postreceptor events, or to failure of normal metabolic activation of the hormone in target tissue requiring such activation.
II. These disorders can be distinguished by measurements of the hormone and any tropic hormones under both basal conditions and during experimental stimulation of each hormone's secretion.

SECTION A REVIEW QUESTIONS

1. What distinguishes exocrine from endocrine glands?
2. What are the three general chemical classes of hormones?
3. What are the major hormones produced by the adrenal cortex? By the testes? By the ovaries?
4. Which classes of hormones are carried in the blood mainly as unbound, dissolved hormone? Mainly bound to plasma proteins?
5. Do protein-bound hormones diffuse out of capillaries?
6. Which organs are the major sites of hormone excretion and metabolic inactivation?
7. How do the rates of metabolism and excretion differ for the various classes of hormones?
8. List some metabolic transformations that prohormones and some hormones must undergo before they become biologically active.
9. Contrast the locations of receptors for the various classes of hormones.
10. How do hormones influence the concentrations of their own receptors and those of other hormones? How does this explain permissiveness in hormone action?
11. Describe the sequence of events when peptide or catecholamine hormones bind to their receptors.
12. Describe the sequence of events when steroid or thyroid hormones bind to their receptors.
13. What are the direct inputs to endocrine glands controlling hormone secretion?
14. How does control of hormone secretion by plasma mineral ions and nutrients achieve negative feedback control of these substances?
15. How would you distinguish between primary and secondary hyposecretion of a hormone? Between hyposecretion and hyporesponsiveness?

SECTION A KEY TERMS

endocrine glands
endocrine system
hormones

11.2 Hormone Structures and Synthesis

adrenal cortex
adrenal gland
adrenal medulla
aldosterone
amine hormones
androgens
angiotensin II
cortisol
1,25-dihydroxyvitamin D [1,25-$(OH)_2D$]
dopamine
epinephrine
estradiol
estrogens
glucocorticoids
gonads
mineralocorticoid
norepinephrine
peptide hormones
progesterone
prohormones
steroid hormones
testosterone
thyroid hormones

11.5 Mechanisms of Hormone Action

down-regulation
permissiveness
up-regulation

11.6 Inputs That Control Hormone Secretion

tropic hormone

SECTION A CLINICAL TERMS

11.2 Hormone Structures and Synthesis

congenital adrenal hyperplasia (CAH)

11.5 Mechanisms of Hormone Action

pharmacological effects

11.7 Types of Endocrine Disorders

hyperresponsiveness
hypersecretion
hyporesponsiveness
hyposecretion
primary hypersecretion
primary hyposecretion
secondary hypersecretion
secondary hyposecretion
type 2 diabetes mellitus

11.8 Control Systems Involving the Hypothalamus and Pituitary Gland

The **pituitary gland,** or hypophysis (from a Greek term meaning "to grow underneath"), lies in a pocket (called the sella turcica) of the sphenoid bone at the base of the brain (**Figure 11.13**) just below the **hypothalamus.** The pituitary gland is connected to the hypothalamus by the **infundibulum,** or pituitary stalk, containing axons from neurons in the hypothalamus and small blood vessels. In humans, the pituitary gland is primarily composed of two adjacent lobes called the *anterior lobe*—usually referred to as the **anterior pituitary gland** or adenohypophysis—and the *posterior*

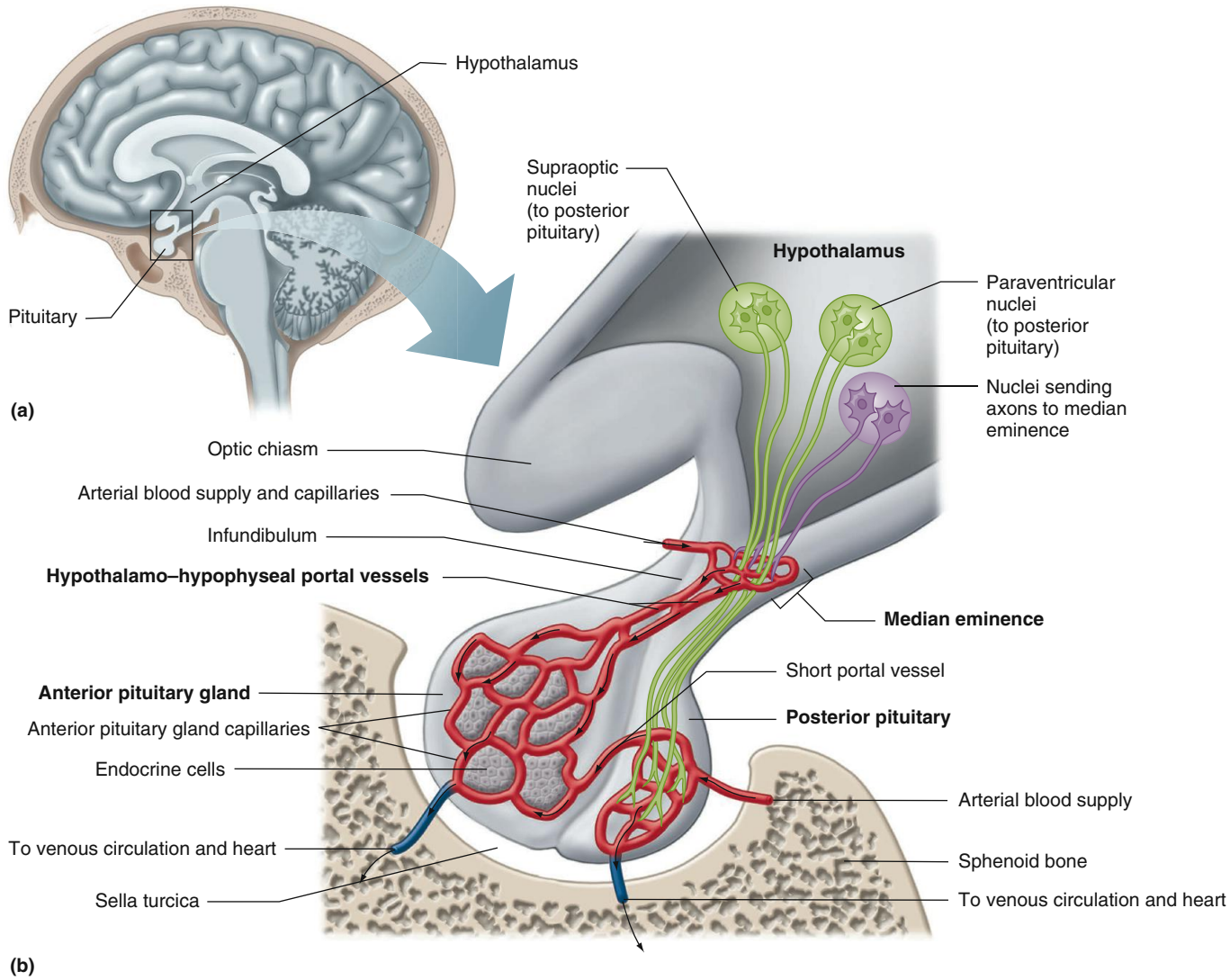


Figure 11.13 (a) Relation of the pituitary gland to the brain and hypothalamus. (b) Neural and vascular connections between the hypothalamus and pituitary gland. Hypothalamic neurons from the paraventricular and supraoptic nuclei travel down the infundibulum to end in the posterior pituitary, whereas others (shown for simplicity as a single nucleus, but in reality several nuclei, including some cells from the paraventricular nuclei) end in the median eminence. Almost the entire blood supply to the anterior pituitary gland comes via the hypothalamo–hypophyseal portal vessels, which originate in the median eminence. Long portal vessels connect the capillaries in the median eminence with those in the anterior pituitary gland. (The short portal vessels, which originate in the posterior pituitary, carry only a small fraction of the blood leaving the posterior pituitary and supply only a small fraction of the blood received by the anterior pituitary gland.) Arrows indicate direction of blood flow.

PHYSIOLOGICAL INQUIRY

- Why does it take only very small quantities of hypophysiotropic hormones to regulate anterior pituitary gland hormone secretion?

Answer can be found at end of chapter.

lobe—usually called the **posterior pituitary** or neurohypophysis. The anterior pituitary gland arises embryologically from an invagination of the pharynx called Rathke's pouch, whereas the posterior pituitary is not actually a gland but, rather, an extension of the neural components of the hypothalamus.

The axons of two well-defined clusters of hypothalamic neurons (the supraoptic and paraventricular nuclei) pass down the infundibulum and end within the posterior pituitary in close proximity to capillaries (small blood vessels where exchange of solutes occurs between the blood and interstitium) (**Figure 11.13b**). Therefore, these neurons do not form a synapse with other neurons. Instead, their terminals end directly on capillaries. The terminals release hormones into these capillaries, which then drain into veins and the general circulation.

In contrast to the neural connections between the hypothalamus and posterior pituitary, there are no important neural connections between the hypothalamus and anterior pituitary gland. There is, however, a special type of vascular connection (see Figure 11.13b). The junction of the hypothalamus and infundibulum is known as the **median eminence.** Capillaries in the median eminence recombine to form the **hypothalamo–hypophyseal portal vessels** (or portal veins). The term *portal* denotes veins that connect two sets of capillaries; normally, as you will learn in Chapter 12, capillaries drain into veins that return blood to the heart. Only in portal systems does one set of capillaries drain into veins that then form a *second* set of capillaries before eventually emptying again into veins that return to the heart. The hypothalamo–hypophyseal portal vessels pass down the infundibulum and enter the anterior pituitary gland, where they drain into a second set of capillaries, the anterior pituitary gland capillaries. Thus, the hypothalamo–hypophyseal portal vessels offer a local route for blood to be delivered directly from the median eminence to the cells of the anterior pituitary gland. As we will see shortly, this local blood system provides a mechanism for hormones synthesized in cell bodies in the hypothalamus to directly alter the activity of the cells of the anterior pituitary gland, bypassing the general circulation and thus efficiently and specifically regulating hormone release from that gland.

We begin our survey of pituitary gland hormones and their major physiological actions with the two hormones of the posterior pituitary.

Posterior Pituitary Hormones

We emphasized that the posterior pituitary is really a neural extension of the hypothalamus (see Figure 11.13). The hormones are synthesized not in the posterior pituitary itself but in the hypothalamus—specifically, in the cell bodies of the supraoptic and paraventricular nuclei, whose axons pass down the infundibulum and terminate in the posterior pituitary. Enclosed in small vesicles, the hormone is transported down the axons to accumulate at the axon terminals in the posterior pituitary. Various stimuli activate inputs to these neurons, causing action potentials that propagate to the axon terminals and trigger the release of the stored hormone by exocytosis. The hormone then enters capillaries to be carried away by the blood returning to the heart. In this way, the brain can receive stimuli and respond as if it were an endocrine organ. By releasing its hormones into the general circulation, the posterior pituitary can modify the functions of distant organs.

The two posterior pituitary hormones are the peptides **oxytocin** and **vasopressin.** Oxytocin is involved in two reflexes related to reproduction. In one case, oxytocin stimulates contraction of smooth muscle cells in the breasts, which results in milk ejection during lactation. This occurs in response to stimulation of the nipples of the breast during nursing of the infant. Sensory cells within the nipples send stimulatory neural signals to the brain that terminate on the hypothalamic cells that make oxytocin, causing their activation and thus release of the hormone. In a second reflex, one that occurs during labor in a pregnant woman, stretch receptors in the cervix send neural signals back to the hypothalamus, which releases oxytocin in response. Oxytocin then stimulates contraction of uterine smooth muscle cells, until eventually the baby is born (see Chapter 17 for details). Although oxytocin is also present in males, its systemic endocrine functions in males are uncertain. Recent research suggests that oxytocin may be involved in various aspects of memory and behavior in male and female mammals, possibly including humans. These include such things as pair bonding, maternal behavior, and emotions such as love. If true in humans, this is likely due to oxytocin-containing neurons in other parts of the brain, as it is unclear whether any systemic oxytocin can cross the blood–brain barrier and enter the brain.

The other posterior pituitary hormone, vasopressin, acts on smooth muscle cells around blood vessels to cause their contraction, which constricts the blood vessels and thereby increases blood pressure. This may occur, for example, in response to a decrease in blood pressure that resulted from a loss of blood due to an injury. Vasopressin also acts within the kidneys to decrease water excretion in the urine, thereby retaining fluid in the body and helping to maintain blood volume. One way in which this would occur would be if a person were to become dehydrated. Because of its kidney function, vasopressin is also known as **antidiuretic hormone** (**ADH**). (A loss of excess water in the urine is known as a *diuresis,* and because vasopressin decreases water loss in the urine, it has *anti*diuretic properties.) The actions of vasopressin will be discussed in the context of circulatory control (Chapter 12, Section 12.9) and fluid balance (Chapter 14, Section 14.7)

Anterior Pituitary Gland Hormones and the Hypothalamus

Other nuclei of hypothalamic neurons secrete hormones that control the secretion of all the anterior pituitary gland hormones. For simplicity's sake, Figure 11.13 depicts these neurons as arising from a single nucleus, but in fact several hypothalamic nuclei send axons whose terminals end in the median eminence. The hypothalamic hormones that regulate anterior pituitary gland function are collectively termed **hypophysiotropic hormones** (recall that another name for the pituitary gland is *hypophysis*); they are also commonly called hypothalamic releasing or inhibiting hormones.

With one exception (dopamine), each of the hypophysiotropic hormones is the first in a three-hormone sequence: (1) A hypophysiotropic hormone controls the secretion of (2) an anterior pituitary gland hormone, which controls the secretion of (3) a hormone from some other endocrine gland (**Figure 11.14**). This last hormone then acts on its target cells. The adaptive value of such sequences is that they permit a variety of types of important hormonal feedback (described in detail later in this chapter). They also allow amplification of a response of a small number of hypothalamic neurons into a large peripheral hormonal signal. We begin our description of these

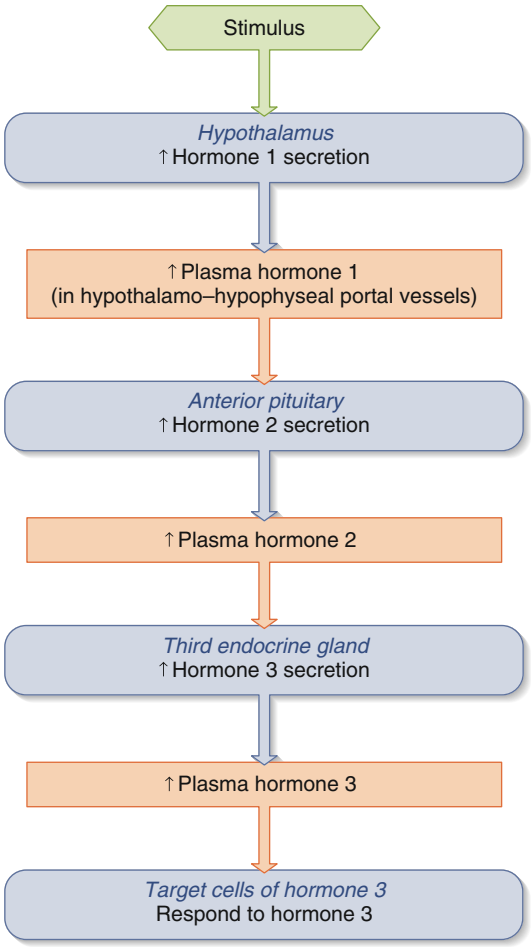


Figure 11.14 Typical sequential pattern by which a hypophysiotropic hormone (hormone 1 from the hypothalamus) controls the secretion of an anterior pituitary gland hormone (hormone 2), which in turn controls the secretion of a hormone by a third endocrine gland (hormone 3). The hypothalamo–hypophyseal portal vessels are illustrated in Figure 11.13.

sequences in the middle—that is, with the anterior pituitary gland hormones—because the names of the hypophysiotropic hormones are mostly based on the names of the anterior pituitary gland hormones.

Overview of Anterior Pituitary Gland Hormones

As shown in Table 11.1, the anterior pituitary gland secretes at least eight hormones, but only six have well-established functions in humans. These six hormones—all peptides—are **follicle-stimulating hormone** (**FSH**), **luteinizing hormone** (**LH**), **growth hormone** (**GH**, also known as *somatotropin*), **thyroid-stimulating hormone** (**TSH**, also known as *thyrotropin*), **prolactin,** and **adrenocorticotropic hormone** (**ACTH**, also known as *corticotropin*). Each of the last four is secreted by a distinct cell type in the anterior pituitary gland, whereas FSH and LH, collectively termed **gonadotropic hormones** (or gonadotropins) because they stimulate the gonads, are often secreted by the same cells.

The other two peptides—**beta-lipotropin** and **beta-endorphin**—are both derived from the same prohormone as ACTH, but their physiological roles in humans are unclear. In animal studies, however, beta-endorphin has been shown to have pain-killing effects, and beta-lipotropin can mobilize fats in the circulation to provide a source of energy. Both of these functions may contribute to the ability to cope with stressful challenges.

Figure 11.15 summarizes the target organs and major functions of the six classical anterior pituitary gland hormones. Note that the only major function of two of the six is to stimulate their target cells to synthesize and secrete other hormones (and to maintain the growth and function of these cells). Thyroid-stimulating hormone induces the thyroid to secrete thyroxine and triiodothyronine. Adrenocorticotropic hormone stimulates the adrenal cortex to secrete cortisol.

Three other anterior pituitary gland hormones also stimulate the secretion of another hormone but have additional functions as well. Growth hormone stimulates the liver to secrete a growth-promoting peptide hormone known as **insulin-like growth factor 1** (**IGF-1**) and, in addition, exerts direct effects on bone and on metabolism (Section E in this chapter). Follicle-stimulating hormone and luteinizing hormone stimulate the gonads to secrete the sex hormones—estradiol and progesterone from the ovaries, or testosterone from the testes; in addition, however, they regulate the growth and development of ova and sperm. The actions of FSH and LH are described in detail in Chapter 17 and therefore are not covered further here.

Prolactin is unique among the six classical anterior pituitary gland hormones in that its major function is not to exert control over the secretion of a hormone by another endocrine gland. Its most important action is to stimulate development of the mammary glands during pregnancy and milk production when a woman is nursing (lactating); this occurs by direct effects upon gland cells in the breasts. During lactation, prolactin exerts a secondary action to inhibit gonadotropin secretion, thereby decreasing

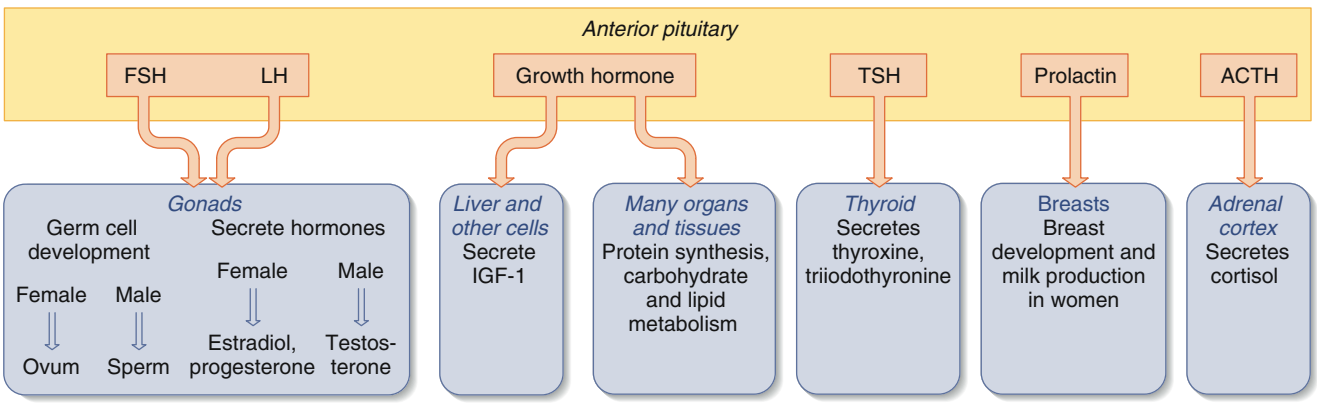


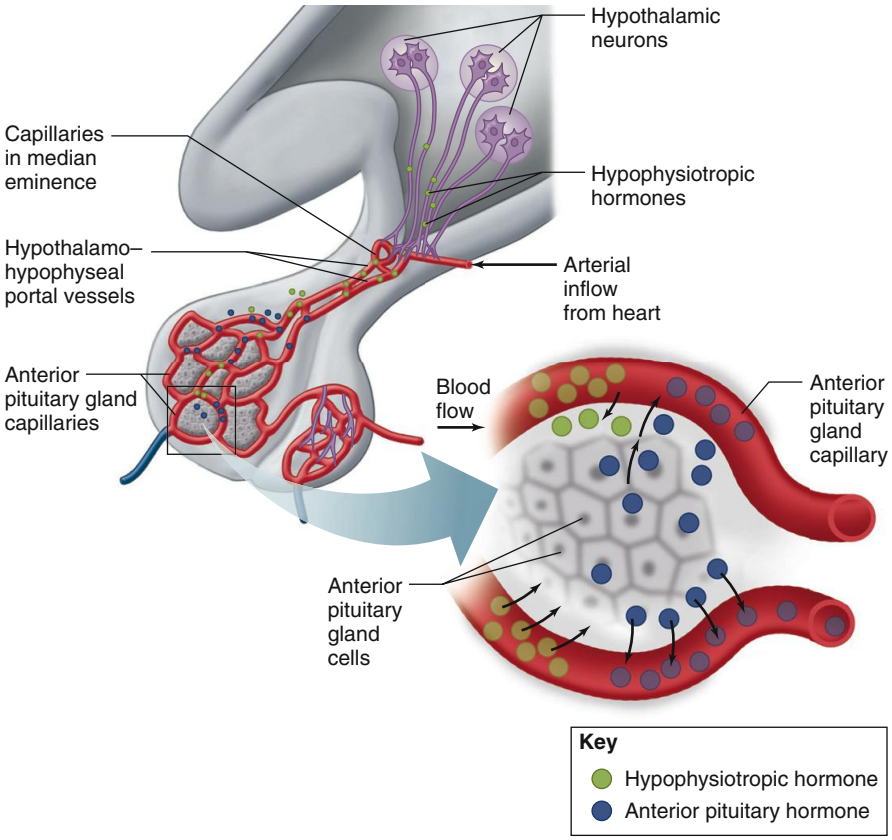
Figure 11.15 Targets and major functions of the six classical anterior pituitary gland hormones.

fertility when a woman is nursing. In the male, the physiological functions of prolactin are still under investigation.

Hypophysiotropic Hormones As stated previously, secretion of the anterior pituitary gland hormones is largely regulated by hormones produced by the hypothalamus and collectively called hypophysiotropic hormones. These hormones are secreted by neurons that originate in discrete nuclei of the hypothalamus and terminate in the median eminence around the capillaries that are the origins of the hypothalamo–hypophyseal portal vessels. The generation of action potentials in these neurons causes them to secrete their hormones by exocytosis, much as action potentials cause other neurons to release neurotransmitters by exocytosis. Hypothalamic hormones, however, enter the median eminence capillaries and are carried by the hypothalamo–hypophyseal portal vessels to the anterior pituitary gland (**Figure 11.16**). There, they diffuse out of the anterior pituitary gland capillaries into the interstitial fluid surrounding the various anterior pituitary gland cells. Upon binding to specific membrane-bound receptors, the hypothalamic hormones act to stimulate or inhibit the secretion of the different anterior pituitary gland hormones.

These hypothalamic neurons secrete hormones in a manner identical to that described previously for the hypothalamic neurons whose axons end in the posterior pituitary. In both cases, the hormones are synthesized in cell bodies of the hypothalamic neurons, pass down axons to the neuron terminals, and are released in response to action potentials in the neurons. Two crucial differences, however, distinguish the two systems. First, the axons of the hypothalamic neurons that secrete the posterior pituitary hormones leave the hypothalamus and end in the posterior pituitary, whereas those that secrete the hypophysiotropic hormones remain in the hypothalamus, ending on capillaries in the median eminence. Second, most of the capillaries into which the posterior pituitary hormones are secreted immediately drain into the general circulation, which carries the hormones to the heart for distribution to the entire body. In contrast, the hypophysiotropic hormones enter capillaries in the median eminence of the hypothalamus that do not directly join the main bloodstream but empty into the hypothalamo–hypophyseal portal vessels, which carry them to the cells of the anterior pituitary gland.

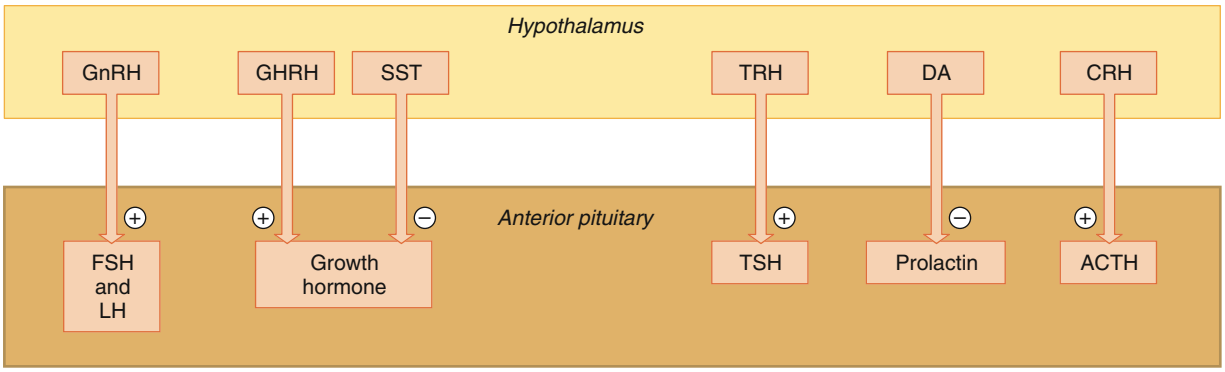
When an anterior pituitary gland hormone is secreted, it will diffuse into the same capillaries that delivered the hypophysiotropic hormone. These capillaries then drain into veins, which enter the general blood circulation, from which the anterior pituitary gland hormones come into contact with their target cells. The portal circulatory system ensures that hypophysiotropic hormones can reach the cells of the anterior pituitary gland with very little delay. The small total blood flow in the portal veins allows extremely small amounts of hypophysiotropic hormones from relatively few hypothalamic neurons to control the secretion of anterior pituitary hormones without dilution in the systemic circulation. This is an excellent illustration of the general principle of physiology that structure is a determinant of—and has coevolved with—function. By having relatively few neurons releasing hypophysiotropic factors into relatively few veins with a low total blood flow, the concentration of hypophysiotropic factors can increase rapidly leading to a larger increase in the release of anterior pituitary hormones (amplification). Also, the total amount of hypophysiotropic hormones entering the general circulation is very low, which prevents them from having unintended effects in the rest of the body.



AP|R **Figure 11.16** Hormone secretion by the anterior pituitary gland is controlled by hypophysiotropic hormones released by hypothalamic neurons and reaching the anterior pituitary gland by way of the hypothalamo–hypophyseal portal vessels. The hypophysiotropic hormones stimulate the anterior pituitary cells, which then release their hormones into the general circulation.

There are multiple hypophysiotropic hormones, each influencing the release of one or, in at least one case, two of the anterior pituitary gland hormones. For simplicity, **Figure 11.17** and the text of this chapter summarize only those hypophysiotropic hormones that have clearly documented physiological roles in humans.

Several of the hypophysiotropic hormones are named for the anterior pituitary gland hormone whose secretion they control. Thus, secretion of ACTH (corticotropin) is stimulated by **corticotropin-releasing hormone (CRH),** secretion of growth hormone is stimulated by **growth hormone–releasing hormone (GHRH),** secretion of thyroid-stimulating hormone (thyrotropin) is stimulated by **thyrotropin-releasing hormone (TRH)**, and secretion of both luteinizing hormone and



Major known hypophysiotropic hormones	Major effect on anterior pituitary
Corticotropin-releasing hormone (CRH)	Stimulates secretion of ACTH
Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH
Growth hormone–releasing hormone (GHRH)	Stimulates secretion of GH
Somatostatin (SST)	Inhibits secretion of GH
Gonadotropin-releasing hormone (GnRH)	Stimulates secretion of LH and FSH
Dopamine (DA)*	Inhibits secretion of prolactin

*Dopamine is a catecholamine; all the other hypophysiotropic hormones are peptides. Evidence exists for PRL-releasing hormones, but they have not been unequivocally identified in humans. One possibility is that TRH may serve this role in addition to its actions on TSH.

Figure 11.17 The effects of definitively established hypophysiotropic hormones on the anterior pituitary gland. The hypophysiotropic hormones reach the anterior pituitary gland via the hypothalamo–hypophyseal portal vessels. The ⊕ and ⊖ symbols indicate stimulatory and inhibitory actions, respectively.

follicle-stimulating hormone (the gonadotropins) is stimulated by **gonadotropin-releasing hormone (GnRH).**

However, note in Figure 11.17 that two of the hypophysiotropic hormones do not *stimulate* the release of an anterior pituitary gland hormone but, rather, *inhibit* its release. One of them, **somatostatin (SST),** inhibits the secretion of growth hormone. The other, **dopamine (DA),** inhibits the secretion of prolactin.

As Figure 11.17 shows, growth hormone is controlled by *two* hypophysiotropic hormones—somatostatin, which inhibits its release, and growth hormone–releasing hormone, which stimulates it. The rate of growth hormone secretion depends, therefore, upon the relative amounts of the opposing hormones released by the hypothalamic neurons, as well as upon the relative sensitivities of the GH-producing cells of the anterior pituitary gland to them. This is a key example of the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition. Such dual controls may also exist for the other anterior pituitary gland hormones. This is particularly true in the case of prolactin where the evidence for a prolactin-releasing hormone in laboratory animals is reasonably strong (the importance of such control for prolactin in humans, if it exists, is uncertain).

Figure 11.18 summarizes the information presented in Figures 11.15 and 11.17 to illustrate the full sequence of hypothalamic control of endocrine function.

Given that the hypophysiotropic hormones control anterior pituitary gland function, we must now ask, What controls secretion of the hypophysiotropic hormones themselves? Some of the neurons that secrete hypophysiotropic hormones may possess spontaneous activity, but the firing of most of them requires neural and hormonal input.

Neural Control of Hypophysiotropic Hormones

Neurons of the hypothalamus receive stimulatory and inhibitory synaptic input from virtually all areas of the central nervous system, and specific neural pathways influence the secretion of the individual hypophysiotropic hormones. A large number of neurotransmitters, such as the catecholamines and serotonin, are released at synapses on the hypothalamic neurons that produce hypophysiotropic hormones. Not surprisingly, drugs that influence these neurotransmitters can alter the secretion of the hypophysiotropic hormones.

In addition, there is a strong circadian influence (see Chapter 1) over the secretion of certain hypophysiotropic hormones. The neural inputs to these cells arise from other regions of the hypothalamus, which in turn are linked to inputs from visual pathways that recognize the presence or absence of light. A good example of this type of neural control is that of CRH, the secretion of which is tied to the day/night cycle in mammals. This pattern results in ACTH and cortisol concentrations in the blood that begin to increase just prior to the waking period.

Hormonal Feedback Control of the Hypothalamus and Anterior Pituitary Gland

A prominent feature of each of the hormonal sequences initiated by a hypophysiotropic hormone is negative feedback exerted upon the hypothalamo–hypophyseal system by one or more of the hormones in its sequence. Negative feedback is a key component of most

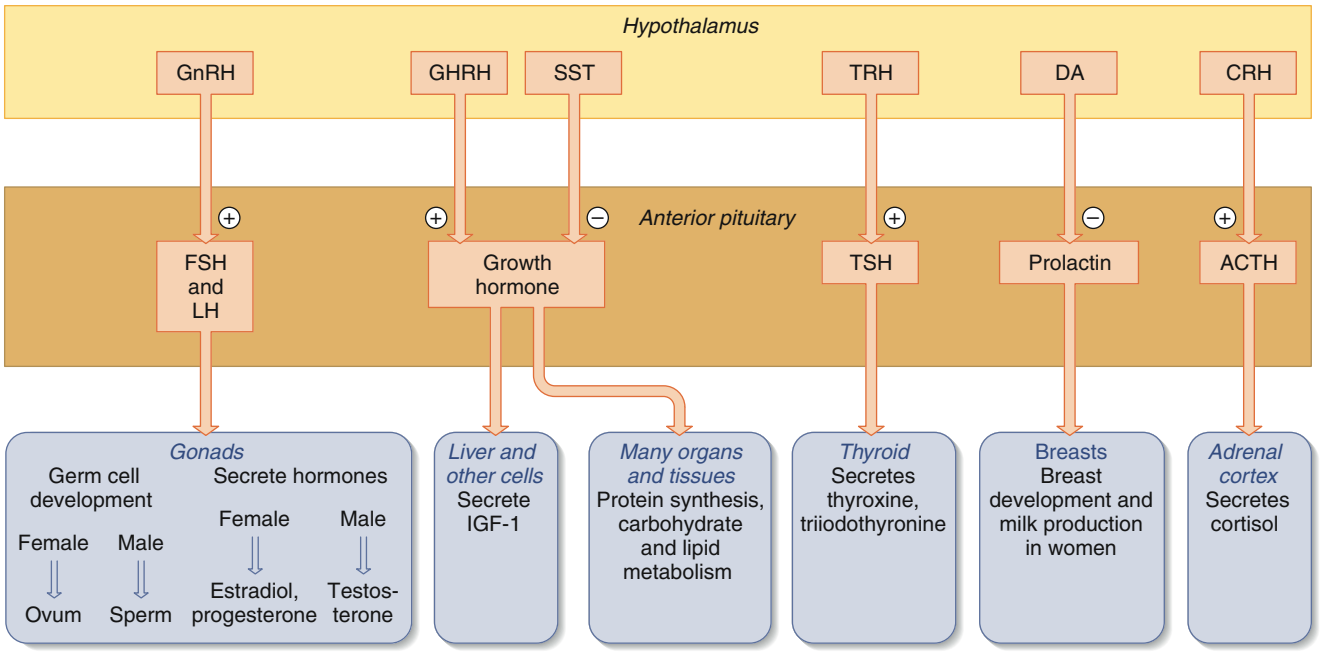


Figure 11.18 A combination of Figures 11.15 and 11.17 summarizes the hypothalamic–anterior pituitary gland system. The ⊕ and ⊖ symbols indicate stimulatory and inhibitory actions, respectively.

homeostatic control systems, as introduced in Chapter 1. In this case, it is effective in dampening hormonal responses—that is, in limiting the extremes of hormone secretory rates. For example, when a stressful stimulus elicits increased secretion, in turn, of CRH, ACTH, and cortisol, the resulting increase in plasma cortisol concentration feeds back to inhibit the CRH-secreting neurons of the hypothalamus and the ACTH-secreting cells of the anterior pituitary gland. Therefore, cortisol secretion does not increase as much as it would without negative feedback. Cortisol negative feedback is also critical in terminating the ACTH response to a stress. As you will see in Section D, this is important because of the potentially damaging effects of excess cortisol on immune function and metabolic reactions, among others.

The situation described for cortisol, in which the hormone secreted by the third endocrine gland in a sequence exerts a negative feedback effect over the anterior pituitary gland and/or hypothalamus, is known as a **long-loop negative feedback** (**Figure 11.19**).

Long-loop feedback does not exist for prolactin because this is one anterior pituitary gland hormone that does not have major control over another endocrine gland—that is, it does not participate in a three-hormone sequence. Nonetheless, there is negative feedback in the prolactin system, for this hormone itself acts upon the hypothalamus to *stimulate* the secretion of dopamine, which then *inhibits* the secretion of prolactin. The influence of an anterior pituitary gland hormone on the hypothalamus is known as a **short-loop negative feedback** (see Figure 11.19). Like prolactin, several other anterior pituitary gland hormones, including growth hormone, also exert such feedback on the hypothalamus.

The Role of "Nonsequence" Hormones on the Hypothalamus and Anterior Pituitary Gland

There are many stimulatory and inhibitory hormonal influences on the hypothalamus and/or anterior pituitary gland other than those that fit the feedback patterns just described. In other words, a hormone

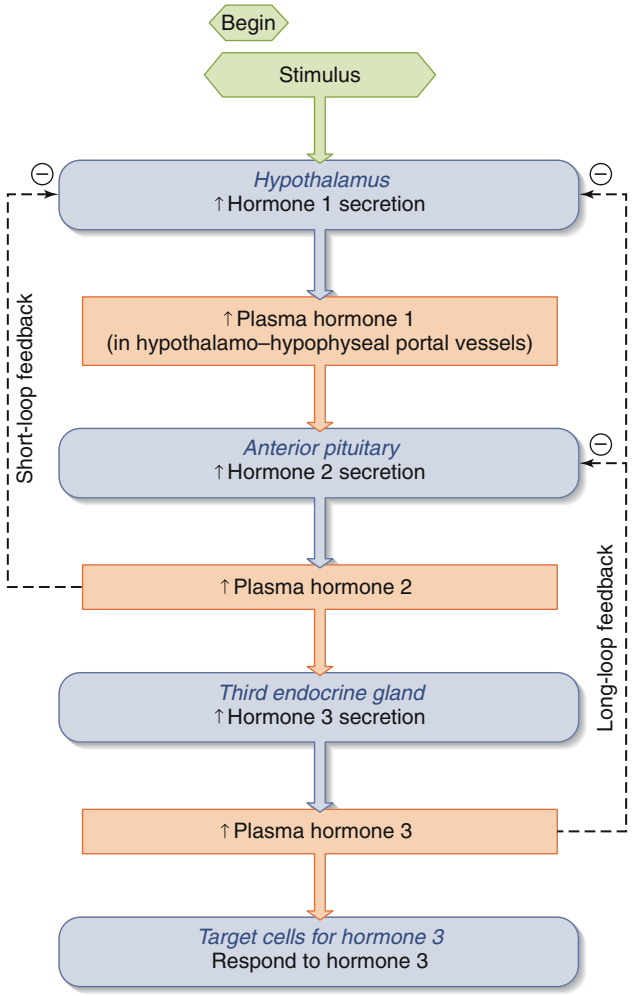


Figure 11.19 Short-loop and long-loop feedbacks. Long-loop feedback is exerted on the hypothalamus and/or anterior pituitary gland by the third hormone in the sequence. Short-loop feedback is exerted by the anterior pituitary gland hormone on the hypothalamus.

that is not itself in a particular hormonal sequence may nevertheless exert important influences on the secretion of the hypophysiotropic or anterior pituitary gland hormones in that sequence. For example, estradiol markedly enhances the secretion of prolactin by the anterior pituitary gland, even though estradiol secretion is not normally controlled by prolactin. Thus, the sequences we have been describing should not be viewed as isolated units.

SECTION B SUMMARY

Control Systems Involving the Hypothalamus and Pituitary Gland

I. The pituitary gland, comprising the anterior pituitary gland and the posterior pituitary, is connected to the hypothalamus by an infundibulum, or stalk, containing neuron axons and blood vessels.
II. Specific axons, whose cell bodies are in the hypothalamus, terminate in the posterior pituitary and release oxytocin and vasopressin.
III. The anterior pituitary gland secretes growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin, and two gonadotropic hormones—follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The functions of these hormones are summarized in Figure 11.15.
IV. Secretion of the anterior pituitary gland hormones is controlled mainly by hypophysiotropic hormones secreted into capillaries in the median eminence of the hypothalamus and reaching the anterior pituitary gland via the portal vessels connecting the hypothalamus and anterior pituitary gland. The actions of the hypophysiotropic hormones on the anterior pituitary gland are summarized in Figure 11.17.
V. The secretion of each hypophysiotropic hormone is controlled by neuronal and hormonal input to the hypothalamic neurons producing it.
    a. In each of the three-hormone sequences beginning with a hypophysiotropic hormone, the third hormone exerts negative feedback effects on the secretion of the hypothalamic and/or anterior pituitary gland hormone.
    b. The anterior pituitary gland hormone may exert a short-loop negative feedback inhibition of the hypothalamic releasing hormone(s) controlling it.
    c. Hormones not in a particular sequence can also influence secretion of the hypothalamic and/or anterior pituitary gland hormones in that sequence.

SECTION B REVIEW QUESTIONS

1. Describe the anatomical relationships between the hypothalamus and the pituitary gland.
2. Name the two posterior pituitary hormones and describe the site of synthesis and mechanism of release of each.
3. List all six well-established anterior pituitary gland hormones and their major functions.
4. List the major hypophysiotropic hormones and the anterior pituitary gland hormone(s) whose release each controls.
5. What kinds of inputs control secretion of the hypophysiotropic hormones?
6. What is the difference between long-loop and short-loop negative feedback in the hypothalamo–anterior pituitary gland system?

SECTION B KEY TERMS

11.8 Control Systems Involving the Hypothalamus and Pituitary Gland

adrenocorticotropic hormone (ACTH)
anterior pituitary gland
antidiuretic hormone (ADH)
beta-endorphin
beta-lipotropin
corticotropin-releasing hormone (CRH)
dopamine (DA)
follicle-stimulating hormone (FSH)
gonadotropic hormones
gonadotropin-releasing hormone (GnRH)
growth hormone (GH)
growth hormone–releasing hormone (GHRH)
hypophysiotropic hormones
hypothalamo–hypophyseal portal vessels
hypothalamus
infundibulum
insulin-like growth factor 1 (IGF-1)
long-loop negative feedback
luteinizing hormone (LH)
median eminence
oxytocin
pituitary gland
posterior pituitary
prolactin
short-loop negative feedback
somatostatin (SST)
thyroid-stimulating hormone (TSH)
thyrotropin-releasing hormone (TRH)
vasopressin

SECTION C The Thyroid Gland

11.9 Synthesis of Thyroid Hormone

Thyroid hormone exerts diverse effects throughout much of the body. The actions of this hormone are so widespread—and the consequences of imbalances in its concentration so significant—that it is worth examining thyroid gland function in detail.

The thyroid gland produces two iodine-containing molecules of physiological importance, **thyroxine** (called **T_4** because it contains four iodines) and **triiodothyronine** (**T_3**, three iodines; review Figure 11.2). Most T_4 is converted to T_3 in target tissues by enzymes known as deiodinases. We will therefore consider T_3 to be the major thyroid hormone, even though the concentration of T_4 in the blood is usually greater than that of T_3. (You may think of T_4 as a sort of reservoir for additional T_3.) For practical reasons, T_4 is typically prescribed when thyroid function is decreased.

The thyroid gland sits within the neck in front of and straddling the trachea (**Figure 11.20a**). It first becomes functional early in fetal life. Within the thyroid gland are numerous **follicles,** each composed of an enclosed sphere of epithelial cells surrounding a core containing a protein-rich material called the **colloid** (**Figure 11.20b**). The follicular epithelial cells participate in almost all phases of thyroid hormone synthesis and secretion. Synthesis begins when circulating iodide is actively cotransported with sodium ions across the basolateral membranes of the epithelial cells (step 1 in **Figure 11.21**), a process known as

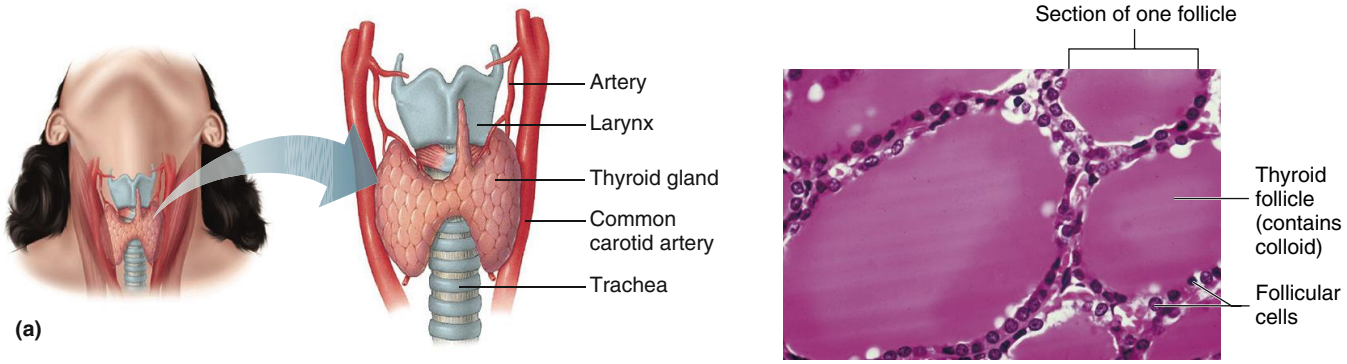


Figure 11.20 (a) Location of the bilobed thyroid gland. (b) A cross section through several adjoining follicles filled with colloid.

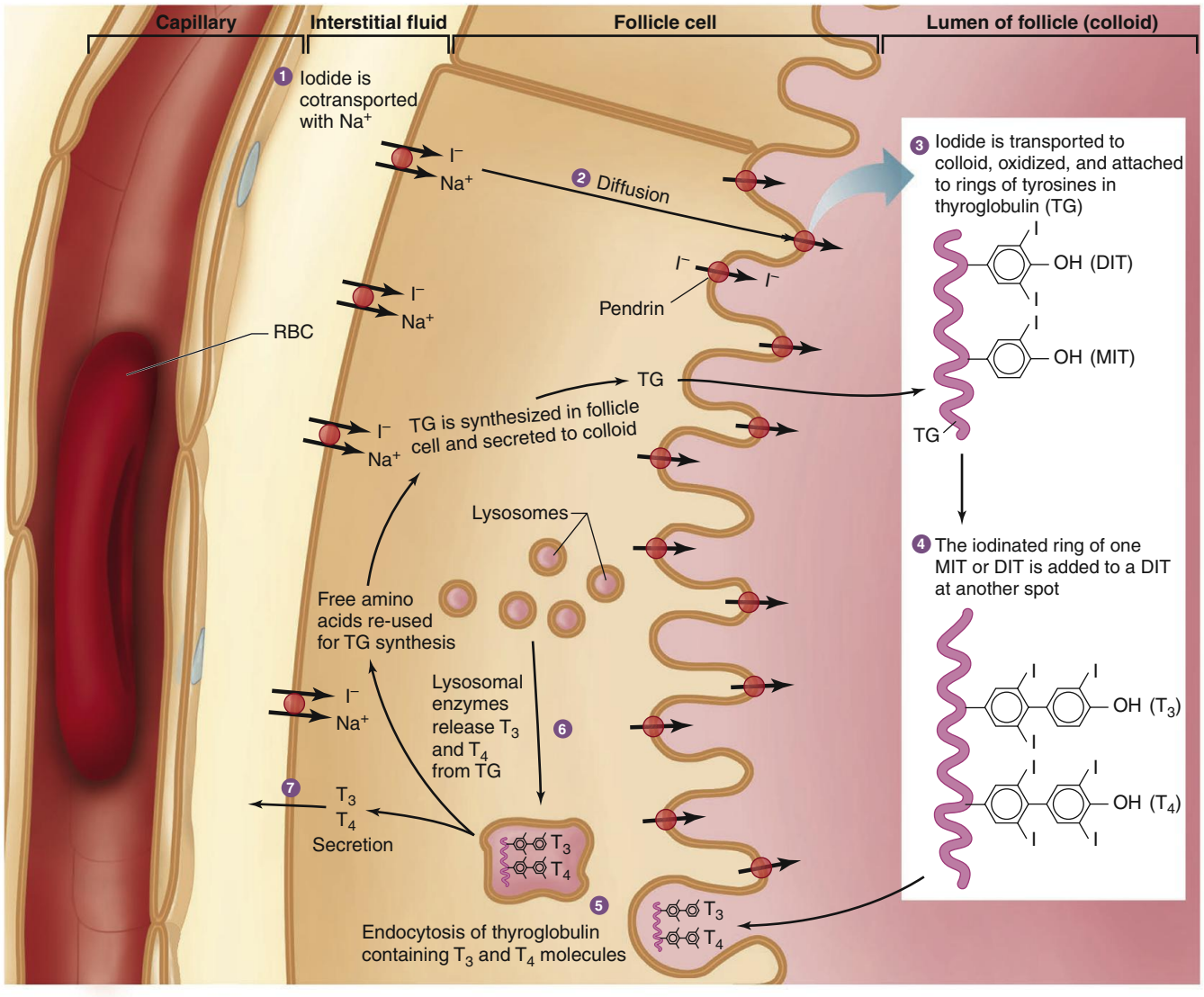


Figure 11.21 Steps involved in T_3 and T_4 formation. Steps are keyed to the text.

PHYSIOLOGICAL INQUIRY

- What is the benefit of storing iodinated thyroglobulin in the colloid?

Answer can be found at end of chapter.

iodide trapping. The Na^+ is pumped back out of the cell by Na^+/K^+-ATPases.

The negatively charged iodide ions diffuse to the apical membrane of the follicular epithelial cells and are transported into the colloid by an integral membrane protein called **pendrin** (step 2). Pendrin is a sodium-independent chloride/iodide transporter. The colloid of the follicles contains large amounts of a protein called **thyroglobulin.** Once in the colloid, iodide is rapidly oxidized at the luminal surface of the follicular epithelial cells to iodine, which is then attached to the phenolic rings of tyrosine residues within thyroglobulin (step 3). Thyroglobulin itself is synthesized by the follicular epithelial cells and secreted by exocytosis into the colloid. The enzyme responsible for oxidizing iodides and attaching them to tyrosines on thyroglobulin in the colloid is called **thyroid peroxidase,** and it, too, is synthesized by follicular epithelial cells. Iodine may be added to either of two positions on a given tyrosine within thyroglobulin. A tyrosine with one iodine attached is called **monoiodotyrosine** (**MIT**)**;** if two iodines are attached, the product is **diiodotyrosine** (**DIT**)**.** Next, the phenolic ring of a molecule of MIT or DIT is removed from the remainder of its tyrosine and coupled to another DIT on the thyroglobulin molecule (step 4). This reaction may also be mediated by thyroid peroxidase. If two DIT molecules are coupled, the result is thyroxine (T_4). If one MIT and one DIT are coupled, the result is T_3. Therefore, the synthesis of T_4 and T_3 is unique in that it actually occurs in the extracellular (colloidal) space within the thyroid follicles.

Finally, for thyroid hormone to be secreted into the blood, extensions of the colloid-facing membranes of follicular epithelial cells engulf portions of the colloid (with its iodinated thyroglobulin) by endocytosis (step 5). The thyroglobulin, which contains T_4 and T_3, is brought into contact with lysosomes in the cell interior (step 6). Proteolysis of thyroglobulin releases T_4 and T_3, which then diffuse out of the follicular epithelial cell into the interstitial fluid and from there to the blood (step 7). There is sufficient iodinated thyroglobulin stored within the follicles of the thyroid to provide thyroid hormone for several weeks even in the absence of dietary iodine. This storage capacity makes the thyroid gland unique among endocrine glands but is an essential adaptation considering the unpredictable intake of iodine in the diets of most animals.

The processes shown in Figure 11.21 are an important example of the general principle of physiology that controlled exchange of materials occurs between compartments and across cellular membranes. A pump is necessary to transport iodide from the interstitial space against a concentration gradient across the cell membrane into the cytosol of the follicular cell, and pendrin is necessary to mediate the efflux of iodide from the cytoplasm into the colloidal space. This process is exploited clinically by giving very low doses of radioactive iodine, which is concentrated in the thyroid gland, allowing it to be visualized by a nuclear medicine scan.

11.10 Control of Thyroid Function

Essentially all of the actions of the follicular epithelial cells just described are stimulated by TSH, which, as we have seen, is stimulated by TRH. The basic control mechanism of TSH production is the negative feedback action of T_3 and T_4 on the anterior pituitary gland and, to a lesser extent, the hypothalamus (**Figure 11.22**). However, TSH does more than just stimulate T_3 and T_4 production. TSH also increases protein synthesis in follicular epithelial cells, increases DNA replication and cell division, and increases the amount of rough endoplasmic reticulum and other cellular machinery required by follicular epithelial cells for protein synthesis. Therefore, if thyroid cells are exposed to greater TSH concentrations than normal, they will undergo **hypertrophy;** that is, they will increase in size. An enlarged thyroid gland from any cause is called a ***goiter.*** There are several other ways in which goiters can occur that will be described later in this section and in one of the case studies in Chapter 19.

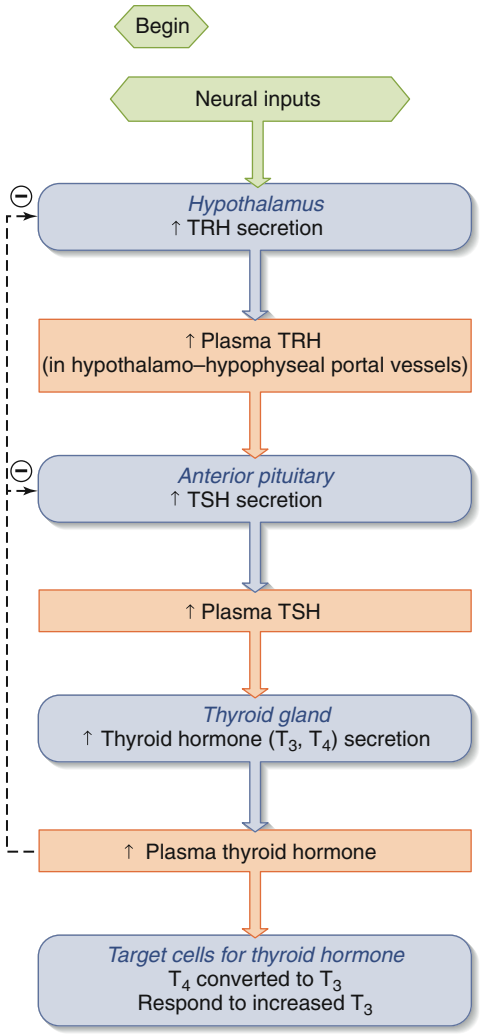


Figure 11.22 TRH-TSH-thyroid hormone sequence. T_3 and T_4 inhibit secretion of TSH and TRH by negative feedback, indicated by the ⊖ symbol.

11.11 Actions of Thyroid Hormone

Receptors for thyroid hormone are present in the nuclei of most of the cells of the body, unlike receptors for many other hormones, whose distribution is more limited. Therefore, the actions of T_3 are widespread and affect many organs and tissues. Like steroid hormones, T_3 acts by inducing gene transcription and protein synthesis.

Metabolic Actions

T_3 has several effects on carbohydrate and lipid metabolism, although not to the extent as other hormones such as insulin. Nonetheless, T_3 stimulates carbohydrate absorption from the small intestine and increases fatty acid release from adipocytes. These actions provide energy that helps maintain metabolism at a high rate. Much of that energy is used to support the activity of Na^+/K^+-ATPases throughout the body; these enzymes are stimulated by T_3. The cellular concentration of ATP, therefore, is critical for the ability of cells to maintain Na^+/K^+-ATPase activity in response to thyroid hormone stimulation. ATP concentrations are controlled in part by a negative feedback mechanism; ATP negatively feeds back on the glycolytic enzymes within cells that participate in ATP generation. A decrease in cellular stores of ATP, therefore, releases the feedback and triggers an increase in glycolysis; this results in the metabolism of additional glucose that restores ATP concentrations. One of the by-products of this process is heat. Thus, as ATP is consumed in cells by Na^+/K^+-ATPases at a high rate due to T_3 stimulation, the cellular stores of ATP must be maintained by increased metabolism of fuels. This calorigenic action of T_3 represents a significant fraction of the total heat produced each day in a typical person. This action is essential for body temperature homeostasis, just one of many ways in which the actions of thyroid hormone demonstrate the general principle of physiology that homeostasis is essential for health and survival. Without thyroid hormone, heat production would decrease and body temperature (and most physiological processes) would be compromised.

Permissive Actions

Some of the actions of T_3 are attributable to its permissive effects on the actions of catecholamines. T_3 up-regulates beta-adrenergic receptors in many tissues, notably the heart and nervous system. It should not be surprising, therefore, that the symptoms of excess thyroid hormone concentration closely resemble some of the symptoms of excess epinephrine and norepinephrine (sympathetic nervous system activity). That is because the increased T_3 potentiates the actions of the catecholamines, even though the latter are within normal concentrations. Because of this potentiating effect, people with excess T_3 are often treated with drugs that block beta-adrenergic receptors to alleviate the anxiety, nervousness, and "racing heart" associated with excessive sympathetic activity.

Growth and Development

T_3 is required for normal production of growth hormone from the anterior pituitary gland. Therefore, when T_3 is very low, growth in children is decreased. In addition, T_3 is a very important developmental hormone for the nervous system. T_3 exerts many effects on central nervous system during development, including the formation of axon terminals and the production of synapses, the growth of dendrites and dendritic extensions (called "spines"), and the formation of myelin. Absence of T_3 results in the syndrome called ***congenital hypothyroidism.*** This syndrome is characterized by a poorly developed nervous system and severely compromised intellectual function (mental retardation). In the United States, the most common cause is the failure of the thyroid gland to develop normally. With neonatal screening, it can be treated with T_4 at birth which prevents long-term impairment of growth and mental development.

The most common cause of congenital hypothyroidism around the world (although rare in the United States) is dietary iodine deficiency in the mother. Without iodine in her diet, iodine is not available to the fetus. Thus, even though the fetal thyroid gland may be normal, it cannot synthesize sufficient thyroid hormone. If the condition is discovered and corrected with iodine and thyroid hormone administration shortly after birth, mental and physical abnormalities can be prevented. Furthermore, if the treatment is not initiated in the neonatal period, the intellectual impairment resulting from congenital hypothyroidism cannot be reversed. The availability of iodized salt products has essentially eliminated congenital hypothyroidism in many countries, but it is still a common disorder in some parts of the world where iodized salt is not available.

The effects of T_3 on nervous system function are not limited to fetal and neonatal life. For example, T_3 is required for proper nerve and muscle reflexes and for normal cognition in adults.

11.12 Hypothyroidism and Hyperthyroidism

Any condition characterized by plasma concentrations of thyroid hormones that are chronically below normal is known as ***hypothyroidism.*** Most cases of hypothyroidism—about 95%—are primary defects resulting from damage to or loss of functional thyroid tissue or from inadequate iodine consumption.

In iodine deficiency, the synthesis of thyroid hormone is compromised, leading to a decrease in the plasma concentration of this hormone. This, in turn, releases the hypothalamus and anterior pituitary gland from negative feedback inhibition. This leads to an increase in TRH concentration in the portal circulation that drains into the anterior pituitary gland. Plasma TSH concentration is increased due to the increased TRH and loss of thyroid hormone negative feedback on the anterior pituitary gland. The resulting overstimulation of the thyroid gland can produce goiters that can achieve astounding sizes if untreated (**Figure 11.23**). This form of hypothyroidism is reversible if iodine is added to the diet. It is rare in the United States because of the widespread use of iodized salt, in which a small fraction of NaCl molecules is replaced with NaI.

The most common cause of hypothyroidism in the United States is autoimmune disruption of the normal function of the thyroid gland, a condition known as ***autoimmune thyroiditis.***

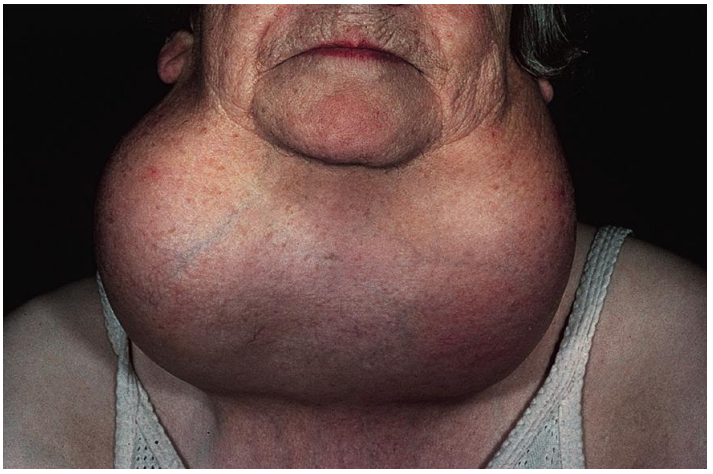


Figure 11.23 Goiter at an advanced stage.

One form of autoimmune thyroiditis results from ***Hashimoto's disease,*** in which cells of the immune system attack thyroid tissue. Like many other autoimmune diseases, Hashimoto's disease is more common in women and can slowly progress with age. As thyroid hormone begins to decrease because of the decrease in thyroid function due to inflammation, TSH concentrations increase due to the decreased negative feedback. The overstimulation of the thyroid gland results in cellular hypertrophy, and a goiter can develop. The usual treatment for autoimmune thyroiditis is daily replacement with a pill containing T_4. This causes the TSH concentration to decrease to normal due to negative feedback. Another cause of hypothyroidism can occur when the release of TSH from the anterior pituitary is inadequate for long periods of time. This is called secondary hypothyroidism and can lead to atrophy of the thyroid gland due to the long-term loss of the trophic effects of TSH.

The features of hypothyroidism in adults may be mild or severe, depending on the degree of hormone deficiency. These include an increased sensitivity to cold (***cold intolerance***) and a tendency toward weight gain. Both of these symptoms are related to the decreased calorigenic actions normally produced by thyroid hormone. Many of the other symptoms appear to be diffuse and nonspecific, such as fatigue and changes in skin tone, hair, appetite, gastrointestinal function, and neurological function (for example, depression). The basis of the last effect in humans is uncertain, but it is now clear from work on laboratory animals that thyroid hormone has widespread effects on the adult mammalian brain.

In severe, untreated hypothyroidism, certain hydrophilic polymers called glycosaminoglycans accumulate in the interstitial space in scattered regions of the body. Normally, thyroid hormone acts to prevent overexpression of these extracellular compounds that are secreted by connective tissue cells. When T_3 is too low, therefore, these hydrophilic molecules accumulate and water tends to be trapped with them. This combination causes a characteristic puffiness of the face and other regions that is known as ***myxedema.***

As in the case of hypothyroidism, there are a variety of ways in which ***hyperthyroidism,*** or ***thyrotoxicosis,*** can develop. Among these are hormone-secreting tumors of the thyroid gland (rare), but the most common form of hyperthyroidism is an autoimmune disease called ***Graves' disease.*** This disease is characterized by the production of antibodies that bind to and activate the TSH receptors on thyroid gland cells, leading to chronic overstimulation of the growth and activity of the thyroid gland (see Chapter 19 for a case study related to this disease).

The signs and symptoms of thyrotoxicosis can be predicted in part from the previous discussion about hypothyroidism. Hyperthyroid patients tend to have ***heat intolerance,*** weight loss, and increased appetite, and often show signs of increased sympathetic nervous system activity (anxiety, tremors, jumpiness, increased heart rate).

Hyperthyroidism can be very serious, particularly because of its effects on the cardiovascular system (largely secondary to its permissive actions on catecholamines). It may be treated with drugs that inhibit thyroid hormone synthesis, by surgical removal of the thyroid gland, or by destroying a portion of the thyroid gland using radioactive iodine. In the last case, the radioactive iodine is ingested. Because the thyroid gland is the chief region of iodine uptake in the body, most of the radioactive iodine appears within the gland, where its high-energy radiation partly destroys the tissue.

SECTION C SUMMARY

Synthesis of Thyroid Hormone

I. T_3 and T_4 are synthesized by sequential iodinations of thyroglobulin in the thyroid follicle lumen, or colloid. Iodinated tyrosines on thyroglobulin are coupled to produce either T_3 or T_4. Whereas T_4 is the main secretory product of the thyroid gland, T_3 (produced from T_4 in target tissue) is the active hormone.
II. The enzyme responsible for T_3 and T_4 synthesis is thyroid peroxidase.

Control of Thyroid Function

I. All of the synthetic steps involved in T_3 and T_4 synthesis are stimulated by TSH. TSH also stimulates uptake of iodide, where it is trapped in the follicle.
II. TSH causes growth (hypertrophy) of thyroid tissue. Excessive exposure of the thyroid gland to TSH can cause goiter.

Actions of Thyroid Hormone

I. T_3 increases the metabolic rate and therefore promotes consumption of calories (calorigenic effect). This results in heat production.
II. The actions of the sympathetic nervous system are potentiated by T_3. This is called the permissive action of T_3.
III. Thyroid hormone is essential for normal growth and development—particularly of the nervous system—during fetal life and childhood.

Hypothyroidism and Hyperthyroidism

I. Hypothyroidism most commonly results from autoimmune attack of the thyroid gland. It is characterized by weight gain, fatigue, cold intolerance, and changes in skin tone and cognition. It may also result in goiter.
II. Hyperthyroidism is also typically the result of an autoimmune disorder. It is characterized by weight loss, heat intolerance, irritability and anxiety, and often goiter.

SECTION C REVIEW QUESTIONS

1. Describe the steps leading to T_3 and T_4 production, beginning with the transport of iodide into the thyroid follicular epithelial cell.
2. What are the major actions of TSH on thyroid function and growth?
3. What is the major way in which the TRH-TSH-thyroid hormone pathway is regulated?
4. Explain why the symptoms of hyperthyroidism may be confused with a disorder of the autonomic nervous system.

SECTION C KEY TERMS

11.9 Synthesis of Thyroid Hormone

colloid
diiodotyrosine (DIT)
follicles
iodide trapping
monoiodotyrosine (MIT)
pendrin
thyroglobulin
thyroid peroxidase
thyroxine (T_4)
triiodothyronine (T_3)

11.10 Control of Thyroid Function

hypertrophy

SECTION C CLINICAL TERMS

11.10 Control of Thyroid Function

goiter

11.11 Actions of Thyroid Hormone

congenital hypothyroidism

11.12 Hypothyroidism and Hyperthyroidism

autoimmune thyroiditis
cold intolerance
Graves' disease
Hashimoto's disease
heat intolerance
hyperthyroidism
hypothyroidism
myxedema
thyrotoxicosis

SECTION D
The Endocrine Response to Stress

Much of this book is concerned with the body's response to **stress** in its broadest meaning as a real or perceived threat to homeostasis. Thus, any change in external temperature, water intake, or other homeostatic factors sets into motion responses designed to minimize a significant change in some physiological variable. In this section, the basic endocrine response to stress is described. These threats to homeostasis comprise a large number of situations, including physical trauma, prolonged exposure to cold, prolonged heavy exercise, infection, shock, decreased oxygen supply, sleep deprivation, pain, and emotional stresses.

It may seem obvious that the physiological response to cold exposure must be very different from that to infection or emotional stresses such as fright, but in one respect the response to all these situations is the same: Invariably, the secretion from the adrenal cortex of the glucocorticoid hormone cortisol is increased. Activity of the sympathetic nervous system, including release of the hormone epinephrine from the adrenal medulla, also increases in response to many types of stress.

The increased cortisol secretion during stress is mediated by the hypothalamus–anterior pituitary gland system described earlier. As illustrated in **Figure 11.24**, neural input to the hypothalamus from portions of the nervous system responding to a particular stress induces secretion of CRH. This hormone is carried by the hypothalamo–hypophyseal portal vessels to the anterior pituitary gland, where it stimulates ACTH secretion. ACTH in turn circulates through the blood, reaches the adrenal cortex, and stimulates cortisol release.

The secretion of ACTH, and therefore of cortisol, is also stimulated to a lesser extent by vasopressin, which usually increases in response to stress and which may reach the anterior pituitary gland either from the general circulation or by the short portal vessels shown in Figure 11.13. Some of the cytokines (secretions from cells that comprise the immune system, Chapter 18) also stimulate ACTH secretion both directly and by stimulating the secretion of CRH. These cytokines provide a means for eliciting an endocrine stress response when the immune system is stimulated in, for example, systemic infection. The possible significance of this relationship for immune function is described next and in additional detail in Chapter 18.

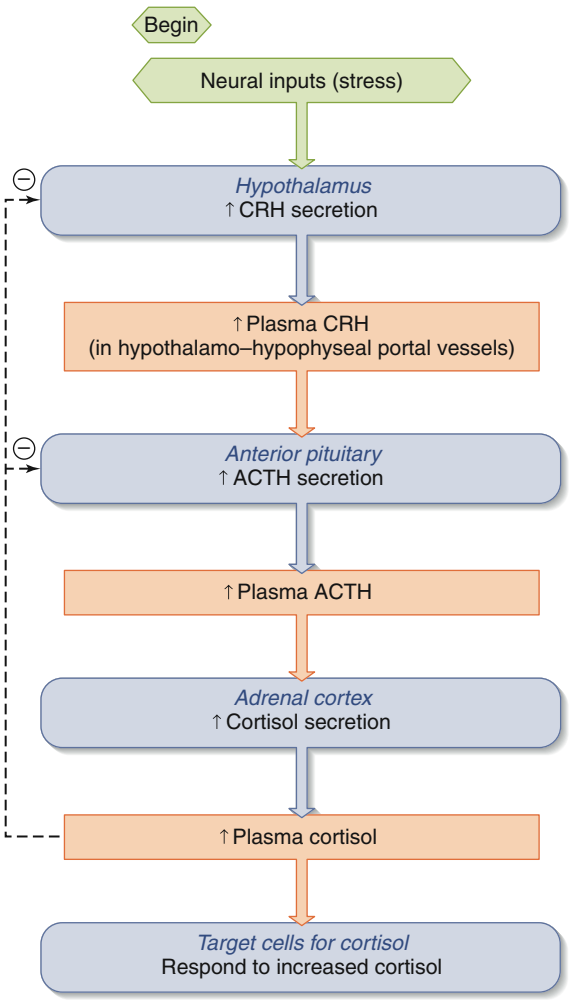


Figure 11.24 CRH-ACTH-cortisol pathway. Neural inputs include those related to stressful stimuli and nonstress inputs like circadian rhythms. Cortisol exerts a negative feedback control (⊖ symbols) over the system by acting on (1) the hypothalamus to inhibit CRH synthesis and secretion and (2) the anterior pituitary gland to inhibit ACTH production.

PHYSIOLOGICAL INQUIRY

- What hormonal changes in this pathway would be expected if a patient developed a benign tumor of the left adrenal cortex that secreted extremely large amounts of cortisol in the absence of external stimulation? What might happen to the right adrenal gland?

Answer can be found at end of chapter.

11.13 Physiological Functions of Cortisol

Although the effects of cortisol are best illustrated during the response to stress, cortisol is always produced by the adrenal cortex and exerts many important actions even in nonstress situations. For example, cortisol has permissive actions on the

responsiveness to epinephrine and norepinephrine of smooth muscle cells that surround the lumen of blood vessels such as arterioles. Partly for this reason, cortisol helps maintain normal blood pressure; when cortisol secretion is greatly decreased, low blood pressure can occur. Likewise, cortisol is required to maintain the cellular concentrations of certain enzymes involved in metabolic homeostasis. These enzymes are expressed primarily in the liver, and they act to increase hepatic glucose production between meals, thereby preventing plasma glucose concentration from significantly decreasing below normal.

Two important systemic actions of cortisol are its anti-inflammatory and anti-immune functions. The mechanisms by which cortisol inhibits immune system function are numerous and complex. Cortisol inhibits the production of leukotrienes and prostaglandins, both of which are involved in inflammation. Cortisol also stabilizes lysosomal membranes in damaged cells, preventing the release of their proteolytic contents. In addition, cortisol decreases capillary permeability in injured areas (thereby decreasing fluid leakage to the interstitium), and it suppresses the growth and function of certain key immune cells such as lymphocytes. Thus, cortisol may serve as a "brake" on the immune system, which may overreact to minor infections in the absence of cortisol.

During fetal and neonatal life, cortisol is also an important developmental hormone. It has been implicated in the proper differentiation of numerous tissues and glands, including various parts of the brain, the adrenal medulla, the intestine, and the lungs. In the last case, cortisol is very important for the production of surfactant, a substance that decreases surface tension in the lungs, thereby making it easier for the lungs to inflate (see Chapter 13).

Thus, although it is common to define the actions of cortisol in the context of the stress response, it is worth remembering that the maintenance of homeostasis in the absence of external stresses is also a critical function of cortisol.

11.14 Functions of Cortisol in Stress

Table 11.3 summarizes the major effects of increased plasma concentration of cortisol during stress. The effects on organic metabolism are to mobilize energy sources to increase the plasma concentrations of amino acids, glucose, glycerol, and free fatty acids. These effects are ideally suited to meet a stressful situation. First, an animal faced with a potential threat is often forced to forgo eating, making these metabolic changes adaptive for coping with stress while fasting. Second, the amino acids liberated by catabolism of body protein not only provide a potential source of glucose, via hepatic gluconeogenesis, but also constitute a potential source of amino acids for tissue repair should injury occur.

A few of the medically important implications of these cortisol-induced effects on organic metabolism are as follows. (1) Any patient who is ill or is subjected to surgery catabolizes considerable quantities of body protein; (2) a person with diabetes mellitus who suffers an infection requires more insulin than usual; and (3) a child subjected to severe stress of any kind may show a decreased rate of growth.

Cortisol has important effects during stress other than those on organic metabolism. For example, it increases the ability of vascular smooth muscle to contract in response to norepinephrine, thereby improving cardiovascular performance.

TABLE 11.3 Effects of Increased Plasma Cortisol Concentration During Stress

I. Effects on organic metabolism
   A. Stimulation of protein catabolism in bone, lymph, muscle, and elsewhere
   B. Stimulation of liver uptake of amino acids and their conversion to glucose (gluconeogenesis)
   C. Maintenance of plasma glucose concentrations
   D. Stimulation of triglyceride catabolism in adipose tissue, with release of glycerol and fatty acids into the blood

II. Enhanced vascular reactivity (increased ability to maintain vasoconstriction in response to norepinephrine and other stimuli)

III. Unidentified protective effects against the damaging influences of stress

IV. Inhibition of inflammation and specific immune responses

V. Inhibition of nonessential functions (e.g., reproduction and growth)

As item III in Table 11.3 notes, we still do not know the other reasons that increased cortisol is so important for the body's optimal response to stress. What is clear is that a person exposed to severe stress can die, usually of circulatory failure, if his or her plasma cortisol concentration is abnormally low; the complete absence of cortisol is always fatal.

Effect IV in Table 11.3 reflects the fact that administration of large amounts of cortisol or its synthetic analogs profoundly reduces the inflammatory response to injury or infection. Because of this effect, the synthetic analogs of cortisol are useful in the treatment of allergy, arthritis (inflammation of the joints), other inflammatory diseases, and graft rejection (all of which are discussed in detail in Chapter 18). These anti-inflammatory and anti-immune effects have been classified as pharmacological effects of cortisol because it was assumed they could be achieved only by large doses of administered glucocorticoids. It is now clear that such effects also occur, albeit to a lesser degree, at the plasma concentrations achieved during stress. Thus, the increased plasma cortisol typical of infection or trauma exerts a dampening effect on the body's immune responses, protecting against possible damage from excessive inflammation. This effect explains the significance of the fact, mentioned earlier, that certain cytokines (immune cell secretions) stimulate the secretion of ACTH and thereby cortisol. Such stimulation is part of a negative feedback system in which the increased cortisol then partially inhibits the inflammatory processes in which the cytokines participate. Moreover, cortisol normally dampens the fever an infection causes.

Whereas the acute cortisol responses to stress are adaptive, it is now clear that chronic stress, including emotional stress, can have deleterious effects on the body. In some studies, it has been demonstrated that chronic stress results in sustained increases in cortisol secretion. In such a case, the abnormally high cortisol concentrations may sufficiently decrease the activity of the immune system to reduce the body's resistance to infection.

It can also worsen the symptoms of diabetes because of its effects on blood glucose concentrations, and it may possibly cause an increase in the death rate of certain neurons in the brain. Finally, chronic stress may be associated with decreased reproductive fertility, delayed puberty, and suppressed growth during childhood and adolescence. Some but not all of these effects are linked with the catabolic actions of glucocorticoids.

In summary, stress is a broadly defined situation in which there exists a real or potential threat to homeostasis. In such a scenario, it is important to maintain blood pressure, to provide extra energy sources in the blood, and to temporarily reduce nonessential functions. Cortisol is the most important hormone that carries out these activities. Cortisol enhances vascular reactivity, catabolizes protein and fat to provide energy, and inhibits growth and reproduction. The price the body pays during stress is that cortisol is strongly catabolic. Thus, cells of the immune system, bone, muscles, skin, and numerous other tissues undergo catabolism to provide substrates for gluconeogenesis. In the short term, this is not of any major consequence. Chronic stress, however, can lead to severe decreases in bone density, immune function, and reproductive fertility.

11.15 Adrenal Insufficiency and Cushing's Syndrome

Cortisol is one of several hormones essential for life. The absence of cortisol leads to the body's inability to maintain homeostasis, particularly when confronted with a stress such as infection, which is usually fatal within days without cortisol. The general term for any situation in which plasma concentrations of cortisol are chronically lower than normal is ***adrenal insufficiency.*** Patients with adrenal insufficiency have a diffuse array of symptoms, depending on the severity and cause of the disease. These patients typically report weakness, fatigue, and loss of appetite and weight. Examination may reveal low blood pressure (in part because cortisol is needed to permit the full extent of the cardiovascular actions of epinephrine) and low blood sugar, especially after fasting (because of the loss of the normal metabolic actions of cortisol).

There are several causes of adrenal insufficiency. ***Primary adrenal insufficiency*** is due to a loss of adrenocortical function, as may rarely occur, for example, when infectious diseases such as ***tuberculosis*** infiltrate the adrenal glands and destroy them. The adrenals can also (rarely) be destroyed by invasive tumors. Most commonly by far, however, the syndrome is due to autoimmune attack in which the immune system mistakenly recognizes some component of a person's own adrenal cells as "foreign." The resultant immune reaction causes inflammation and eventually the destruction of many of the cells of the adrenal glands. Because of this, all of the zones of the adrenal cortex are affected. Thus, not only cortisol but also aldosterone concentrations are decreased below normal in primary adrenal insufficiency. This decrease in aldosterone concentration creates the additional problem of an imbalance in Na^+, K^+, and water in the blood because aldosterone is a key regulator of those variables. The loss of salt and water balance may lead to ***hypotension*** (low blood pressure). Primary adrenal insufficiency from any of these causes is also known as ***Addison's disease,*** after the nineteenth-century physician who first discovered the syndrome.

The diagnosis of primary adrenal insufficiency is made by measuring the plasma concentration of cortisol. In primary adrenal insufficiency, the cortisol concentration is well below normal, whereas the ACTH concentration is greatly increased due to the loss of the negative feedback actions of cortisol. Treatment of this disease requires daily oral administration of glucocorticoids and mineralocorticoids. In addition, the patient must carefully monitor his or her diet to ensure an adequate consumption of carbohydrates and controlled K^+ and Na^+ intake.

Adrenal insufficiency can also be due to inadequate ACTH secretion, ***secondary adrenal insufficiency,*** which may arise from pituitary disease. Its symptoms are often less dramatic than primary adrenal insufficiency because aldosterone secretion, which does not rely on ACTH, is maintained by other mechanisms (discussed in detail in Chapter 14, Section 14.8).

Adrenal insufficiency can be life threatening if not treated aggressively. The flip side of this disorder—*excess* glucocorticoids—is usually not as immediately dangerous but can also be very severe. In ***Cushing's syndrome,*** even the nonstressed individual has excess cortisol in the blood. The cause may be a primary defect (e.g., a cortisol-secreting tumor of the adrenal) or may be secondary (usually due to an ACTH-secreting tumor of the anterior pituitary gland). In the latter case, the condition is known as ***Cushing's disease,*** which accounts for most cases of Cushing's syndrome. The increased blood concentration of cortisol, particularly at night when cortisol is usually low, promotes uncontrolled catabolism of bone, muscle, skin, and other organs. As a result, bone strength diminishes and can even lead to ***osteoporosis*** (loss of bone mass), muscles weaken, and the skin becomes thinned and easily bruised. The increased catabolism may produce such a large quantity of precursors for hepatic gluconeogenesis that the blood sugar concentration increases to that observed in diabetes mellitus. A person with Cushing's syndrome, therefore, may show some of the same symptoms as a person with diabetes. Equally troubling is the possibility of ***immunosuppression,*** which may be brought about by the anti-immune actions of cortisol. Cushing's syndrome is often associated with loss of fat mass from the extremities and with redistribution of the fat in the trunk, face, and the back of the neck. Combined with an increased appetite, often triggered by high concentrations of cortisol, this results in obesity (particularly abdominal) and a characteristic facial appearance in many patients (**Figure 11.25**). A further problem associated with

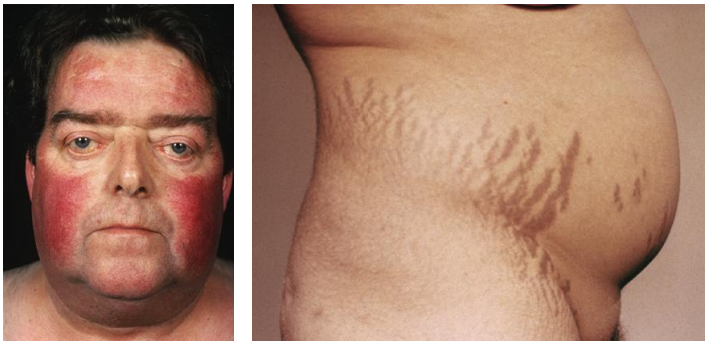


Figure 11.25 Patient with florid Cushing's syndrome. *Left:* Notice "moon face" and facial plethora (high blood flow leading to redness). *Right:* Notice pendulous abdomen (from increased visceral fat) and striae (stretch marks) from thin skin and stretching of the skin due to increased girth.

Cushing's syndrome is the possibility of developing ***hypertension*** (high blood pressure). This is due not to increased aldosterone production but instead to the pharmacological effects of cortisol, because at high concentrations, cortisol exerts aldosterone-like actions on the kidney, resulting in salt and water retention, which contributes to hypertension.

Treatment of Cushing's syndrome depends on the cause. In Cushing's disease, for example, surgical removal of the pituitary tumor, if possible, is the best alternative.

Of importance is the fact that glucocorticoids are often used therapeutically to treat inflammation, lung disease, and other disorders. If glucocorticoids are administered at a high enough dosage for long periods, the side effect of such treatment can be Cushing's syndrome.

11.16 Other Hormones Released During Stress

Other hormones that are usually released during many kinds of stress are aldosterone, vasopressin, growth hormone, glucagon, and beta-endorphin (which is coreleased from the anterior pituitary gland with ACTH). Insulin secretion usually decreases. Vasopressin and aldosterone act to retain water and Na^+ within the body, an important response in the face of potential losses by dehydration, hemorrhage, or sweating. The overall effects of the changes in growth hormone, glucagon, and insulin are, like those of cortisol and epinephrine, to mobilize energy stores and increase the plasma concentration of glucose. The role, if any, of beta-endorphin in stress may be related to its painkilling effects.

In addition, the sympathetic nervous system has a key function in the stress response. Activation of the sympathetic nervous system during stress is often termed the fight-or-flight response, as described in Chapter 6. A list of the major effects of increased sympathetic activity, including secretion of epinephrine from the adrenal medulla, almost constitutes a guide to how to meet emergencies in which physical activity may be required and bodily damage may occur (**Table 11.4**).

TABLE 11.4 **Actions of the Sympathetic Nervous System, Including Epinephrine Secreted by the Adrenal Medulla, During Stress**

Increased hepatic and muscle glycogenolysis (provides a quick source of glucose)
Increased breakdown of adipose tissue triglyceride (provides a supply of glycerol for gluconeogenesis and of fatty acids for oxidation)
Increased cardiac function (e.g., increased heart rate)
Diversion of blood from viscera to skeletal muscles by means of vasoconstriction in the former beds and vasodilation in the latter
Increased lung ventilation by stimulating brain breathing centers and dilating airways

This description of hormones whose secretion rates are altered by stress is by no means complete. It is likely that the secretion of almost every known hormone may be influenced by stress. For example, prolactin is increased, although the adaptive significance of this change is unclear. By contrast, the pituitary gonadotropins and the sex steroids are decreased. As noted previously, reproduction is not an essential function during a crisis.

The response to stress is a classic example of the general principle of physiology that the functions of organ systems are coordinated with each other. The target organs of this extensive number of hormones must respond in a coordinated way to maintain homeostasis.

SECTION D SUMMARY

Physiological Functions of Cortisol

I. Cortisol is released from the adrenal cortex upon stimulation with ACTH. ACTH, in turn, is stimulated by the release of corticotropin-releasing hormone (CRH) from the hypothalamus.
II. The physiological functions of cortisol are to maintain the responsiveness of target cells to epinephrine and norepinephrine, to provide a "check" on the immune system, to participate in energy homeostasis, and to promote normal differentiation of tissues during fetal life.

Functions of Cortisol in Stress

I. The stimulus that activates the CRH-ACTH-cortisol pathway is stress, which encompasses a wide array of sensory and physical inputs that disrupt, or potentially disrupt, homeostasis.
II. In response to stress, the usual physiological functions of cortisol are enhanced as cortisol concentrations in the plasma increase. Thus, gluconeogenesis, lipolysis, and inhibition of insulin actions increase. This results in increased blood concentrations of energy sources (glucose, fatty acids) required to cope with stressful situations.
III. High cortisol concentrations also inhibit "nonessential" processes, such as reproduction, during stressful situations and inhibit immune function.

Adrenal Insufficiency and Cushing's Syndrome

I. Adrenal insufficiency may result from adrenal destruction (primary adrenal insufficiency, or Addison's disease) or from hyposecretion of ACTH (secondary adrenal insufficiency).
II. Adrenal insufficiency is associated with decreased ability to maintain blood pressure and blood sugar. It may be fatal if untreated.
III. Cushing's syndrome is the result of chronically increased plasma cortisol concentration. When the cause of the increased cortisol is secondary to an ACTH-secreting pituitary tumor, the condition is known as Cushing's disease.
IV. Cushing's syndrome is associated with hypertension, high blood sugar, redistribution of body fat, obesity, and muscle and bone weakness. If untreated, it can also lead to immunosuppression.

Other Hormones Released During Stress

I. In addition to CRH, ACTH, and cortisol, several other hormones are released during stress. Beta-endorphin is coreleased with ACTH and may act to reduce pain. Vasopressin stimulates ACTH secretion and also acts on the kidney to increase water retention. Other hormones that are increased in the blood by stress are aldosterone, growth hormone, and glucagon. Insulin secretion, by contrast, decreases during stress.

II. Epinephrine is secreted from the adrenal medulla in response to stimulation from the sympathetic nervous system. The norepinephrine from sympathetic neuron terminals, combined with the circulating epinephrine, prepare the body for stress in several ways. These include increased heart rate and heart pumping strength, increased ventilation, increased shunting of blood to skeletal muscle, and increased generation of energy sources that are released into the blood.

SECTION D REVIEW QUESTIONS

1. Diagram the CRH-ACTH-cortisol pathway.
2. List the physiological functions of cortisol.
3. Define *stress,* and list the functions of cortisol during stress.
4. List the major effects of activation of the sympathetic nervous system during stress.
5. Contrast the symptoms of adrenal insufficiency and Cushing's syndrome.

SECTION D KEY TERMS

stress

SECTION D CLINICAL TERMS

11.15 Adrenal Insufficiency and Cushing's Syndrome

Addison's disease
adrenal insufficiency
Cushing's disease
Cushing's syndrome
hypertension
hypotension
immunosuppression
osteoporosis
primary adrenal insufficiency
secondary adrenal insufficiency
tuberculosis

SECTION E

Endocrine Control of Growth

One of the major functions of the endocrine system is to control growth. At least a dozen hormones directly or indirectly have important functions in stimulating or inhibiting growth. This complex process is also influenced by genetics and a variety of environmental factors, including nutrition, and provides an illustration of the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition. The growth process involves cell division and net protein synthesis throughout the body, but a person's height is determined specifically by bone growth, particularly of the vertebral column and legs. We first provide an overview of bone and the growth process before describing the roles of hormones in determining growth rates.

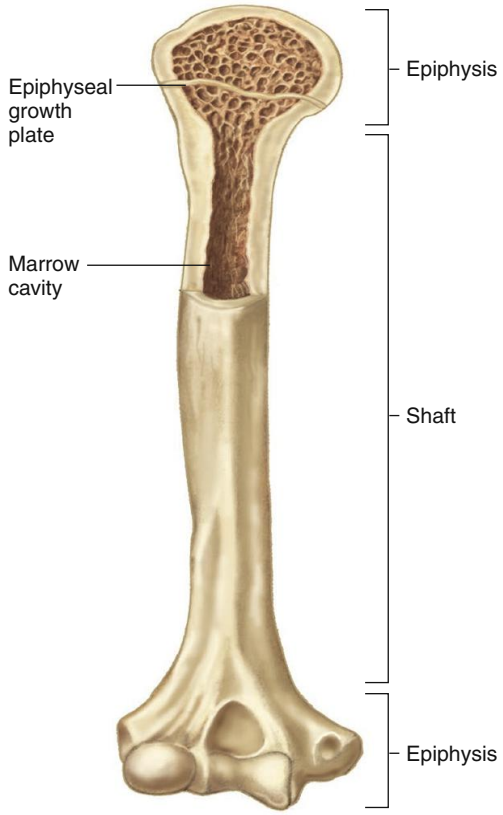
11.17 Bone Growth

Bone is a living, metabolically active tissue consisting of a protein (collagen) matrix upon which calcium salts, particularly calcium phosphates, are deposited. A growing long bone is divided, for descriptive purposes, into the ends, or **epiphyses,** and the remainder, the **shaft.** The portion of each epiphysis in contact with the shaft is a plate of actively proliferating cartilage (connective tissue composed of collagen and other fibrous proteins) called the **epiphyseal growth plate** (Figure 11.26). **Osteoblasts,** the bone-forming cells at the shaft edge of the epiphyseal growth plate, convert the cartilaginous tissue at this edge to bone, while cells called **chondrocytes** simultaneously lay down new cartilage in the interior of the plate. In this manner, the epiphyseal growth plate widens and is gradually pushed away from the center of the bony shaft as the shaft lengthens.

Linear growth of the shaft can continue as long as the epiphyseal growth plates exist but ceases when the growth plates themselves are converted to bone as a result of other hormonal influences toward the end of puberty. This is known as **epiphyseal closure** and occurs at different times in different bones. Thus, a person's **bone age** can be determined by taking an x-ray of bones and determining which ones have undergone epiphyseal closure.

As shown in Figure 11.27, children manifest two periods of rapid increase in height, the first during the first 2 years of life and the second during puberty. Note that increase in height is not necessarily correlated with the rates of growth of specific organs.

The pubertal growth spurt lasts several years in both sexes, but growth during this period is greater in boys. In addition, boys grow more before puberty because they begin puberty approximately 2 years later than girls. These factors account for the differences in average height between men and women.



AP|R **Figure 11.26** Anatomy of a long bone during growth.

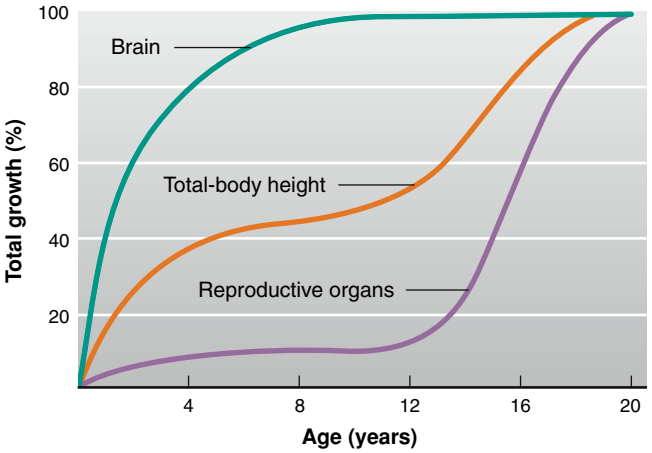


Figure 11.27 Relative growth in brain, total-body height (a measure of long-bone and vertebral growth), and reproductive organs. Note that brain growth is nearly complete by age 5, whereas maximal height (maximal bone lengthening) and reproductive-organ size are not reached until the late teens.

11.18 Environmental Factors Influencing Growth

Adequate nutrition and good health are the primary environmental factors influencing growth. Lack of sufficient amounts of protein, fatty acids, vitamins, or minerals interferes with growth.

The growth-inhibiting effects of malnutrition can be seen at any time of development but are most profound when they occur early in life. For this reason, maternal malnutrition may cause growth retardation in the fetus. Because low birth weight is strongly associated with increased infant mortality and adult disease, prenatal malnutrition causes increased numbers of prenatal and early postnatal deaths. Moreover, irreversible stunting of brain development may be caused by prenatal malnutrition. During infancy and childhood, too, malnutrition can interfere with both intellectual development and total-body growth.

Following a temporary period of stunted growth due to malnutrition or illness, and given proper nutrition and recovery from illness, a child can manifest a remarkable growth spurt called **catch-up growth** that brings the child to within the range of normal heights expected for his or her age. The mechanisms that account for this accelerated growth are unknown, but recent evidence suggests that it may be related to the rate of stem cell differentiation within the growth plates.

11.19 Hormonal Influences on Growth

The hormones most important to human growth are growth hormone, insulin-like growth factors 1 and 2, T_3, insulin, testosterone, and estradiol, all of which exert widespread effects. In addition to all these hormones, a large group of peptide growth factors exert effects, most of them acting in a paracrine or autocrine manner to stimulate differentiation and/or cell division of certain cell types. Molecules that stimulate cell division are called mitogens.

The various hormones and growth factors do not all stimulate growth at the same periods of life. For example, fetal growth is less dependent on fetal growth hormone, the thyroid hormones, and the sex steroids than are the growth periods that occur during childhood and adolescence.

Growth Hormone and Insulin-Like Growth Factors

Growth hormone, secreted by the anterior pituitary gland, has little effect on fetal growth but is the most important hormone for growth after the age of 1–2 years. Its major growth-promoting effect is stimulation of cell division in its many target tissues. Thus, growth hormone promotes bone lengthening by stimulating maturation and cell division of the chondrocytes in the epiphyseal plates, thereby continuously widening the plates and providing more cartilaginous material for bone formation.

Importantly, growth hormone exerts most of its mitogenic effect not *directly* on cells but *indirectly* through the mediation of the mitogenic hormone IGF-1, whose synthesis and release by the liver are induced by growth hormone. Despite some structural similarities to insulin (from which its name is derived), this messenger has its own unique effects distinct from those of insulin. Under the influence of growth hormone, IGF-1 is secreted by the liver, enters the blood, and functions as a hormone. In addition, growth hormone stimulates many other types of cells, including bone, to secrete IGF-1, where it functions as an autocrine or paracrine substance.

Current concepts of how growth hormone and IGF-1 interact on the epiphyseal plates of bone are as follows. (1) Growth hormone stimulates the chondrocyte precursor cells (prechondrocytes) and/or young differentiating chondrocytes in the epiphyseal plates to differentiate into chondrocytes. (2) During this differentiation, the cells begin both to secrete IGF-1 and to become responsive to IGF-1. (3) The IGF-1 then acts as an autocrine or paracrine substance (probably along with blood-borne IGF-1) to stimulate the differentiating chondrocytes to undergo cell division.

The importance of IGF-1 in mediating the major growth-promoting effect of growth hormone is illustrated by the fact that ***short stature*** can be caused not only by decreased growth hormone secretion but also by decreased production of IGF-1 or failure of the tissues to respond to IGF-1. For example, one rare form of short stature (called ***growth hormone–insensitivity syndrome***) is due to a genetic mutation that causes a change in the growth hormone receptor such that it fails to respond to growth hormone (an example of hyporesponsiveness). The result is failure to produce IGF-1 in response to growth hormone, and a consequent decreased growth rate in a child.

The secretion and activity of IGF-1 can be influenced by the nutritional status of the individual and by many hormones other than growth hormone. For example, malnutrition during childhood can inhibit the production of IGF-1 even if plasma growth hormone concentration is increased.

In addition to its specific growth-promoting effect on cell division via IGF-1, growth hormone directly stimulates protein synthesis in various tissues and organs, particularly muscle. It does this by increasing amino acid uptake and both the synthesis and activity of ribosomes. All of these events are essential for protein synthesis. This anabolic effect on protein metabolism facilitates the ability of tissues and organs to enlarge. Growth hormone also contributes to the control of energy homeostasis. It does this in part by facilitating the breakdown of triglycerides that are stored in adipose cells, which then release fatty acids into the blood. It also

TABLE 11.5 Major Effects of Growth Hormone

I. Promotes growth: Induces precursor cells in bone and other tissues to differentiate and secrete insulin-like growth factor 1 (IGF-1), which stimulates cell division. Also stimulates liver to secrete IGF-1.

II. Stimulates protein synthesis, predominantly in muscle.

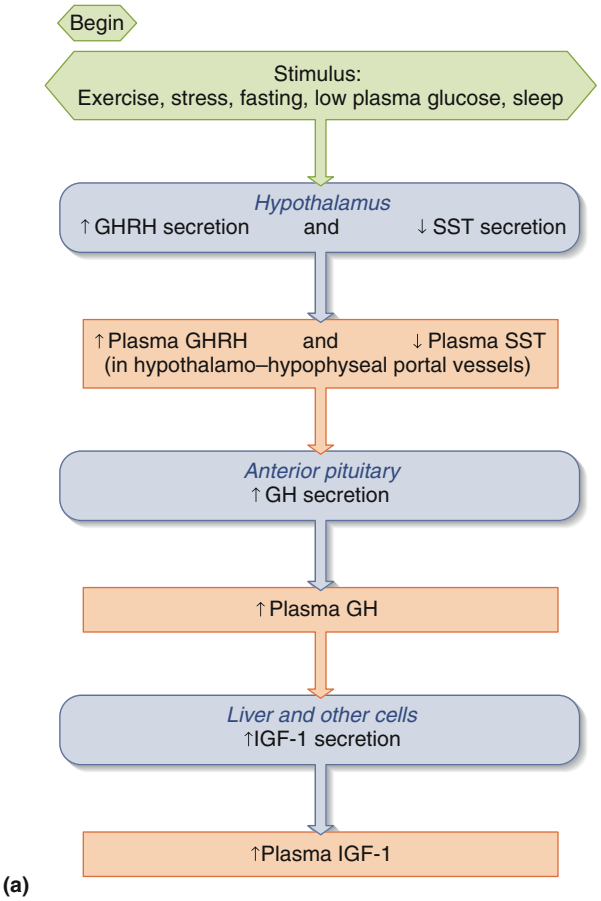
III. Anti-insulin effects (particularly at high concentrations):
   A. Renders adipocytes more responsive to stimuli that induce breakdown of triglycerides, releasing fatty acids into the blood.
   B. Stimulates gluconeogenesis.
   C. Reduces the ability of insulin to stimulate glucose uptake by adipose and muscle cells, resulting in higher blood glucose concentrations.

stimulates gluconeogenesis in the liver and inhibits the ability of insulin to promote glucose transport into cells. Growth hormone, therefore, tends to increase circulating energy sources. Not surprisingly, therefore, situations such as exercise, stress, or fasting, for which increased energy availability is beneficial, result in stimulation of growth hormone secretion into the blood. The metabolic effects of growth hormone are important throughout life and continue in adulthood long after bone growth has ceased. **Table 11.5** summarizes some of the major effects of growth hormone.

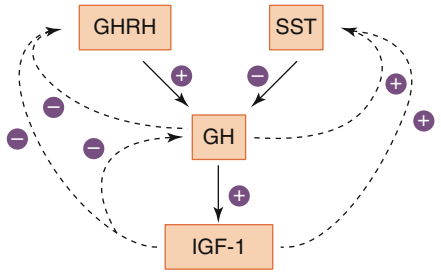
Figure 11.28 shows the control of growth hormone secretion. Briefly, the control system begins with two of the hormones secreted by the hypothalamus. Growth hormone secretion is stimulated by growth hormone–releasing hormone (GHRH) and inhibited by somatostatin (SST). As a result of changes in these two signals, which are usually out of phase with each other (i.e., one is high when the other is low), growth hormone secretion occurs in episodic bursts and manifests a striking daily rhythm. During most of the day, little or no growth hormone is secreted, although bursts may be elicited by certain stimuli, such as exercise. In contrast, 1 to 2 hours after a person falls asleep, one or more larger, prolonged bursts of secretion may occur. The negative feedback controls that growth hormone and IGF-1 exert on the hypothalamus and anterior pituitary gland are summarized in Figure 11.28.

In addition to the hypothalamic controls, a variety of hormones—notably, the sex steroids, insulin, and thyroid hormones—influence the secretion of growth hormone. The net result of all these inputs is that the secretion rate of growth hormone is highest during adolescence (the period of most rapid growth), next highest in children, and lowest in adults. The decreased growth hormone secretion associated with aging is responsible, in part, for the decrease in lean-body and bone mass, the expansion of adipose tissue, and the thinning of the skin that occur as people age.

The availability of human growth hormone produced by recombinant DNA technology has greatly facilitated the treatment of children with short stature due to growth hormone deficiency. Controversial at present is the administration of growth hormone to short children who do not have growth hormone deficiency, to athletes in an attempt to increase muscle mass, and to elderly persons to reverse growth hormone–related aging changes. It should be clear from Table 11.5 that administration of GH to an otherwise healthy individual (such as an athlete) can lead to serious side effects. Abuse of GH in such situations can lead to symptoms similar to those of diabetes mellitus, as well as numerous other



(a)



(b)

Figure 11.28 Hormonal pathways controlling the secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1).
(a) Various stimuli can increase GH and IGF-1 concentrations by increasing GHRH secretion and decreasing SST secretion.
(b) Feedback control of GH and IGF-1 secretion is accomplished by inhibition (⊖ symbol) of GHRH and GH, and stimulation (⊕ symbol) of SST. The existence of GH short-loop inhibition of GHRH is not fully established in humans. Not shown in the figure is that several hormones not in the sequence (e.g., thyroid hormone and cortisol) influence growth hormone secretion via effects on the hypothalamus and/or anterior pituitary gland.

PHYSIOLOGICAL INQUIRY

- What might happen to plasma concentrations of GH in a person who was intravenously infused with a solution containing a high concentration of glucose, such that his plasma glucose concentrations were significantly increased?

Answer can be found at end of chapter.

problems. The consequences of chronically increased growth hormone concentrations are dramatically illustrated in the disease called acromegaly (described later in this chapter).

As noted earlier, the role of GH in fetal growth, while still under investigation, appears not to be nearly as significant as at later stages of postnatal life. IGF-1, however, is required for normal fetal total-body growth and, specifically, for normal maturation of the fetal nervous system. The chief stimulus for IGF-1 secretion during prenatal life appears to be placental lactogen, a hormone released by cells of the placenta, which shares sequence similarity with growth hormone.

Finally, it should be noted that there is another messenger—**insulin-like growth factor 2** (**IGF-2**), which is closely related to IGF-1. IGF-2, the secretion of which is *independent* of growth hormone, is also a crucial mitogen during the prenatal period. It continues to be secreted throughout life, but its postnatal function is not definitively known. Recent evidence suggests a link between IGF-2 concentrations and the maintenance of skeletal muscle mass and strength in elderly persons.

Thyroid Hormone

Thyroid hormone is essential for normal growth because it facilitates the synthesis of growth hormone. T_3 also has direct actions on bone, where it stimulates chondrocyte differentiation, growth of new blood vessels in developing bone, and responsiveness of bone cells to other growth factors such as fibroblast growth factor. Consequently, infants and children with hypothyroidism have slower growth rates than would be predicted.

Insulin

The major actions of insulin are described in Chapter 16. Insulin is an anabolic hormone that promotes the transport of glucose and amino acids from the extracellular fluid into adipose tissue and skeletal and cardiac muscle cells. Insulin stimulates storage of fat and inhibits protein degradation. Thus, it is not surprising that adequate amounts of insulin are necessary for normal growth. Its inhibitory effect on protein degradation is particularly important with regard to growth. In addition to this general anabolic effect, however, insulin exerts direct growth-promoting effects on cell differentiation and cell division during fetal life and, possibly, during childhood.

Sex Steroids

As Chapter 17 will explain, sex steroid secretion (testosterone in the male and estrogens in the female) begins to increase between the ages of 8 and 10 and reaches a plateau over the next 5 to 10 years. A normal pubertal growth spurt, which reflects growth of the long bones and vertebrae, requires this increased production of the sex steroids. The major growth-promoting effect of the sex steroids is to stimulate the secretion of growth hormone and IGF-1.

Unlike growth hormone, however, the sex steroids not only *stimulate* bone growth but ultimately *stop* it by inducing epiphyseal closure. The dual effects of the sex steroids explain the pattern seen in adolescence—rapid lengthening of the bones culminating in complete cessation of growth for life.

In addition to these dual effects on bone, testosterone exerts a direct anabolic effect on protein synthesis in many nonreproductive organs and tissues of the body. This accounts, at least in part, for the increased muscle mass of men in comparison to women. This effect of testosterone is also why athletes sometimes use androgens called ***anabolic steroids*** in an attempt to increase muscle mass and strength. These steroids include testosterone, synthetic androgens, and the hormones dehydroepiandrosterone (DHEA) and androstenedione. However, these steroids have multiple potential toxic side effects, such as liver damage, increased risk of prostate cancer, infertility, and changes in behavior and emotions. Moreover, in females, they can produce virilization.

Cortisol

Cortisol, the major hormone the adrenal cortex secretes in response to stress, can have potent *antigrowth* effects under certain conditions. When present in high concentrations, it inhibits DNA synthesis and stimulates protein catabolism in many organs, and it inhibits bone growth. Moreover, it breaks down bone and inhibits the secretion of growth hormone and IGF-1. For all these reasons, in children, the increase in plasma cortisol that accompanies infections and other stressors is, at least in part, responsible for the decreased growth that occurs with chronic illness. One of the hallmarks of Cushing's syndrome in children is a dramatic decrease in the rate of linear growth. Furthermore, the administration of pharmacological glucocorticoid therapy for asthma or other disorders may decrease linear growth in children in a dose-related way.

This completes our survey of the major hormones that affect growth. **Table 11.6** summarizes their actions.

TABLE 11.6 Major Hormones Influencing Growth

Hormone	Principal Actions
Growth hormone	Major stimulus of postnatal growth: induces precursor cells to differentiate and secrete insulin-like growth factor 1 (IGF-1), which stimulates cell division Stimulates liver to secrete IGF-1 Stimulates protein synthesis
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-1 Stimulates protein synthesis
Thyroid hormone	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone Causes eventual epiphyseal closure Stimulates protein synthesis in male
Estrogen	Stimulates the secretion of growth hormone at puberty Causes eventual epiphyseal closure
Cortisol	Inhibits growth Stimulates protein catabolism

SECTION E SUMMARY

Bone Growth

I. A bone lengthens as osteoblasts at the shaft edge of the epiphyseal growth plates convert cartilage to bone while new cartilage is simultaneously being laid down in the plates.
II. Growth ceases when the plates are completely converted to bone.

Environmental Factors Influencing Growth

I. The major environmental factors influencing growth are nutrition and disease.
II. Maternal malnutrition during pregnancy may produce irreversible growth stunting and mental deficiency in offspring.

Hormonal Influences on Growth

I. Growth hormone is the major stimulus of postnatal growth.
   a. It stimulates the release of IGF-1 from the liver and many other cells, and IGF-1 then acts locally (and also as a circulating hormone) to stimulate cell division.
   b. Growth hormone also acts directly on cells to stimulate protein synthesis.
   c. Growth hormone secretion is highest during adolescence.
II. Because thyroid hormone is required for growth hormone synthesis and the growth-promoting effects of this hormone, it is essential for normal growth during childhood and adolescence. It is also permissive for brain development during infancy.
III. Insulin stimulates growth mainly during fetal life.
IV. Mainly by stimulating growth hormone secretion, testosterone and estrogen promote bone growth during adolescence, but these hormones also cause epiphyseal closure. Testosterone also stimulates protein synthesis.
V. High concentrations of cortisol inhibit growth and stimulate protein catabolism.

SECTION E REVIEW QUESTIONS

1. Describe the process by which bone lengthens.
2. What are the effects of malnutrition on growth?
3. List the major hormones that control growth.
4. Describe the relationship between growth hormone and IGF-1 and the roles of each in growth.
5. What are the effects of growth hormone on protein synthesis?
6. What is the status of growth hormone secretion at different stages of life?
7. State the effects of the thyroid hormones on growth.
8. Describe the effects of testosterone on growth, cessation of growth, and protein synthesis. Which of these effects does estrogen also exert?
9. What is the effect of cortisol on growth?
10. Give two ways in which short stature can occur.

SECTION E KEY TERMS

11.17 Bone Growth

bone age
chondrocytes
epiphyseal closure
epiphyseal growth plate
epiphyses
osteoblasts
shaft

11.18 Environmental Factors Influencing Growth

catch-up growth

11.19 Hormonal Influences on Growth

insulin-like growth factor 2 (IGF-2)

SECTION E CLINICAL TERMS

11.19 Hormonal Influences on Growth

anabolic steroids
growth hormone–insensitivity syndrome
short stature

SECTION F

Endocrine Control of Ca^{2+} Homeostasis

Many of the hormones of the body control functions that, though important, are not necessarily vital for survival, such as growth. By contrast, some hormones control functions so vital that the absence of the hormone would be catastrophic, even life threatening. One such function is calcium homeostasis. Calcium exists in the body fluids in its soluble, ionized form (Ca^{2+}) and bound to proteins. For simplicity in this chapter, we will refer hereafter to the physiologically active, ionic form of Ca^{2+}.

Extracellular Ca^{2+} concentration normally remains within a narrow homeostatic range. Large deviations in either direction can disrupt neurological and muscular activity, among others. For example, a low plasma Ca^{2+} concentration increases the excitability of neuronal and muscle plasma membranes. A high plasma Ca^{2+} concentration causes cardiac arrhythmias and depresses neuromuscular excitability via effects on membrane potential. In this section, we discuss the mechanisms by which Ca^{2+} homeostasis is achieved and maintained by actions of hormones.

11.20 Effector Sites for Ca^{2+} Homeostasis

Ca^{2+} homeostasis depends on the interplay among bone, the kidneys, and the gastrointestinal tract. The activities of the gastrointestinal tract and kidneys determine the net intake and output of Ca^{2+} for the entire body and, thereby, the overall Ca^{2+} balance. In contrast, interchanges of Ca^{2+} between extracellular fluid and bone do not alter total-body balance but instead change the *distribution* of Ca^{2+} within the body. We begin, therefore, with a discussion of the cellular and mineral composition of bone.

Bone

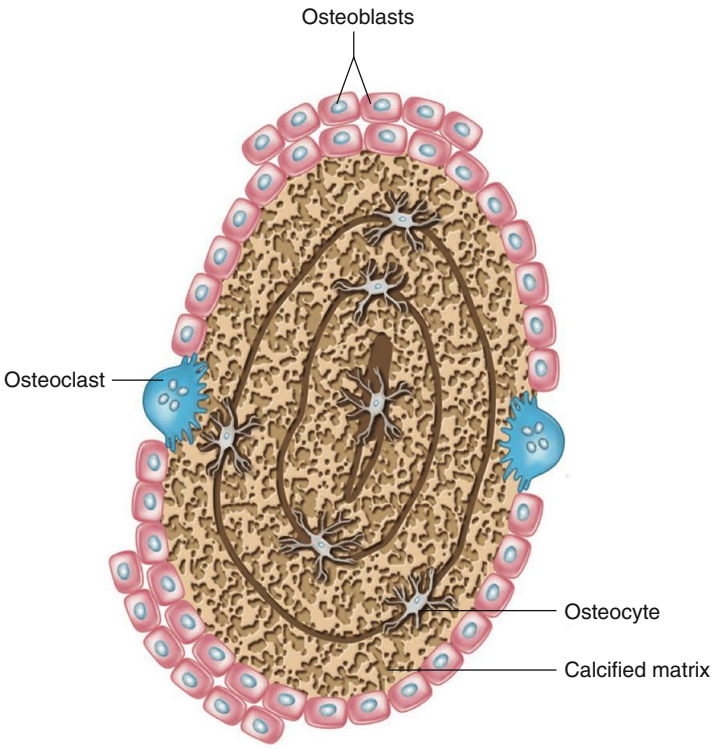
Approximately 99% of total-body calcium is contained in bone. Therefore, the movement of Ca^{2+} into and out of bone is critical in controlling the plasma Ca^{2+} concentration.

Bone is a connective tissue made up of several cell types surrounded by a collagen matrix called **osteoid,** upon which are

deposited minerals, particularly the crystals of calcium, phosphate, and hydroxyl ions known as **hydroxyapatite.** In some instances, bones have central marrow cavities where blood cells form. Approximately one-third of a bone, by weight, is osteoid, and two-thirds is mineral (the bone cells contribute negligible weight).

The three types of bone cells involved in bone formation and breakdown are osteoblasts, osteocytes, and osteoclasts (**Figure 11.29**). As described in Section E, osteoblasts are the bone-forming cells. They secrete collagen to form a surrounding matrix, which then becomes calcified, a process called **mineralization.** Once surrounded by calcified matrix, the osteoblasts are called **osteocytes.** The osteocytes have long cytoplasmic processes that extend throughout the bone and form tight junctions with other osteocytes. **Osteoclasts** are large, multinucleated cells that break down (resorb) previously formed bone by secreting hydrogen ions, which dissolve the crystals, and hydrolytic enzymes, which digest the osteoid.

Throughout life, bone is constantly remodeled by the osteoblasts (and osteocytes) and osteoclasts working together. Osteoclasts resorb old bone, and then osteoblasts move into the area and lay down new matrix, which becomes mineralized. This process depends in part on the stresses that gravity and muscle tension impose on the bones, stimulating osteoblastic activity. Many hormones, as summarized in **Table 11.7**, and a variety of autocrine or paracrine growth factors produced locally in the bone also have functions. Of the hormones listed, only parathyroid hormone (described later) is controlled primarily by the plasma Ca^{2+} concentration. Nonetheless, changes in the other listed hormones have important influences on bone mass and plasma Ca^{2+} concentration.



AP|R **Figure 11.29** Cross section through a small portion of bone. The brown area is mineralized osteoid. The osteocytes have long processes that extend through small canals and connect with each other and to osteoblasts via tight junctions (not shown).

TABLE 11.7 Summary of Major Hormonal Influences on Bone Mass

Hormones That Favor Bone Formation and Increased Bone Mass
Insulin
Growth hormone
Insulin-like growth factor 1 (IGF-1)
Estrogen
Testosterone
Calcitonin
Hormones That Favor Increased Bone Resorption and Decreased Bone Mass
Parathyroid hormone (chronic increases)
Cortisol
Thyroid hormone T_3

Kidneys

As you will learn in Chapter 14, the kidneys filter the blood and eliminate soluble wastes. In the process, cells in the tubules that make up the functional units of the kidneys recapture (reabsorb) most of the necessary solutes that were filtered, which minimizes their loss in the urine. Therefore, the urinary excretion of Ca^{2+} is the difference between the amount filtered into the tubules and the amount reabsorbed and returned to the blood. The control of Ca^{2+} excretion is exerted mainly on reabsorption. Reabsorption decreases when plasma Ca^{2+} concentration increases, and it increases when plasma Ca^{2+} decreases.

The hormonal controllers of Ca^{2+} also regulate phosphate ion balance. Phosphate ions, too, are subject to a combination of filtration and reabsorption, with the latter hormonally controlled.

Gastrointestinal Tract

The absorption of solutes such as Na^+ and K^+ from the gastrointestinal tract into the blood is normally about 100%. In contrast, a considerable amount of ingested Ca^{2+} is not absorbed from the small intestine and leaves the body along with the feces. Moreover, the active transport system that achieves Ca^{2+} absorption from the small intestine is under hormonal control. Therefore, large regulated increases or decreases can occur in the amount of Ca^{2+} absorbed from the diet. Hormonal control of this absorptive process is the major means for regulating total-body-calcium balance, as we see next.

11.21 Hormonal Controls

The two major hormones that regulate plasma Ca^{2+} concentration are parathyroid hormone and 1,25-dihydroxyvitamin D. A third hormone, calcitonin, has a very limited function in humans, if any.

Parathyroid Hormone

Bone, kidneys, and the gastrointestinal tract are subject, directly or indirectly, to control by a protein hormone called **parathyroid hormone (PTH),** which is produced by the **parathyroid glands.**

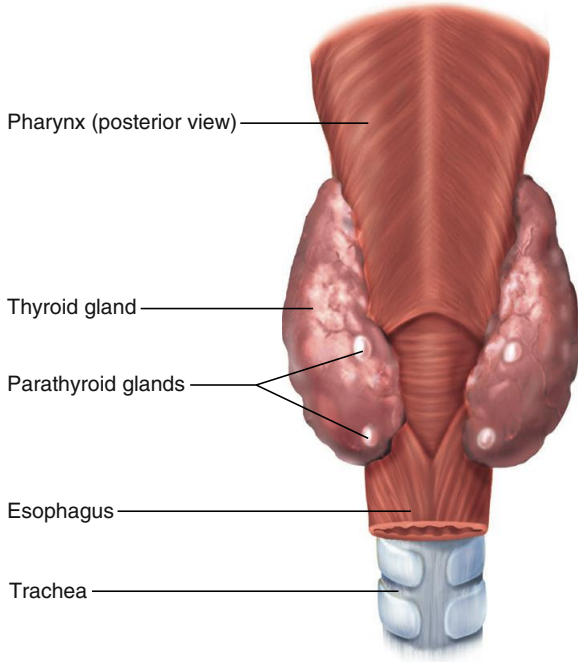
These endocrine glands are in the neck, embedded in the posterior surface of the thyroid gland, but are distinct from it (**Figure 11.30**). PTH production is controlled by the extracellular Ca^{2+} concentration acting directly on the secretory cells via a plasma membrane Ca^{2+} receptor. *Decreased* plasma Ca^{2+} concentration *stimulates* PTH secretion, and an *increased* plasma Ca^{2+} concentration does just the opposite.

PTH exerts multiple actions that increase extracellular Ca^{2+} concentration, thereby compensating for the decreased concentration that originally stimulated secretion of this hormone (**Figure 11.31**):

1. It directly increases the resorption of bone by osteoclasts, which causes calcium (and phosphate) ions to move from bone into extracellular fluid.
2. It directly stimulates the formation of 1,25-dihydroxyvitamin D, which then increases intestinal absorption of calcium (and phosphate) ions. Thus, the effect of PTH on the intestines is indirect.
3. It directly increases Ca^{2+} reabsorption in the kidneys, thereby decreasing urinary Ca^{2+} excretion.
4. It directly *decreases* the reabsorption of phosphate ions in the kidneys, thereby increasing its excretion in the urine. This keeps plasma phosphate ions from increasing when PTH causes an increased resorption of both calcium and phosphate ions from bone, and an increased production of 1,25-dihydroxyvitamin D leading to increased calcium and phosphate ion absorption in the intestine.

1,25-Dihydroxyvitamin D

The term **vitamin D** denotes a group of closely related compounds. **Vitamin D_3** (**cholecalciferol**) is formed by the action of ultraviolet radiation from sunlight on a cholesterol derivative (7-dehydrocholesterol) in skin. **Vitamin D_2** (**ergocalciferol**) is derived from plants. Both can be found in vitamin pills and enriched foods and are collectively called vitamin D.



AP|R **Figure 11.30** The parathyroid glands. There are usually four parathyroid glands embedded in the posterior surface of the thyroid gland.

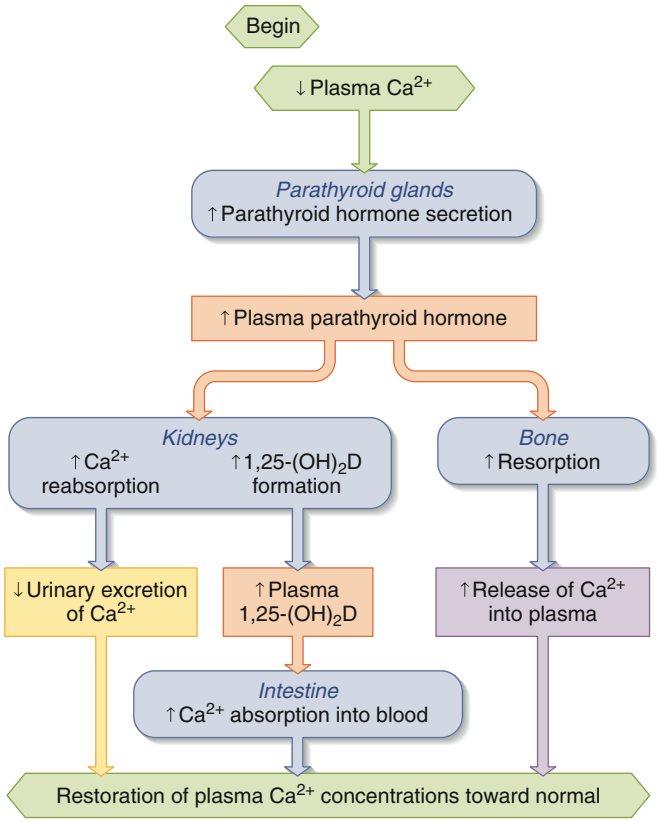


Figure 11.31 Mechanisms that allow parathyroid hormone to reverse a reduction in plasma Ca^{2+} concentration. See Figure 11.32 for a more complete description of 1,25-$(OH)_2$D (1,25-dihydroxyvitamin D). Parathyroid hormone and 1,25-$(OH)_2$D are also involved in the control of phosphate ion concentrations.

PHYSIOLOGICAL INQUIRY

- Explain how this figure illustrates the general principle of physiology outlined in Chapter 1 that the functions of organ systems are coordinated with each other.

Answer can be found at end of chapter.

Because of clothing, climate, and other factors, people are often dependent upon dietary vitamin D. For this reason, it was originally classified as a vitamin. Regardless of source, vitamin D is metabolized by the addition of hydroxyl groups, first in the liver by the enzyme 25-hydroxylase and then in certain kidney cells by 1-hydroxylase (**Figure 11.32**). The end result of these changes is 1,25-dihydroxyvitamin D [abbreviated 1,25-$(OH)_2$D], the active hormonal form of vitamin D.

The major action of 1,25-$(OH)_2$D is to stimulate the intestinal absorption of Ca^{2+}. Thus, the major consequence of vitamin D deficiency is decreased intestinal Ca^{2+} absorption, resulting in decreased plasma Ca^{2+}.

The blood concentration of 1,25-$(OH)_2$D is subject to physiological control. The major control point is the second hydroxylation step that occurs primarily in the kidneys by the action of 1-hydroxylase, and which is stimulated by PTH.

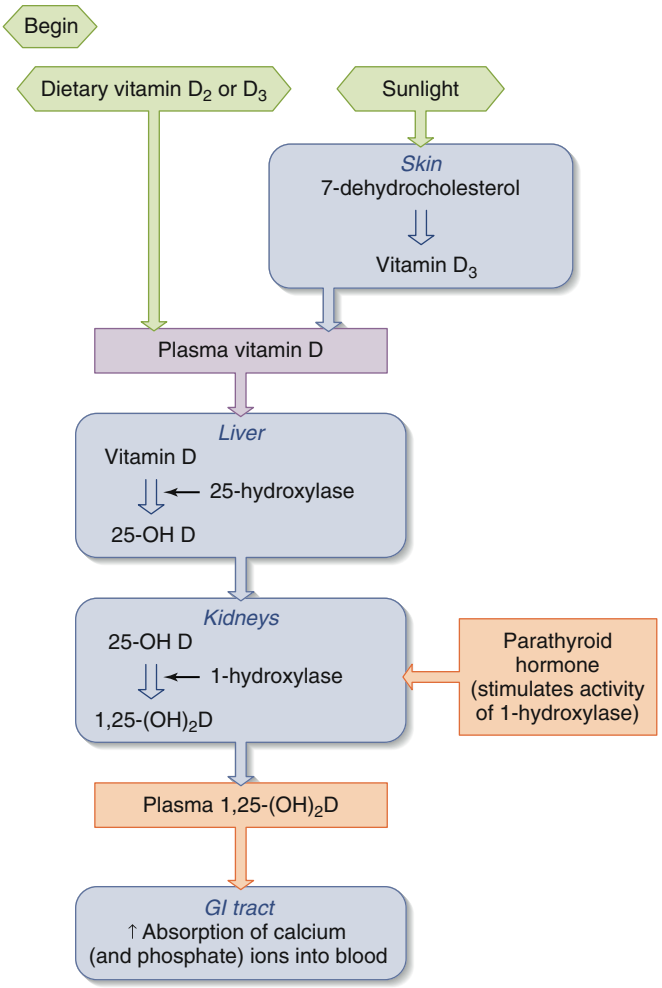


Figure 11.32 Metabolism of vitamin D to the active form, $1,25\text{-}(OH)_2D$.

PHYSIOLOGICAL INQUIRY

- Sarcoidosis is a disease that affects a variety of organs (usually the lungs). It is characterized by the development of nodules of inflamed tissue known as granulomas. These granulomas can express significant 1-hydroxylase activity that is not controlled by parathyroid hormone. What will happen to plasma Ca^{2+} and parathyroid hormone concentrations under these circumstances?

Answer can be found at end of chapter.

Because a low plasma Ca^{2+} concentration stimulates the secretion of PTH, the production of $1,25\text{-}(OH)_2D$ is increased as well under such conditions. Both hormones work together to restore plasma Ca^{2+} to normal.

Calcitonin

Calcitonin is a peptide hormone secreted by cells called parafollicular cells that are within the thyroid gland but are distinct from the thyroid follicles. Calcitonin decreases plasma Ca^{2+} concentration, mainly by inhibiting osteoclasts, thereby reducing bone resorption. Its secretion is stimulated by an increased plasma Ca^{2+} concentration, just the opposite of the stimulus for PTH. Unlike PTH and $1,25\text{-}(OH)_2D$, however, calcitonin has no function in the normal day-to-day regulation of plasma Ca^{2+} in humans. It may be a factor in decreasing bone resorption when the plasma Ca^{2+} concentration is very high.

11.22 Metabolic Bone Diseases

Various diseases reflect abnormalities in the metabolism of bone. ***Rickets*** (in children) and ***osteomalacia*** (in adults) are conditions in which mineralization of bone matrix is deficient, causing the bones to be soft and easily fractured. In addition, a child suffering from rickets is typically severely bowlegged due to weight bearing on the weakened developing leg bones. A major cause of rickets and osteomalacia is deficiency of vitamin D.

In contrast to these diseases, in ***osteoporosis,*** both matrix and minerals are lost as a result of an imbalance between bone resorption and bone formation. The resulting decrease in bone mass and strength leads to an increased fragility of bone and the incidence of fractures. Osteoporosis can occur in people who are immobilized ("disuse osteoporosis"), in people who have an *excessive* plasma concentration of a hormone that favors bone resorption, and in people who have a *deficient* plasma concentration of a hormone that favors bone formation (see Table 11.7). It is most commonly seen, however, with aging. Everyone loses bone as he or she ages, but osteoporosis is more common in elderly women than men. The major reason for this is that menopause removes the antiresorptive effect of estrogen.

Prevention is the focus of attention for osteoporosis. Treatment of postmenopausal women with estrogen or its synthetic analogs is effective in reducing the rate of bone loss, but long-term estrogen replacement can have serious consequences in some women (e.g., increasing the likelihood of breast cancer). A regular weight-bearing exercise program, such as brisk walking and stair climbing, is also helpful. Adequate dietary Ca^{2+} intake and vitamin D intake throughout life are important to build up and maintain bone mass. Several substances also provide effective therapy once osteoporosis is established. Most prominent is a group of drugs called ***bisphosphonates*** that interfere with the resorption of bone by osteoclasts. Other antiresorptive substances include calcitonin and ***selective estrogen receptor modulators*** (***SERMs***), which, as their name implies, act by interacting with (and activating) estrogen receptors, thereby compensating for the low estrogen after menopause.

A variety of pathophysiological disorders lead to abnormally high or low plasma Ca^{2+} concentrations—*hypercalcemia* or *hypocalcemia,* respectively—as described next.

Hypercalcemia

A relatively common cause of **hypercalcemia** is ***primary hyperparathyroidism.*** This is usually caused by a benign tumor (known as an adenoma) of one of the four parathyroid glands. These tumors are composed of abnormal cells that are not adequately suppressed by extracellular Ca^{2+}. As a result, the adenoma secretes PTH in excess, leading to an increase in Ca^{2+} resorption from bone, increased kidney reabsorption of Ca^{2+}, and the increased production of $1,25\text{-}(OH)_2D$ from the kidney. The increased $1,25\text{-}(OH)_2D$ results in an increase in Ca^{2+} absorption from the small intestine. Primary hyperparathyroidism is most effectively treated by surgical removal of the parathyroid tumor.

Certain types of cancer can lead to ***humoral hypercalcemia of malignancy.*** The cause of the hypercalcemia is often the release of a molecule that is structurally similar to PTH, called ***PTH-related peptide*** (***PTHrp***), that has effects similar to those of PTH. This peptide is produced by certain types of cancerous cells (e.g., some breast-cancer cells). However, authentic PTH release from the normal parathyroid glands is decreased due to the suppression of parathyroid gland function by the hypercalcemia caused by PTHrp released from the cancer cells. The most effective treatment of humoral hypercalcemia of malignancy is to treat the cancer that is releasing PTHrp. In addition, drugs such as bisphosphonates that decrease bone resorption can also provide effective treatment.

Finally, excessive ingestion of vitamin D can lead to hypercalcemia, as may happen in some individuals who consume vitamin D supplements far in excess of what is required.

Regardless of the cause, hypercalcemia causes significant symptoms primarily from its effects on excitable tissues. Among these symptoms are tiredness and lethargy with muscle weakness, as well as nausea and vomiting (due to effects on the GI tract).

Hypocalcemia

Hypocalcemia can result from a loss of parathyroid gland function (***primary hypoparathyroidism***). One cause of this is the removal of parathyroid glands, which may occur (though rarely) when a person with thyroid disease has his or her thyroid gland surgically removed. Because the concentration of PTH is low, 1,25-$(OH)_2$D production from the kidney is also decreased. Decreases in both hormones lead to decreases in bone resorption, kidney Ca^{2+} reabsorption, and intestinal Ca^{2+} absorption.

Resistance to the effects of PTH in target tissue (hyporesponsiveness) can also lead to the symptoms of hypoparathyroidism, even though in such cases PTH concentrations in the blood tend to be elevated. This condition is called ***pseudohypoparathyroidism*** (see Chapter 5 Clinical Case Study).

Another interesting hypocalcemic state is ***secondary hyperparathyroidism.*** Failure to absorb vitamin D from the intestines, or decreased kidney 1,25-$(OH)_2$D production, which can occur in kidney disease, can lead to secondary hyperparathyroidism. The decreased plasma Ca^{2+} that results from decreased intestinal absorption of Ca^{2+} results in stimulation of the parathyroid glands. Although the increased concentration of PTH does act to restore plasma Ca^{2+} toward normal, it does so at the expense of significant loss of Ca^{2+} from bone and the acceleration of metabolic bone disease.

The symptoms of hypocalcemia are also due to its effects on excitable tissue. It increases the excitability of nerves and muscles, which can lead to CNS effects (seizures), muscle spasms (***hypocalcemic tetany***), and neuronal excitability. Long-term treatment of hypoparathyroidism involves giving calcium salts and 1,25-$(OH)_2$D or vitamin D. ■

SECTION F SUMMARY

Effector Sites for Ca^{2+} Homeostasis

I. The effector sites for the regulation of plasma Ca^{2+} concentration are bone, the gastrointestinal tract, and the kidneys.
II. Approximately 99% of total-body Ca^{2+} is contained in bone as minerals on a collagen matrix. Bone is constantly remodeled as a result of the interaction of osteoblasts and osteoclasts, a process that determines bone mass and provides a means for altering plasma Ca^{2+} concentration.
III. Ca^{2+} is actively absorbed by the gastrointestinal tract, and this process is under hormonal control.
IV. The amount of Ca^{2+} excreted in the urine is the difference between the amount filtered and the amount reabsorbed, the latter process being under hormonal control.

Hormonal Controls

I. Parathyroid hormone (PTH) increases plasma Ca^{2+} concentration by influencing all of the effector sites.
   a. It stimulates kidney reabsorption of Ca^{2+}, bone resorption with release of Ca^{2+} into the blood, and formation of the hormone 1,25-dihydroxyvitamin D, which stimulates Ca^{2+} absorption by the intestine.
   b. It also inhibits the reabsorption of phosphate ions in the kidneys, leading to increased excretion of phosphate ions in the urine.
II. Vitamin D is formed in the skin or ingested and then undergoes hydroxylations in the liver and kidneys. The kidneys express the enzyme that catalyzes the production of the active form, 1,25-dihydroxyvitamin D. This process is greatly stimulated by PTH.

Metabolic Bone Diseases

I. Osteomalacia (adults) and rickets (children) are diseases in which the mineralization of bone is deficient—usually due to inadequate vitamin D intake, absorption, or activation.
II. Osteoporosis is a loss of bone density (loss of matrix and minerals).
   a. Bone resorption exceeds formation.
   b. It is most common in postmenopausal (estrogen-deficient) women.
   c. It can be prevented by exercise, adequate Ca^{2+} and vitamin D intake, and medications (such as bisphosphonates).
III. Hypercalcemia (chronically elevated plasma Ca^{2+} concentrations) can occur from several causes.
   a. Primary hyperparathyroidism is usually caused by a benign adenoma, which produces too much PTH. Increased PTH causes hypercalcemia by increasing bone resorption of Ca^{2+}, increasing kidney reabsorption of Ca^{2+}, and increasing kidney production of 1,25-$(OH)_2$D, which increases Ca^{2+} absorption in the intestines.
   b. Humoral hypercalcemia of malignancy is often due to the production of PTH-related peptide (PTHrp) from cancer cells. PTHrp acts like PTH.
   c. Excessive vitamin D intake may also result in hypercalcemia.
IV. Hypocalcemia (chronically decreased plasma Ca^{2+} concentrations) can also be traced to several causes.
   a. Low PTH concentrations from primary hypoparathyroidism (loss of parathyroid function) lead to hypocalcemia by decreasing bone resorption of Ca^{2+}, decreasing urinary reabsorption of Ca^{2+}, and decreasing renal production of 1,25-$(OH)_2$D.
   b. Pseudohypoparathyroidism is caused by target-organ resistance to the action of PTH.
   c. Secondary hyperparathyroidism is caused by vitamin D deficiency due to inadequate intake, absorption, or activation in the kidney (e.g., in kidney disease).

SECTION F REVIEW QUESTIONS

1. Describe bone remodeling.
2. Describe the handling of Ca^{2+} by the kidneys and gastrointestinal tract.

3. What controls the secretion of parathyroid hormone, and what are the major effects of this hormone?
4. Describe the formation and action of 1,25-$(OH)_2$D. How does parathyroid hormone influence the production of this hormone?

SECTION F KEY TERMS

11.20 Effector Sites for Ca^{2+} Homeostasis

hydroxyapatite
mineralization
osteoclasts
osteocytes
osteoid

11.21 Hormonal Controls

calcitonin
parathyroid glands
parathyroid hormone (PTH)
vitamin D
vitamin D_2 (ergocalciferol)
vitamin D_3 (cholecalciferol)

11.22 Metabolic Bone Diseases

hypercalcemia
hypocalcemia

SECTION F CLINICAL TERMS

11.22 Metabolic Bone Diseases

bisphosphonates
humoral hypercalcemia of malignancy
hypocalcemic tetany
osteomalacia
osteoporosis
primary hyperparathyroidism
primary hypoparathyroidism
pseudohypoparathyroidism
PTH-related peptide (PTHrp)
rickets
secondary hyperparathyroidism
selective estrogen receptor modulators (SERMs)

CHAPTER 11

Clinical Case Study: Mouth Pain, Sleep Apnea, and Enlargement of the Hands in a 35-Year-Old Man

A 35-year-old man visited his dentist with a complaint of chronic mouth pain and headaches. After examining the patient, the dentist concluded that the patient's jaw appeared enlarged, there were increased spaces between his teeth, and his tongue was thickened and large. The dentist referred the patient to a physician. The physician noted enlargement of the jaw and tongue, enlargement of the fingers and toes, and a very deep voice. The patient acknowledged that his voice seemed to have deepened over the past few years and that he no longer wore his wedding ring because it was too tight. The patient's height and weight were within normal ranges. His blood pressure was significantly increased, as was his fasting plasma glucose concentration. The patient also mentioned that his wife could no longer sleep in the same room as he because of his loud snoring and sleep apnea. Based on these signs and symptoms, the physician referred the patient to an endocrinologist, who ordered a series of tests to better elucidate the cause of the diverse symptoms.

The enlarged bones and facial features suggested the possibility of ***acromegaly*** (from the Greek *akros,* "extreme" or "extremities," and *megalos,* "large"), a disease characterized by excess growth hormone and IGF-1 concentrations in the blood. This was confirmed with a blood test that revealed increased concentrations of both hormones. Based on these results, an MRI scan was ordered to look for a possible tumor of the anterior pituitary gland. A 1.5 cm mass was discovered in the sella turcica, consistent with the possibility of a growth hormone–secreting tumor. Because the patient was of normal height, it was concluded that the tumor arose at some point after puberty, when linear growth ceased because of closure of the epiphyseal plates. Had the tumor developed prior to puberty, the man would have been well above normal height because of the growth-promoting actions of growth hormone and IGF-1. Such individuals are known as pituitary giants and have a condition called ***gigantism.*** In many cases, the affected person develops both gigantism and later acromegaly, as occurred in the individual shown in **Figure 11.33**.

Acromegaly and gigantism arise when chronic, excess amounts of growth hormone are secreted into the blood. In almost all cases, acromegaly and gigantism are caused by benign (noncancerous) tumors (adenomas) of the anterior pituitary gland that secrete growth hormone at very high rates, which in turn results in increased IGF-1 concentrations in the blood (**Figure 11.34**). Because these tumors are abnormal tissue, they are not suppressed adequately by normal negative feedback inhibitors like IGF-1, so the growth hormone concentrations remain increased. These tumors are typically very slow growing, and, if they arise

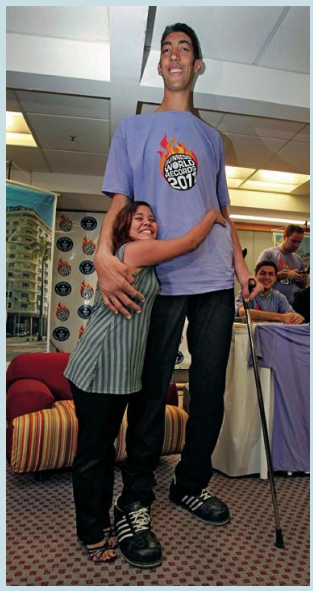


Figure 11.33 Appearance of an individual with gigantism and acromegaly.

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—Continued

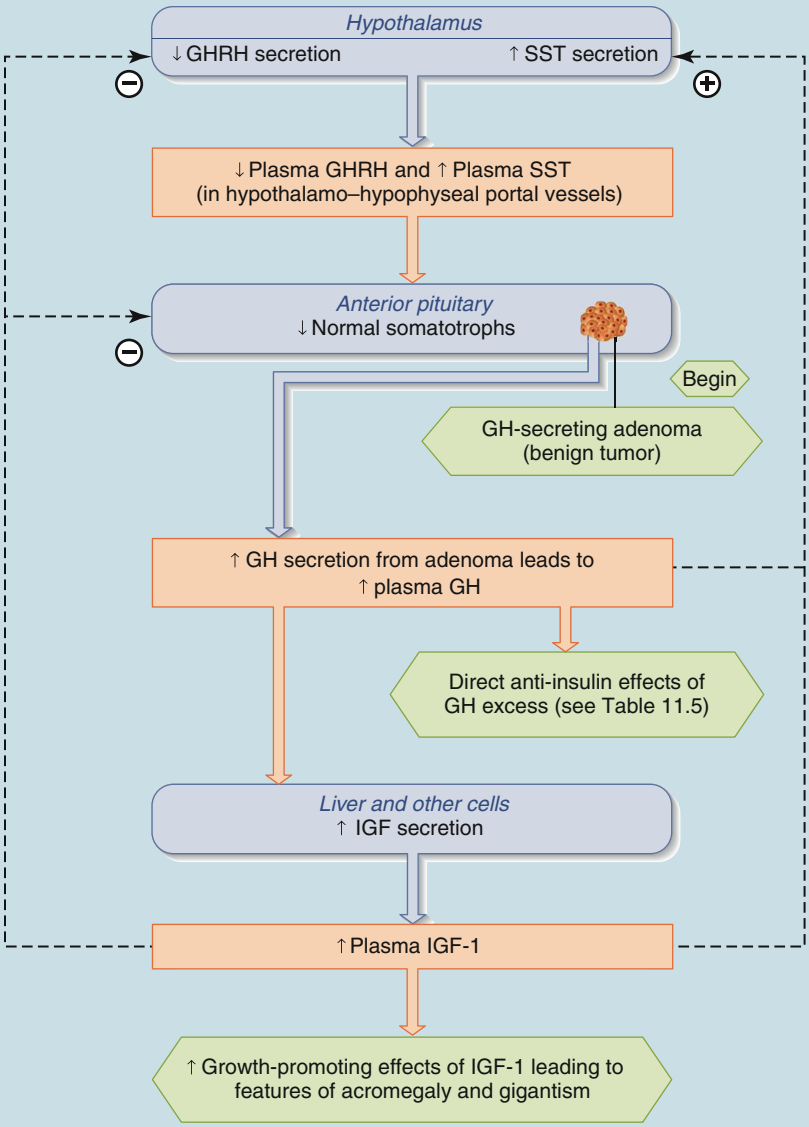


Figure 11.34 A growth hormone-secreting tumor causes features of acromegaly and gigantism by direct GH effects and by GH-induced increases in IGF-1. Increased GH and IGF-1 lead to suppression of normal pituitary somatotrophs (negative feedback). Growth hormone-secreting tumor cells are less sensitive to feedback inhibition by GH and IGF-1.

after puberty, it may be many years before a person realizes that there is something wrong. In our patient, the changes in his appearance were gradual enough that he attributed them simply to "aging," despite his relative youth.

Reflect and Review #1

- Although it is not possible to measure GHRH and SST in the portal blood in people, what you would predict their concentrations would be in a person with a loss of anterior pituitary (somatotroph) function? *(Hint:* Look at the top of Figure 11.28.)

Even when linear growth is no longer possible (after the growth plates have fused), very high plasma concentrations of growth hormone and IGF-1 result in the thickening of many bones in the body, most noticeably in the hands, feet, and head. The jaw, particularly, enlarges to give the characteristic facial appearance called ***prognathism*** (from the Greek *pro,* "forward," and *gnathos,* "jaw") that is associated with acromegaly. This was likely the cause of our patient's chronic mouth pain. The enlarged sinuses that resulted from the thickening of his skull bones may have been responsible in part for his headaches. In addition, many internal organs—such as the heart—also become enlarged due to growth hormone and IGF-1–induced hypertrophy, and this can interfere with their ability to function normally. In some acromegalics, the tissues comprising the larynx enlarge, resulting in a deepening of the voice as in our subject. The enlarged and deformed tongue was likely a contributor to the sleep apnea and snoring reported by the patient; this is called obstructive sleep apnea because the tongue base weakens and, consequently, the tongue obstructs the upper airway (see Chapter 13 for a discussion of sleep apnea). Finally, roughly half of all people with acromegaly have high blood pressure (hypertension). The cause of the hypertension is uncertain, but it is a serious medical condition that requires treatment with antihypertensive drugs.

As described earlier, adults continue to make and secrete growth hormone even after growth ceases. That is because growth hormone has metabolic actions in addition to its effects on growth. The major actions of growth hormone in metabolism are to increase the concentrations of glucose and fatty acids in the blood and decrease the sensitivity of skeletal muscle and adipose tissue to insulin. Not surprisingly, therefore, one of the stimuli that increases growth hormone concentrations in the healthy adult is a decrease in blood glucose or fatty acids. The secretion of growth hormone during these metabolic crises, however, is transient; once glucose or fatty acid concentrations are restored to normal, growth hormone concentrations decrease to baseline. In acromegaly, however, growth hormone concentrations are almost always increased. Consequently, acromegaly is often associated with increased plasma concentrations of glucose and fatty acids, in some cases even reaching the concentrations observed in diabetes mellitus. As in Cushing's syndrome (increased cortisol described in Section D), the presence of chronically increased concentrations of growth hormone may result in diabetes-like symptoms. This explains why our patient had a high fasting plasma glucose concentration.

Our subject was fortunate to have had a quick diagnosis. This case study illustrates one of the confounding features of endocrine disorders. The rarity of some endocrine diseases (e.g., acromegaly occurs in roughly 4 per million individuals), together with the fact that the symptoms of a given endocrine disease can be varied and insidious in their onset, often results in a delayed diagnosis. This means that in many cases, a patient is subjected to numerous tests for more common disorders before a diagnosis of endocrine disease is made.

Treatment of gigantism and acromegaly usually starts with surgical removal of the pituitary tumor. The residual normal pituitary tissue is then sufficient to maintain baseline growth hormone concentrations. If surgical treatment is not possible nor successful, treatment with long-acting analogs of somatostatin is sometimes

necessary. (Figure 11.34 shows that somatostatin is the hypothalamic hormone that inhibits GH secretion.)

Reflect and Review #2

- What other drug could be used to decrease the effects of GH excess? *(Hint:* See the lower part of Figure 11.34.)

Our patient elected to have surgery. This resulted in a reduction in his plasma growth hormone and IGF-1 concentrations. With time, several of his symptoms were reduced, including the increased plasma glucose concentrations. However, within 2 years, his growth hormone and IGF-1 concentrations were three times higher than the normal range for his age and a follow-up MRI revealed that the tumor had regrown. Not wanting a second surgery, the patient was treated with radiation therapy focused on the pituitary tumor, followed by regular administration of a somatostatin analog. This treatment decreased but did not completely normalize his hormone concentrations. His blood pressure remained higher than normal and was treated with two different antihypertensive drugs (see Chapter 12).

Clinical terms: acromegaly, gigantism, prognathism

See Chapter 19 for complete, integrative case studies.

CHAPTER 11 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1–5: Match the hormone with the function or feature (choices a–e).

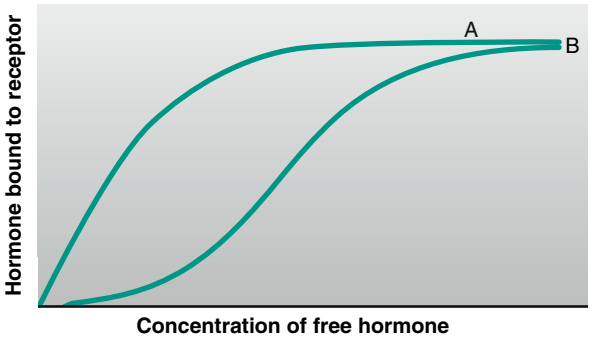
Hormone:

1. vasopressin
2. ACTH
3. oxytocin
4. prolactin
5. luteinizing hormone

Function:

a. tropic for the adrenal cortex
b. is controlled by an amine-derived hormone of the hypothalamus
c. antidiuresis
d. stimulation of testosterone production
e. stimulation of uterine contractions during labor

6. In the following figure, which hormone (A or B) binds to receptor X with higher affinity?



7. Which is *not* a symptom of Cushing's disease?
   a. high blood pressure
   b. bone loss
   c. suppressed immune function
   d. goiter
   e. hyperglycemia (increased blood glucose)
8. Tremors, nervousness, and increased heart rate can all be symptoms of
   a. increased activation of the sympathetic nervous system.
   b. excessive secretion of epinephrine from the adrenal medulla.
   c. hyperthyroidism.
   d. hypothyroidism.
   e. answers a, b, and c (all are correct).
9. Which of the following could theoretically result in short stature?
   a. pituitary tumor making excess thyroid-stimulating hormone
   b. mutations that result in inactive IGF-1 receptors
   c. delayed onset of puberty
   d. decreased hypothalamic concentrations of somatostatin
   e. normal plasma GH but decreased feedback of GH on GHRH
10. Choose the correct statement.
    a. During times of stress, cortisol acts as an anabolic hormone in muscle and adipose tissue.
    b. A deficiency of thyroid hormone would result in increased cellular concentrations of Na^+/K^+-ATPase pumps in target tissues.
    c. The posterior pituitary is connected to the hypothalamus by long portal vessels.
    d. Adrenal insufficiency often results in increased blood pressure and increased plasma glucose concentrations.
    e. A lack of iodide in the diet will not have a significant effect on the concentration of circulating thyroid hormone for at least several weeks.
11. A lower-than-normal concentration of plasma Ca^{2+} causes
    a. a PTH-mediated increase in 25-OH D.
    b. a decrease in renal 1-hydroxylase activity.
    c. a decrease in the urinary excretion of Ca^{2+}.
    d. a decrease in bone resorption.
    e. an increase in vitamin D release from the skin.
12. Which of the following is *not* consistent with primary hyperparathyroidism?
    a. hypercalcemia
    b. increased plasma 1,25-$(OH)_2$D
    c. increased urinary excretion of phosphate ions
    d. a decrease in Ca^{2+} resorption from bone
    e. an increase in Ca^{2+} reabsorption in the kidney

True or False

13. T_4 is the chief circulating form of thyroid hormone but is less active than T_3.
14. Acromegaly is usually associated with hypoglycemia and hypotension.
15. Thyroid hormone and cortisol are both permissive for the actions of epinephrine.

CHAPTER 11 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. In an experimental animal, the sympathetic preganglionic fibers to the adrenal medulla are cut. What happens to the plasma concentration of epinephrine at rest and during stress? *Hint:* See Figure 11.12 for help.
2. During pregnancy, there is an increase in the liver's production and, consequently, the plasma concentration of the major plasma binding protein for thyroid hormone. This causes a sequence of events involving feedback that results in an increase in the plasma concentrations of T_3 but no evidence of hyperthyroidism. Describe the sequence of events. *Hint:* Refer back to the equation in Section 11.3 and Figure 11.22.
3. A child shows the following symptoms: deficient growth, failure to show sexual development, decreased ability to respond to stress. What is the most likely cause of all these symptoms? *Hint:* Refer to Figure 11.15.
4. If all the neural connections between the hypothalamus and pituitary gland below the median eminence were interrupted, the secretion of which pituitary gland hormones would be affected? Which pituitary gland hormones would not be affected? *Hint:* Assume the portal veins are not injured and refer back to Figures 11.12, 11.13, and 11.17.
5. Typically, an antibody to a peptide combines with the peptide and renders it nonfunctional. If an animal were given an antibody to somatostatin, the secretion of which anterior pituitary gland hormone would change and in what direction? *Hint:* See Figure 11.28.
6. A patient has to have a large length of the small intestine removed due to inflammatory bowel disease. What would you predict would happen to the secretion of PTH in this circumstance? *Hint:* See Figure 11.31.
7. A person is receiving very large doses of a synthetic glucocorticoid to treat her arthritis. What happens to her secretion of cortisol? *Hint:* See Figure 11.24.
8. A person with symptoms of hypothyroidism (i.e., sluggishness and intolerance to cold) is found to have abnormally low plasma concentrations of T_4, T_3, and TSH. After an injection of TRH, the plasma concentrations of all three hormones increase. Where is the site of the defect leading to the hypothyroidism? *Hint:* See Figure 11.22.
9. A full-term newborn infant is abnormally small. Is this most likely due to deficient growth hormone, deficient thyroid hormones, or deficient nutrition during fetal life? *Hint:* See Sections 11.18 and 11.19. Recall that the control of fetal growth is quite different than the control of the growth spurt at puberty.
10. Why might the administration of androgens to stimulate growth in a short, 12-year-old male turn out to be counterproductive? *Hint:* See Table 11.6.

CHAPTER 11 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. Referring back to Tables 11.3, 11.4, and 11.5, explain how certain of the actions of epinephrine, cortisol, and growth hormone illustrate in part the general principle of physiology that *most physiological functions are controlled by multiple regulatory systems, often working in opposition.*
2. Another general principle of physiology is that *structure is a determinant of—and has coevolved with—function.* The structure of the thyroid gland is very unlike other endocrine glands. How is the structure of this gland related to its function?
3. *Homeostasis is essential for health and survival.* How do parathyroid hormone, ADH, and thyroid hormone contribute to homeostasis? What might be the consequence of having too little of each of those hormones?

CHAPTER 11 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 11.3 By storing large amounts of hormone in an endocrine cell, the plasma concentration of the hormone can be increased within seconds when the cell is stimulated. Such rapid responses may be critical for an appropriate response to a challenge to homeostasis. Packaging peptides in this way also prevents intracellular degradation.

Figure 11.5 Because steroid hormones are derived from cholesterol, they are lipophilic. Consequently, they can freely diffuse through lipid bilayers, including those that constitute secretory vesicles. Therefore, once a steroid hormone is synthesized, it diffuses out of the cell.

Figure 11.9 One explanation for this patient's symptoms may be that his or her circulating concentration of thyroid hormone was increased. This might occur if the person's thyroid was overstimulated due, for example, to thyroid disease. The increased concentration of thyroid hormone would cause an even greater potentiation of the actions of epinephrine, making it appear as if the patient had excess concentrations of epinephrine.

Figure 11.12 This figure demonstrates how the central nervous system (brain and spinal cord) is the source of afferent information flow that controls many hormonal systems that, in turn, regulate numerous homeostatic processes. For example, the central nervous system is involved in the control of (1) circulatory and metabolic function via release of epinephrine from the adrenal medulla (Chapters 12 and 16); (2) gastrointestinal function via input from autonomic ganglia to endocrine cells in the intestine (Chapter 15); and (3) growth, reproduction, ion and water homeostasis, immune function, and other homeostatic processes via the release of hormones from the anterior and posterior pituitary (this chapter and Chapters 14, 17, and 18). This allows a consistent response throughout the body to threats to homeostasis sent by afferent information from throughout the body to the central nervous system, where the information is interpreted and an appropriate response is generated.

Figure 11.13 Because the volume of blood into which the hypophysiotropic hormones are secreted is far less than would be the case if they were secreted into the general circulation of the body, the absolute amount of hormone required to achieve a given concentration is much less. This means that the cells of the hypothalamus need only synthesize a tiny amount of hypophysiotropic hormone to reach concentrations in the portal blood vessels that are physiologically active (i.e., can activate receptors on pituitary cells). This allows for the tight control of the anterior pituitary gland by a very small number of discrete neurons within the hypothalamus.

Figure 11.21 Iodine is not widely found in foods; in the absence of iodized salt, an acute or chronic deficiency in dietary iodine is possible. The colloid permits a long-term store of iodinated thyroglobulin that can be used during times when dietary iodine intake is reduced or absent.

Figure 11.24 Plasma cortisol concentrations would increase. This would result in decreased ACTH concentrations in the systemic blood, and CRH concentrations in the portal vein blood, due to increased negative feedback at the pituitary gland and hypothalamus, respectively. The right adrenal gland would shrink in size (atrophy) as a consequence of the decreased ACTH concentrations (decreased "trophic" stimulation of the adrenal cortex).

Figure 11.28 Note from the figure that a decrease in plasma glucose concentrations results in an increase in growth hormone concentrations. This makes sense, because one of the metabolic actions of growth hormone is to increase the concentrations of glucose in the blood. By the same reasoning, an *increase* in the concentration of glucose in the blood due to any cause, including an intravenous infusion as described here, would be expected to *decrease* circulating concentrations of growth hormone.

Figure 11.31 The response to hypocalcemia is an excellent example of how the responses of different organ systems function together to restore homeostasis. In this case, the sensor for decreased Ca^{2+} in the plasma is located in cells of the parathyroid gland. The decrease in Ca^{2+} increases the synthesis and release of parathyroid hormone (PTH) from these cells. PTH, in turn, coordinates a response of several organ systems to restore plasma Ca^{2+} to normal. This includes direct effects of PTH on bone to increase resorption (reclamation) of Ca^{2+} from its storage sites, and on the kidneys to minimize the loss of Ca^{2+} in the urine as well as to stimulate the production of 1,25-$(OH)_2$D (the active end product of the vitamin D pathway). 1,25-$(OH)_2$D then stimulates an increase in Ca^{2+} absorption from the small intestine. In this way, an increase in net Ca^{2+} retention to restore plasma Ca^{2+} to normal is coordinated by the combined actions of the endocrine, digestive, musculoskeletal, and urinary systems.

Figure 11.32 The 1-hydroxylase activity will stimulate the conversion of 25-OH D to 1,25-$(OH)_2$D in the granulomas themselves; the 1,25-$(OH)_2$D will then diffuse out of the granuloma cells and enter the plasma, leading to increased Ca^{2+} absorption in the gastrointestinal tract. This will increase plasma Ca^{2+}, which in turn will suppress parathyroid hormone production; consequently, plasma parathyroid hormone concentrations will decrease. This is a form of secondary hypoparathyroidism.

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