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The Endocrine System

You don't have to watch *CSI* to experience action-packed drama. Molecules and cells inside your body have dynamic adventures on microscopic levels all the time. For instance, when insulin molecules, carried passively along in the blood, attach to protein receptors of nearby cells, the response is dramatic: Glucose molecules begin to disappear from the blood into the cells, and cellular activity accelerates. Such is the power of the second great control system of the body, the **endocrine system**, which interacts with the nervous system to coordinate and integrate the activity of body cells.

The Endocrine System: An Overview

- Indicate important differences between hormonal and neural controls of body functioning.
- List the major endocrine organs, and describe their body locations.
- Distinguish between hormones, paracrines, and autocrines.

The means of control and the speed of the endocrine system are very different from those of the nervous system. The nervous system regulates the activity of muscles and glands via electrochemical impulses delivered by neurons, and those organs respond within milliseconds. The endocrine system influences metabolic activity by means of *hormones* (*hormone* = to excite), which are chemical messengers released into the blood to be transported throughout the body. Binding of a hormone to cellular receptors initiates responses that typically occur after a lag period of seconds or even days. But, once initiated, those responses tend to be much more prolonged than those induced by the nervous system.

Hormonal targets ultimately include most cells of the body, and hormones have widespread and diverse effects. The major processes controlled and integrated by these "mighty molecules" are reproduction; growth and development; maintenance of electrolyte, water, and nutrient balance of the blood; regulation of cellular metabolism and energy balance; and mobilization of body defenses. As you can see, the endocrine system orchestrates processes that go on for relatively long periods, in some instances continuously. The scientific study of hormones and the endocrine organs is called **endocrinology**.

Compared with other organs of the body, those of the endocrine system are small and unimpressive. Indeed, to collect 1 kg (2.2 lb) of hormone-producing tissue, you would need to collect all the endocrine tissue from eight or nine adults! Unlike the arrangement in most organ systems, the endocrine organs are not grouped together in the body. Instead, endocrine organs are widely scattered about the body.

As we explained in Chapter 4, there are two kinds of glands. *Exocrine glands* produce nonhormonal substances, such as sweat and saliva, and have ducts that carry these substances to a membrane surface. **Endocrine glands**, also called *ductless glands*, produce hormones and lack ducts. They release their hormones into the surrounding tissue fluid (*endo* = within; *crine* = to secrete), and they typically have a rich vascular and lymphatic drainage that receives their hormones. Most of the hormone-producing cells in endocrine glands are arranged in cords and branching networks—a situation that maximizes contact between them and the capillaries surrounding them.

The endocrine glands include the pituitary, thyroid, parathyroid, adrenal, and pineal glands (Figure 16.1). The hypothalamus, along with its neural functions, produces and releases hormones, so we can consider the hypothalamus a **neuroendocrine organ**. In addition, several organs, such as the pancreas, gonads (ovaries and testes), and placenta, contain endocrine tissue and also perform other functions.

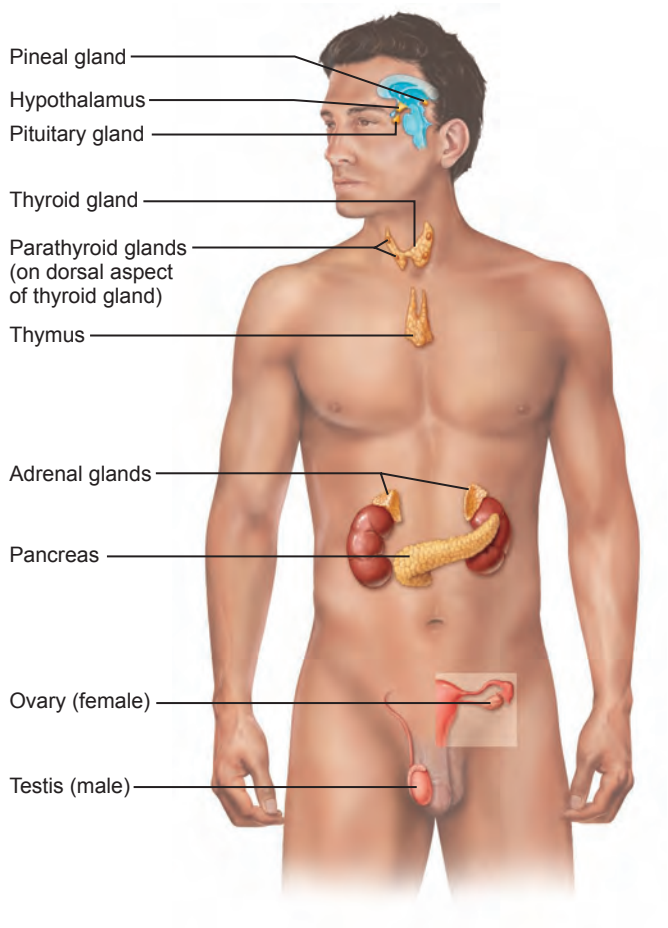

Figure 16.1 Location of selected endocrine organs of the body.

Many other organs also contain scattered endocrine cells or small clusters of endocrine cells. For example, adipose cells release leptin, the thymus releases thymic hormones, and hormone-producing cells are found in the walls of the small intestine, stomach, kidneys, and heart—organs whose chief functions have little to do with hormone production. We describe these other hormone-producing structures on pp. 624–625.

Some physiologists include local chemical messengers—autocrines and paracrines—as part of the endocrine system, but that is not the consensus. Hormones are long-distance chemical signals that travel in blood or lymph throughout the body. **Autocrines** are chemicals that exert their effects on the same cells that secrete them. For example, certain prostaglandins released by smooth muscle cells cause those smooth muscle cells to contract. **Paracrines** also act locally but affect cell types other than those releasing the paracrine chemicals. For example, somatostatin released by one population of pancreatic cells inhibits the release of insulin by a different population of pancreatic cells.

HOMEOSTATIC IMBALANCE

Certain tumor cells, such as those of some cancers of the lung or pancreas, synthesize hormones identical to those made in normal endocrine glands. However, they do so in an excessive and uncontrolled fashion leading to problems due to hormone-mediated pathology. ■

CHECK YOUR UNDERSTANDING

1. For each of the following statements, indicate whether it applies more to the endocrine system or the nervous system: rapid; discrete responses; controls growth and development; long-lasting responses.
2. Which two endocrine glands are found in the neck?
3. What is the difference between a hormone and a paracrine?

For answers, see Appendix G.

Hormones

- Describe how hormones are classified chemically.
- Describe the two major mechanisms by which hormones bring about their effects on their target tissues.
- List three kinds of interaction of different hormones acting on the same target cell.
- Explain how hormone release is regulated.

The Chemistry of Hormones

Hormones are chemical substances, secreted by cells into the extracellular fluids, that regulate the metabolic function of other cells in the body. Although a large variety of hormones are produced, nearly all of them can be classified chemically as either amino acid based or steroids.

Most hormones are **amino acid based**. Molecular size varies widely in this group—from simple amino acid derivatives (which include amines and thyroxine constructed from the amino acid tyrosine), to peptides (short chains of amino acids), to proteins (long polymers of amino acids).

The **steroids** are synthesized from cholesterol. Of the hormones produced by the major endocrine organs, only gonadal and adrenocortical hormones are steroids.

If we also consider the **eicosanoids** (i-ko′să-noyds), which include *leukotrienes* and *prostaglandins*, we must add a third chemical class. These biologically active lipids (made from arachidonic acid) are released by nearly all cell membranes. Leukotrienes are signaling chemicals that mediate inflammation and some allergic reactions. Prostaglandins have multiple targets and effects, ranging from raising blood pressure and increasing the expulsive uterine contractions of birth to enhancing blood clotting, pain, and inflammation.

Because the effects of eicosanoids are typically highly localized, affecting only nearby cells, they generally act as paracrines and autocrines and do not fit the definition of the true *hormones*, which influence distant targets. For this reason, we will not consider this class of hormonelike chemicals here. Instead, we note their important effects in later chapters as appropriate.

Mechanisms of Hormone Action

All major hormones circulate to virtually all tissues, but a given hormone influences the activity of only certain tissue cells, referred to as its **target cells**. Hormones bring about their characteristic effects on target cells by *altering* cell activity. In other words, they increase or decrease the rates of normal cellular processes.

The precise response depends on the target cell type. For example, when the hormone epinephrine binds to certain smooth muscle cells in blood vessel walls, it stimulates them to contract. Epinephrine binding to cells other than muscle cells may have a different effect, but it does not cause those cells to contract.

A hormonal stimulus typically produces one or more of the following changes:

1. Alters plasma membrane permeability or membrane potential, or both, by opening or closing ion channels
2. Stimulates synthesis of proteins or regulatory molecules such as enzymes within the cell
3. Activates or deactivates enzymes
4. Induces secretory activity
5. Stimulates mitosis

How does a hormone communicate with its target cell? In other words, how is hormone receptor binding harnessed to the intracellular machinery needed for hormone action? The answer depends on the chemical nature of the hormone and the cellular location of the receptor, but hormones act at receptors in one of two general ways. On the one hand, *water-soluble hormones* (all amino acid–based hormones except thyroid hormone) act on *receptors in the plasma membrane*. These receptors are coupled via regulatory molecules called G proteins to one or more intracellular second messengers which mediate the target cell's response. On the other hand, *lipid-soluble hormones* (steroid and thyroid hormones) act on *intracellular receptors*, which directly activate genes.

This will be easy for you to remember if you think about *why* the hormones must bind where they do. Receptors for water-soluble hormones must be in the plasma membrane since these hormones *cannot* enter the cell, and receptors for lipid-soluble steroid and thyroid hormones are inside the cell because these hormones *can* enter the cell. Of course, things are not quite that clear-cut. Recent research has shown that steroid hormones exert some of their more immediate effects via plasma membrane receptors, and the second messengers of some water-soluble hormones can turn genes on.

Plasma Membrane Receptors and Second-Messenger Systems

With the exception of thyroid hormone, all amino acid–based hormones exert their signaling effects through intracellular **second messengers** generated when a hormone binds to a receptor on the plasma membrane. You are already familiar with one of these second messengers, **cyclic AMP**, which is used by neurotransmitters (Chapter 11) and olfactory receptors (Chapter 15).

The Cyclic AMP Signaling Mechanism As you recall, this mechanism involves the interaction of three plasma membrane components to determine intracellular levels of cyclic AMP

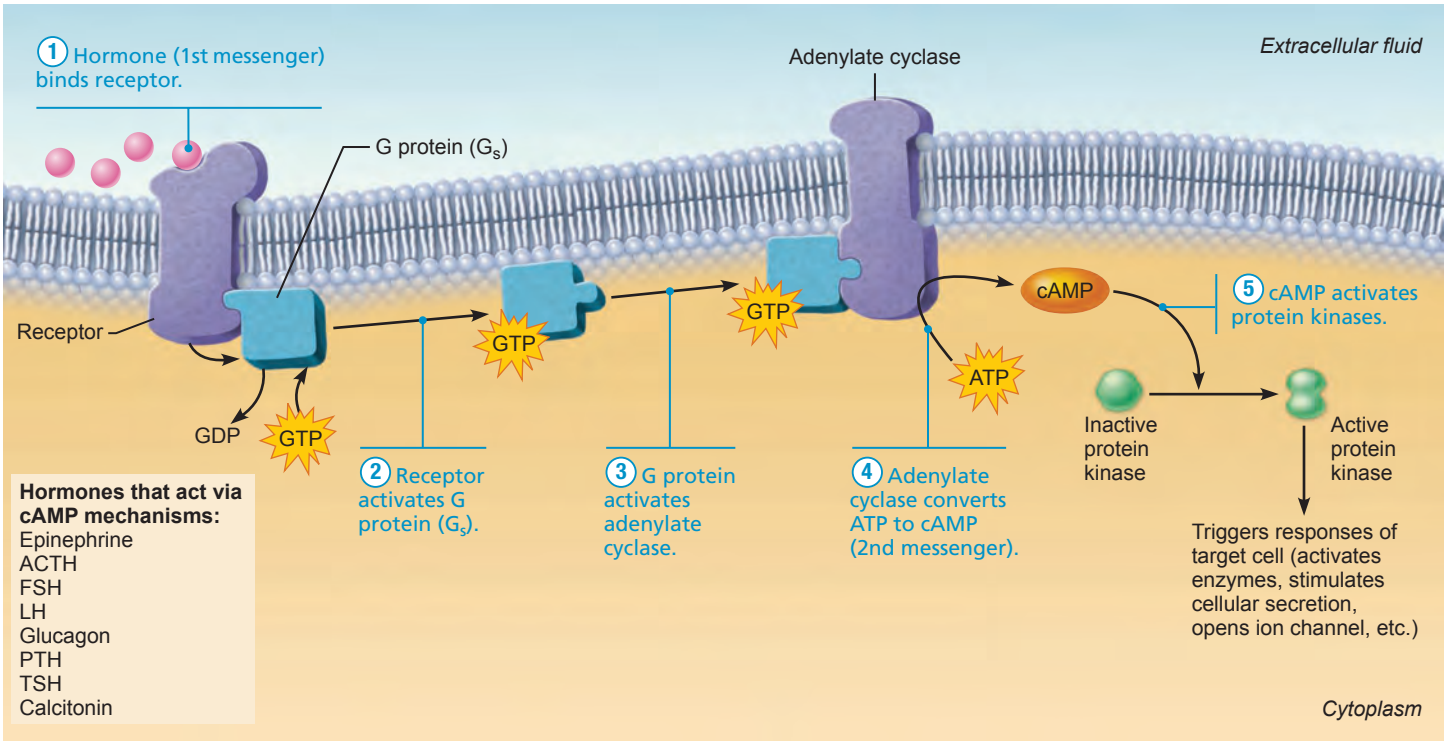

Figure 16.2 Cyclic AMP second-messenger mechanism of water-soluble hormones.

(cAMP)—a hormone receptor, a G protein, and an effector enzyme (adenylate cyclase). Figure 16.2 illustrates these steps:

1. **Hormone binds receptor.** The hormone, acting as the **first messenger**, binds to its receptor on the plasma membrane.
2. **Receptor activates G protein.** Hormone binding causes the receptor to change shape, allowing it to bind a nearby inactive **G protein**. The G protein is activated as the guanosine diphosphate (GDP) bound to it is displaced by the high-energy compound *guanosine triphosphate* (*GTP*). The G protein behaves like a light switch: It is "off" when GDP is bound to it, and "on" when GTP is bound.
3. **G protein activates adenylate cyclase.** The activated G protein (moving along the membrane) binds to the effector enzyme **adenylate cyclase**. Some G proteins (G_s) *stimulate* adenylate cyclase (as shown in Figure 16.2), but others (G_i) *inhibit* adenylate cyclase. Eventually, the GTP bound to the G protein is hydrolyzed to GDP and the G protein becomes inactive once again. (The G protein cleaves the terminal phosphate group off GTP in much the same way that ATPase enzymes hydrolyze ATP.)
4. **Adenylate cyclase converts ATP to cyclic AMP.** For as long as activated G_s is bound to it, adenylate cyclase generates the *second messenger* cAMP from ATP.
5. **Cyclic AMP activates protein kinases.** cAMP, which is free to diffuse throughout the cell, triggers a cascade of chemical reactions by activating *protein kinase A*. **Protein kinases** are enzymes that *phosphorylate* (add a phosphate group to) various proteins, many of which are other enzymes. Because phosphorylation activates some of these proteins and inhibits others, a variety of processes may be affected in the same target cell at the same time.

This type of intracellular enzymatic cascade has a huge amplification effect. Each activated adenylate cyclase generates large numbers of cAMP molecules, and a single kinase enzyme can catalyze hundreds of reactions. As the reaction cascades through one enzyme intermediate after another, the number of product molecules increases dramatically at each step. Receptor binding of a single hormone molecule can generate millions of final product molecules!

The sequence of reactions set into motion by cAMP depends on the type of target cell, the specific protein kinases it contains, and the substrates within that cell available for phosphorylation by the protein kinase. For example, in thyroid cells, binding of thyroid-stimulating hormone promotes synthesis of the thyroid hormone thyroxine; in liver cells, binding of glucagon activates enzymes that break down glycogen, releasing glucose to the blood. Since some G proteins inhibit rather than activate adenylate cyclase, thereby reducing the cytoplasmic concentration of cAMP, even slight changes in levels of antagonistic hormones can influence a target cell's activity. Examples of hormones that act via cyclic AMP second-messenger systems are listed in Figure 16.2.

The action of cAMP persists only briefly because the molecule is rapidly degraded by the intracellular enzyme **phosphodiesterase**. While at first glance this may appear to be a problem, it is quite the opposite. Because of the amplification effect, most hormones need to be present only briefly to cause

the desired results. Continued production of hormones then prompts continued cellular activity, and no extracellular controls are necessary to stop the activity.

The PIP_2-Calcium Signaling Mechanism Cyclic AMP is the activating second messenger in some tissues for at least ten amino acid–based hormones, but some of the same hormones (such as epinephrine) act through a different second-messenger system in other tissues. In one such mechanism, called the PIP_2-calcium signaling mechanism, intracellular calcium ions act as a final mediator.

Like the cAMP signaling mechanism, the PIP_2-calcium signaling mechanism involves a G protein (G_q) and a membrane-bound effector, in this case an enzyme called **phospholipase C**. Phospholipase C splits a plasma membrane phospholipid called **PIP_2** (**p**hosphatidyl **i**nositol bis**p**hosphate) into **diacylglycerol (DAG)** and **inositol trisphosphate (IP_3)**. DAG, like cAMP, activates a protein kinase enzyme (protein kinase C in this case), which triggers responses within the target cell. In addition, IP_3 releases Ca^{2+} from intracellular storage sites.

The liberated Ca^{2+} also takes on a second-messenger role, either by directly altering the activity of specific enzymes and channels or by binding to the intracellular regulatory protein **calmodulin**. Once Ca^{2+} binds to calmodulin, it activates enzymes that amplify the cellular response.

Hormones known to act on their target cells via the PIP_2 mechanism include thyrotropin-releasing hormone (TRH), antidiuretic hormone (ADH), gonadotropin-releasing hormone (GnRH), oxytocin, and epinephrine.

Other Signaling Mechanisms Other hormones that bind plasma membrane receptors act on their target cells through different signaling mechanisms. For example, cyclic guanosine monophosphate (cGMP) is a second messenger for selected hormones.

Insulin (and other growth factors) work without second messengers. The insulin receptor is a *tyrosine kinase* enzyme that is activated by autophosphorylation (addition of phosphate to several of its own tyrosines) when insulin binds. The activated insulin receptor provides docking sites for intracellular *relay proteins* that, in turn, initiate a series of protein phosphorylations that trigger specific cell responses.

In certain instances, any of the second messengers mentioned—and the hormone receptor itself—can cause changes in intracellular Ca^{2+} levels.

Intracellular Receptors and Direct Gene Activation

Being lipid soluble, steroid hormones (and, strangely, thyroid hormone, a small iodinated amine) diffuse into their target cells where they bind to and activate an intracellular receptor **(Figure 16.3)**. The activated receptor-hormone complex then makes its way to the nuclear chromatin, where the hormone receptor binds to a region of DNA (a *hormone response element*) specific for it. (The exception to these generalizations is that thyroid hormone receptors are always bound to DNA even in the absence of thyroid hormone.) This interaction "turns on" a gene, that is, prompts transcription of DNA to produce a messenger RNA (mRNA). The mRNA is then translated on the cytoplasmic ribosomes, producing specific protein molecules. These proteins include enzymes that promote the metabolic activities induced by that particular hormone and, in some cases, promote synthesis of either structural proteins or proteins to be exported from the target cell.

In the absence of hormone, the receptors are bound up in receptor-chaperonin complexes. These associations seem to keep the receptors from binding to DNA and perhaps protect them from proteolysis. (Check back to Chapter 2, pp. 50–51, if your recall of molecular chaperones needs a jog.) When the hormone *is* present, the complex dissociates, which allows the hormone-bound receptor to bind to DNA and influence transcription.

Target Cell Specificity

In order for a target cell to respond to a hormone, the cell must have *specific* protein receptors on its plasma membrane or in its interior to which that hormone can bind. For example, receptors for adrenocorticotropic hormone (ACTH) are normally found only on certain cells of the adrenal cortex. By contrast, thyroxine is the principal hormone stimulating cellular metabolism, and nearly all body cells have thyroxine receptors.

A hormone receptor responds to hormone binding by prompting the cell to perform, or turn on, some gene-determined "preprogrammed" function. As such, hormones are molecular triggers rather than informational molecules. Although binding of a hormone to a receptor is the crucial first step, target cell activation by hormone-receptor interaction depends equally on three factors: (1) blood levels of the hormone, (2) relative numbers of receptors for that hormone on or in the target cells, and (3) *affinity* (strength) of the binding between the hormone and the receptor. All three factors change rapidly in response to various stimuli and changes within the body. As a rule, for a given level of hormone in the blood, a large number of high-affinity receptors produces a pronounced hormonal effect, and a smaller number of low-affinity receptors results in reduced target cell response or outright endocrine dysfunction.

Receptors are dynamic structures. In some instances, target cells form more receptors in response to rising blood levels of the specific hormones to which they respond, a phenomenon called **up-regulation**. In other cases, prolonged exposure to high hormone concentrations desensitizes the target cells, so that they respond less vigorously to hormonal stimulation. This **down-regulation** involves loss of receptors and prevents the target cells from overreacting to persistently high hormone levels.

Hormones influence the number and affinity not only of their own receptors but also of receptors that respond to other hormones. For example, progesterone induces a loss of estrogen receptors in the uterus, thus antagonizing estrogen's actions. On the other hand, estrogen causes the same cells to produce more progesterone receptors, enhancing their ability to respond to progesterone.

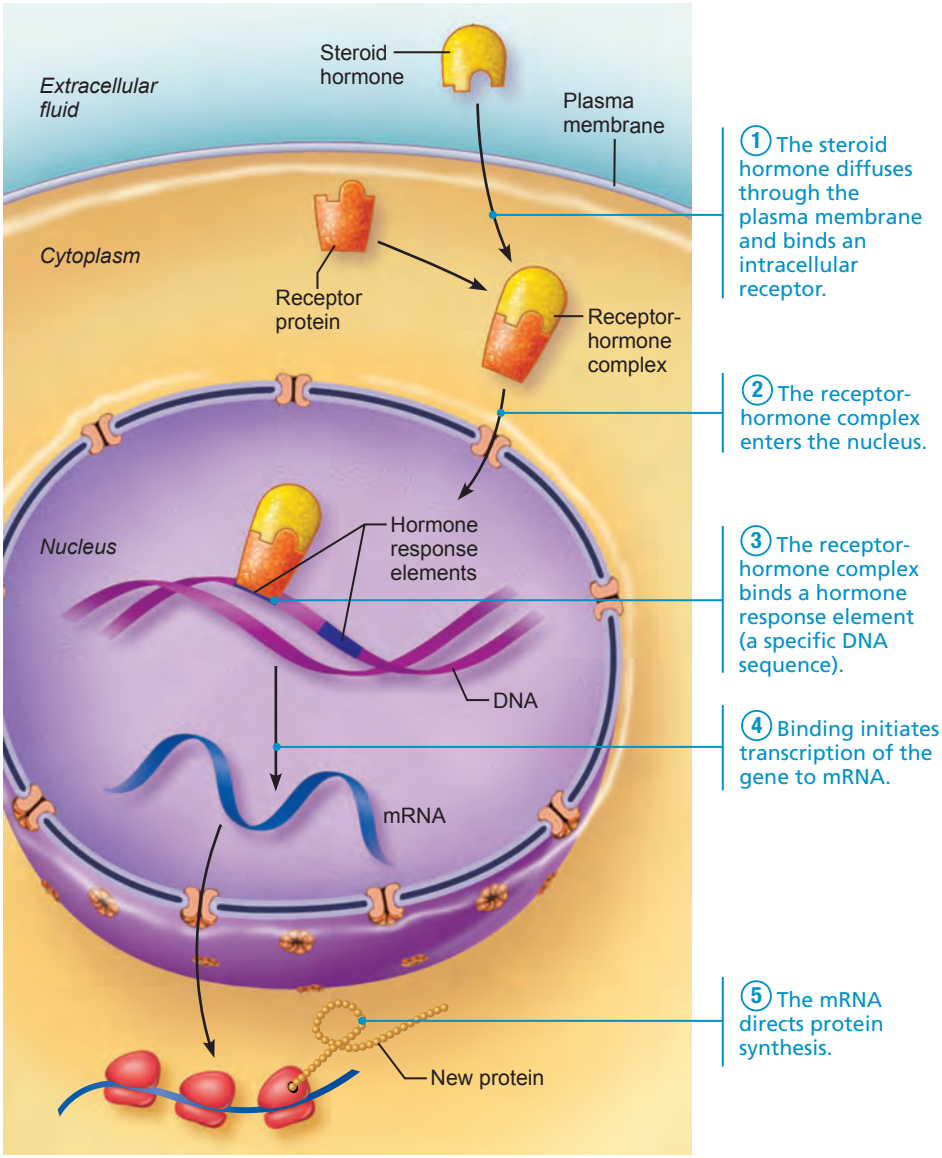

Figure 16.3 Direct gene activation mechanism of lipid-soluble hormones. Steroid hormone is illustrated. Thyroid hormone binds its receptor in the nucleus.

Half-Life, Onset, and Duration of Hormone Activity

Hormones are potent chemicals, and they exert profound effects on their target organs at very low concentrations. Hormones circulate in the blood in two forms—free or bound to a protein carrier. In general, lipid-soluble hormones (steroids and thyroid hormone) travel in the bloodstream attached to plasma proteins. Most others circulate without carriers.

The concentration of a circulating hormone in blood at any time reflects (1) its rate of release, and (2) the speed at which it is inactivated and removed from the body. Some hormones are rapidly degraded by enzymes in their target cells, but most are removed from the blood by the kidneys or liver, and their breakdown products are excreted from the body in urine or, to a lesser extent, in feces. As a result, the length of time for a hormone's blood level to decrease by half, referred to as its **half-life**, varies from a fraction of a minute to a week. The water-soluble hormones exhibit the shortest half-lives.

How long does it take for a hormone to have an effect? The time required for hormone effects to appear varies greatly. Some hormones provoke target organ responses almost immediately, while others, particularly the steroid hormones, require hours to days before their effects are seen. Additionally, some hormones are secreted in a relatively inactive form and must be activated in the target cells.

The duration of hormone action is limited, ranging from 10 seconds to several hours, depending on the hormone. Effects may disappear rapidly as blood levels drop, or they may persist for hours after very low hormone levels have been reached. Because of these many variations, hormonal blood levels must be precisely and individually controlled to meet the continuously changing needs of the body.

Interaction of Hormones at Target Cells

Understanding hormonal effects is a bit more complicated than you might expect because multiple hormones may act on the same target cells at the same time. In many cases the result of such an interaction is not predictable, even when you know the effects of the individual hormones. Here we will look at three types of hormone interaction—permissiveness, synergism, and antagonism.

Permissiveness is the situation when one hormone cannot exert its full effects without another hormone being present. For example, the development of the reproductive system is largely regulated by reproductive system hormones, as we might expect. However, thyroid hormone is necessary (has a permissive effect) for normal *timely* development of reproductive structures. Without thyroid hormone, reproductive system development is delayed.

Synergism of hormones occurs in situations where more than one hormone produces the same effects at the target cell and their combined effects are amplified. For example, both glucagon (produced by the pancreas) and epinephrine cause the liver to release glucose to the blood. When they act together, the amount of glucose released is about 150% of what is released when each hormone acts alone.

When one hormone opposes the action of another hormone, the interaction is called **antagonism**. For example, insulin, which lowers blood glucose levels, is antagonized by glucagon, which acts to raise blood glucose levels. How does antagonism occur? Antagonists may compete for the same receptors, act through different metabolic pathways, or even, as noted in the progesterone-estrogen interaction at the uterus, cause down-regulation of the receptors for the antagonistic hormone.

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Control of Hormone Release

The synthesis and release of most hormones are regulated by some type of **negative feedback system** (see Chapter 1). In such a system, some internal or external stimulus triggers hormone secretion. As hormone levels rise, they cause target organ effects, which then inhibit further hormone release. As a result, blood levels of many hormones vary only within a narrow range.

Endocrine Gland Stimuli

Three major types of stimuli trigger endocrine glands to manufacture and release their hormones: *humoral* (hu′mer-ul), *neural*, and *hormonal* stimuli.

Humoral Stimuli Some endocrine glands secrete their hormones in direct response to changing blood levels of certain critical ions and nutrients. These stimuli are called *humoral stimuli* to distinguish them from hormonal stimuli, which are also bloodborne chemicals. The term *humoral* harks back to the ancient use of the term *humor* to refer to various body fluids (blood, bile, and others).

Humoral stimuli are the simplest endocrine controls. For example, cells of the parathyroid glands monitor the body's crucial blood Ca^{2+} levels. When they detect a decline from normal values, they secrete parathyroid hormone (PTH) **(Figure 16.4a)**. Because PTH acts by several routes to reverse that decline, blood Ca^{2+} levels soon rise, ending the initiative for PTH release. Other hormones released in response to humoral stimuli include insulin, produced by the pancreas, and aldosterone, one of the adrenal cortex hormones.

Neural Stimuli In a few cases, nerve fibers stimulate hormone release. The classic example of neural stimuli is sympathetic nervous system stimulation of the adrenal medulla to release catecholamines (norepinephrine and epinephrine) during periods of stress (Figure 16.4b).

Hormonal Stimuli Finally, many endocrine glands release their hormones in response to hormones produced by other endocrine organs, and the stimuli in these cases are called hormonal stimuli. For example, release of most anterior pituitary hormones is regulated by releasing and inhibiting hormones produced by the hypothalamus, and many anterior pituitary hormones in turn stimulate other endocrine organs to release their hormones (Figure 16.4c). As blood levels of the hormones produced by the final target glands increase, they inhibit the release of anterior pituitary hormones and thus their own release.

This hypothalamic–pituitary–target endocrine organ feedback loop lies at the very core of endocrinology, and it will come up many times in this chapter. Hormonal stimuli promote rhythmic hormone release, with hormone blood levels rising and falling in a specific pattern.

Although these three types of stimuli are typical of most systems that control hormone release, they are by no means all-inclusive or mutually exclusive, and some endocrine organs respond to multiple stimuli.

Nervous System Modulation

The nervous system can modify both "turn-on" factors (hormonal, humoral, and neural stimuli) and "turn-off" factors (feedback inhibition and others) that affect the endocrine system. Without this added safeguard, endocrine system activity would be strictly mechanical, much like a household thermostat. A thermostat can maintain the temperature at or around its set value, but it cannot sense that your grandmother visiting from Florida feels cold at that temperature and reset itself accordingly. *You* must make that adjustment. In your body, it is the nervous system that makes certain adjustments to maintain homeostasis by overriding normal endocrine controls.

For example, the action of insulin and several other hormones normally keeps blood glucose levels in the range of 90–110 mg/100 ml of blood. However, when your body is under severe stress, blood glucose levels rise because the hypothalamus and sympathetic nervous system centers are strongly activated. In this way, the nervous system ensures that body cells have sufficient fuel for the more vigorous activity required during periods of stress.

CHECK YOUR UNDERSTANDING

4. Name the two major chemical classes of hormones. Which class consists entirely of lipid-soluble hormones? Name the only hormone in the other chemical class that is lipid soluble.

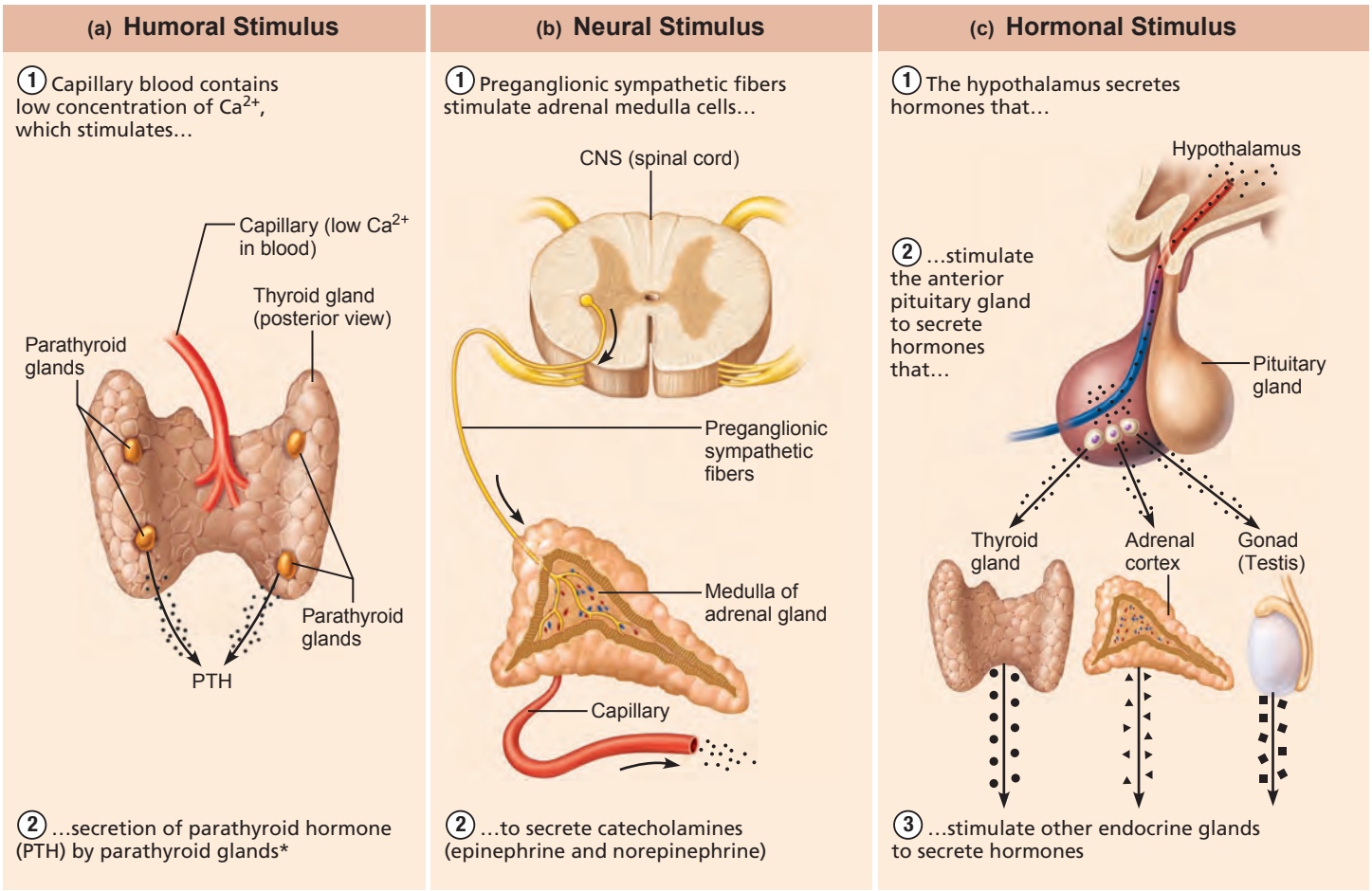

Figure 16.4 Three types of endocrine gland stimuli.
*PTH increases blood Ca^{2+} (see Figure 16.12).

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5. Consider the signaling mechanisms of water-soluble and lipid-soluble hormones. In each case, where are the receptors found and what is the final outcome?
6. What are the three types of stimuli that control hormone release?

For answers, see Appendix G.

The Pituitary Gland and Hypothalamus

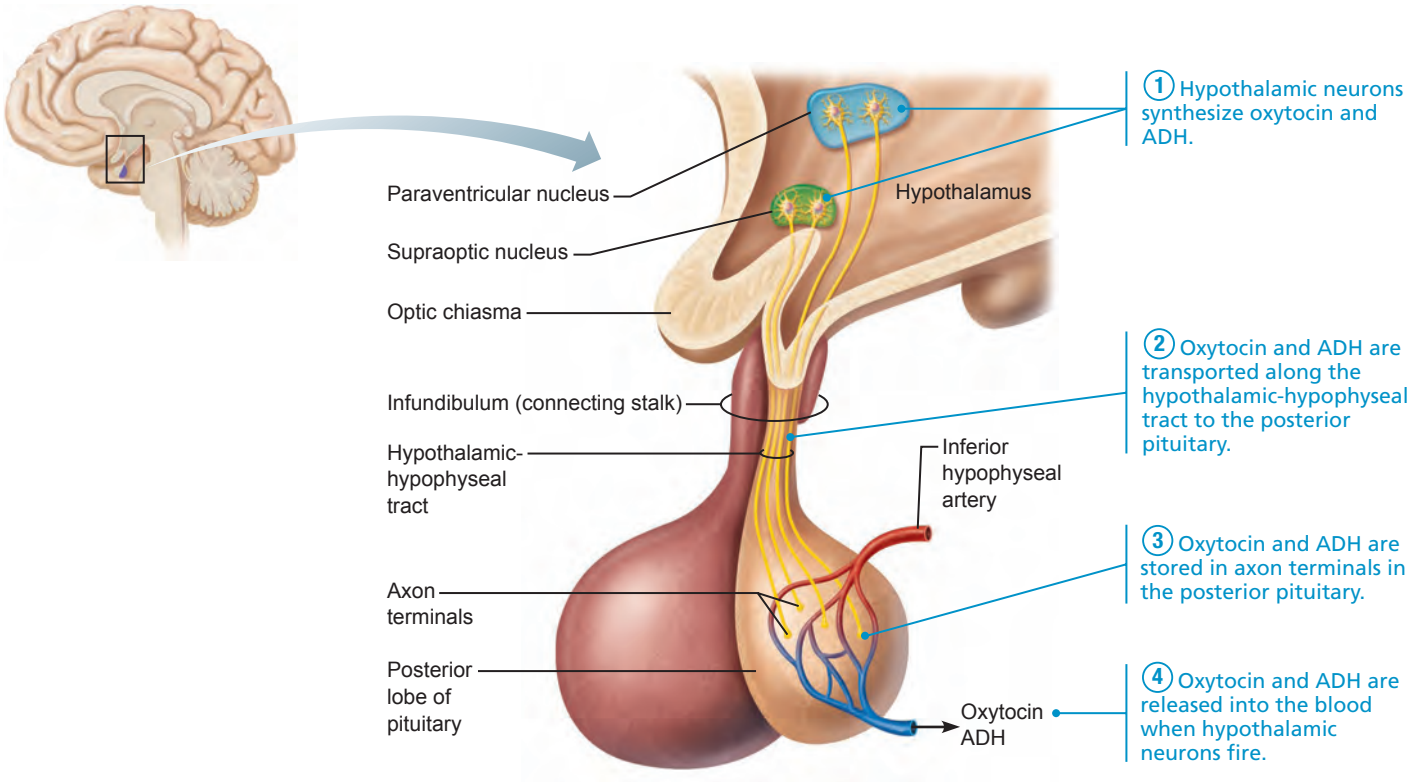
- Describe structural and functional relationships between the hypothalamus and the pituitary gland.
- List and describe the chief effects of anterior pituitary hormones.
- Discuss the structure of the posterior pituitary, and describe the effects of the two hormones it releases.

Securely seated in the sella turcica of the sphenoid bone, the tiny **pituitary gland**, or **hypophysis** (hi-pof′ĭ-sis; "to grow under"), secretes at least nine hormones. Usually said to be the size and shape of a pea, this gland is more accurately described as a pea on a stalk. Its stalk, the funnel-shaped **infundibulum**, connects the gland to the hypothalamus superiorly (Figure 16.5).

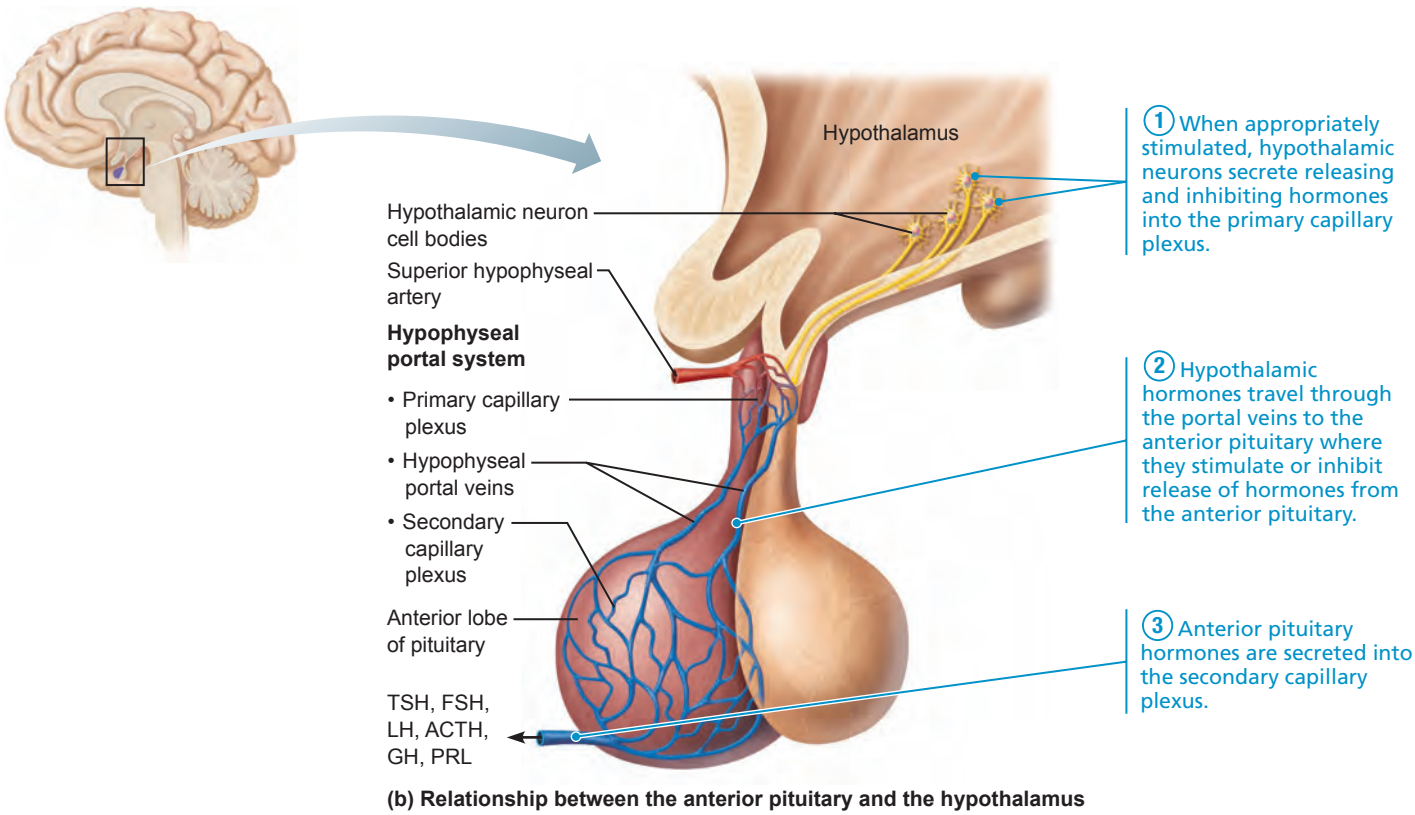
In humans, the pituitary gland has two major lobes. One lobe is neural tissue and the other is glandular. The **posterior pituitary** (lobe) is composed largely of pituicytes (glia-like supporting cells) and nerve fibers (Figure 16.5). It releases **neurohormones** (hormones secreted by neurons) received ready-made from the hypothalamus. Consequently, this lobe is a hormone-storage area and not a true endocrine gland in the precise sense. The posterior lobe plus the infundibulum make up the region called the **neurohypophysis** (nu″ro-hi-pof′ĭ-sis), a term commonly used (incorrectly) to indicate the posterior lobe alone.

The **anterior pituitary** (lobe), or **adenohypophysis** (ad″ĕ-no-hi-pof′ĭ-sis), is composed of glandular tissue (*adeno* = gland). It manufactures and releases a number of hormones (Table 16.1 on pp. 606–607).

Arterial blood is delivered to the pituitary via hypophyseal branches of the internal carotid arteries. The veins leaving the pituitary drain into the dural sinuses.



(a) Relationship between the posterior pituitary and the hypothalamus



(b) Relationship between the anterior pituitary and the hypothalamus

Figure 16.5 Relationships of the pituitary gland and hypothalamus.

Pituitary-Hypothalamic Relationships

The contrasting histology of the two pituitary lobes reflects the dual origin of this tiny gland. The posterior lobe is actually part of the brain. It derives from a downgrowth of hypothalamic tissue and maintains its neural connection with the hypothalamus via a nerve bundle called the **hypothalamic-hypophyseal tract**, which runs through the infundibulum (Figure 16.5). This tract arises from neurons in the **supraoptic** and **paraventricular nuclei** of the hypothalamus. These neurosecretory cells synthesize two neurohormones and transport them along their axons to the posterior pituitary. Oxytocin (ok″sĭ-to′sin) is made primarily by the paraventricular neurons, and antidiuretic hormone (ADH) primarily by the supraoptic neurons. When these hypothalamic neurons fire, they release the stored hormones into a capillary bed in the posterior pituitary for distribution throughout the body.

The glandular anterior lobe originates from a superior outpocketing of the oral mucosa (*Rathke's pouch*) and is formed from epithelial tissue. After touching the posterior lobe, the anterior lobe loses its connection with the oral mucosa and adheres to the neurohypophysis. There is no direct neural connection between the anterior lobe and hypothalamus, but there is a vascular connection. Specifically, the **primary capillary plexus** in the infundibulum communicates inferiorly via the small **hypophyseal portal veins** with a **secondary capillary plexus** in the anterior lobe. The primary and secondary capillary plexuses and the intervening hypophyseal portal veins make up the **hypophyseal portal system** (Figure 16.5). Note that a *portal system* is an unusual arrangement of blood vessels in which a capillary bed feeds into veins, which in turn feed into another capillary bed. Via this portal system, **releasing** and **inhibiting hormones** secreted by neurons in the ventral hypothalamus circulate to the anterior pituitary, where they regulate secretion of its hormones. All these hypothalamic regulatory hormones are amino acid based, but they vary in size from a single amine to peptides to proteins.

Anterior Pituitary Hormones

The anterior pituitary has traditionally been called the "master endocrine gland" because many of the numerous hormones it produces regulate the activity of other endocrine glands. In recent years, however, it has been dethroned by the hypothalamus, which is now known to control the activity of the anterior pituitary.

Researchers have identified six distinct anterior pituitary hormones, all of them proteins (Table 16.1). In addition, a large molecule with the tongue-twisting name **pro-opiomelanocortin (POMC)** (pro″o″pe-o-mah-lan′o-kor″tin) has been isolated from the anterior pituitary. POMC is a *prohormone*, that is, a large precursor molecule that can be split enzymatically into one or more active hormones. POMC is the source of adrenocorticotropic hormone, two natural opiates (an enkephalin and a beta endorphin, described in Chapter 11), and *melanocyte-stimulating hormone* (*MSH*). In amphibians, reptiles, and other animals MSH stimulates melanocytes to increase synthesis of melanin pigment, but this is not an important function of MSH in humans. In humans and other mammals, MSH is a CNS neurotransmitter involved in the control of appetite. Although low levels of MSH are found in plasma, its role in the periphery is not yet well understood.

When the anterior pituitary receives an appropriate chemical stimulus from the hypothalamus, one or more of its hormones are released by certain of its cells. Although many different hormones pass from the hypothalamus to the anterior lobe, each target cell in the anterior lobe distinguishes the messages directed to it and responds in kind—secreting the proper hormone in response to specific releasing hormones, and shutting off hormone release in response to specific inhibiting hormones.

Four of the six anterior pituitary hormones—thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, and luteinizing hormone—are **tropins** or **tropic hormones** (*tropi* = turn on, change), which are hormones that regulate the secretory action of other endocrine glands. All anterior pituitary hormones except for growth hormone affect their target cells via a cyclic AMP second-messenger system.

Growth Hormone

Growth hormone (**GH**; *somatotropin*) is produced by cells called **somatotrophs** of the anterior lobe and has both growth-promoting and metabolic actions, summarized in Figure 16.6. Although GH stimulates most body cells to increase in size and divide, its major targets are the bones and skeletal muscles. Stimulation of the epiphyseal plate leads to long bone growth, and stimulation of skeletal muscles promotes increased muscle mass.

Essentially an anabolic (tissue-building) hormone, GH promotes protein synthesis, and it encourages the use of fats for fuel, thus conserving glucose. Most growth-promoting effects of GH are mediated indirectly by **insulin-like growth factors (IGFs)**, a family of growth-promoting proteins produced by the liver, skeletal muscle, bone, and other tissues. IGFs produced by the liver act as hormones, while IGFs produced in other tissues act locally within those tissues (as paracrines). Specifically, IGFs stimulate actions required for growth: (1) uptake of nutrients from the blood and their incorporation into proteins and DNA, allowing growth by cell division; and (2) formation of collagen and deposition of bone matrix.

Acting directly, GH exerts metabolic effects. It mobilizes fats from fat depots for transport to cells, increasing blood levels of fatty acids. It also decreases the rate of glucose uptake and metabolism. In the liver, it encourages glycogen breakdown and release of glucose to the blood. The elevation in blood glucose levels that occurs as a result of this *glucose sparing* is called the *anti-insulin effect* of GH, because its effects are opposite to those of insulin.

Secretion of GH is regulated chiefly by two hypothalamic hormones with antagonistic effects. **Growth hormone–releasing hormone (GHRH)** stimulates GH release, while **growth hormone–inhibiting hormone (GHIH)**, also called **somatostatin** (so″mah-to-stat′in), inhibits it. GHIH release is (presumably) triggered by the feedback of GH and IGFs. Rising levels of GH also feed back to inhibit its own release. As indicated in Table 16.1, a number of secondary triggers also influence GH release. Typically, GH secretion has a daily cycle, with the highest

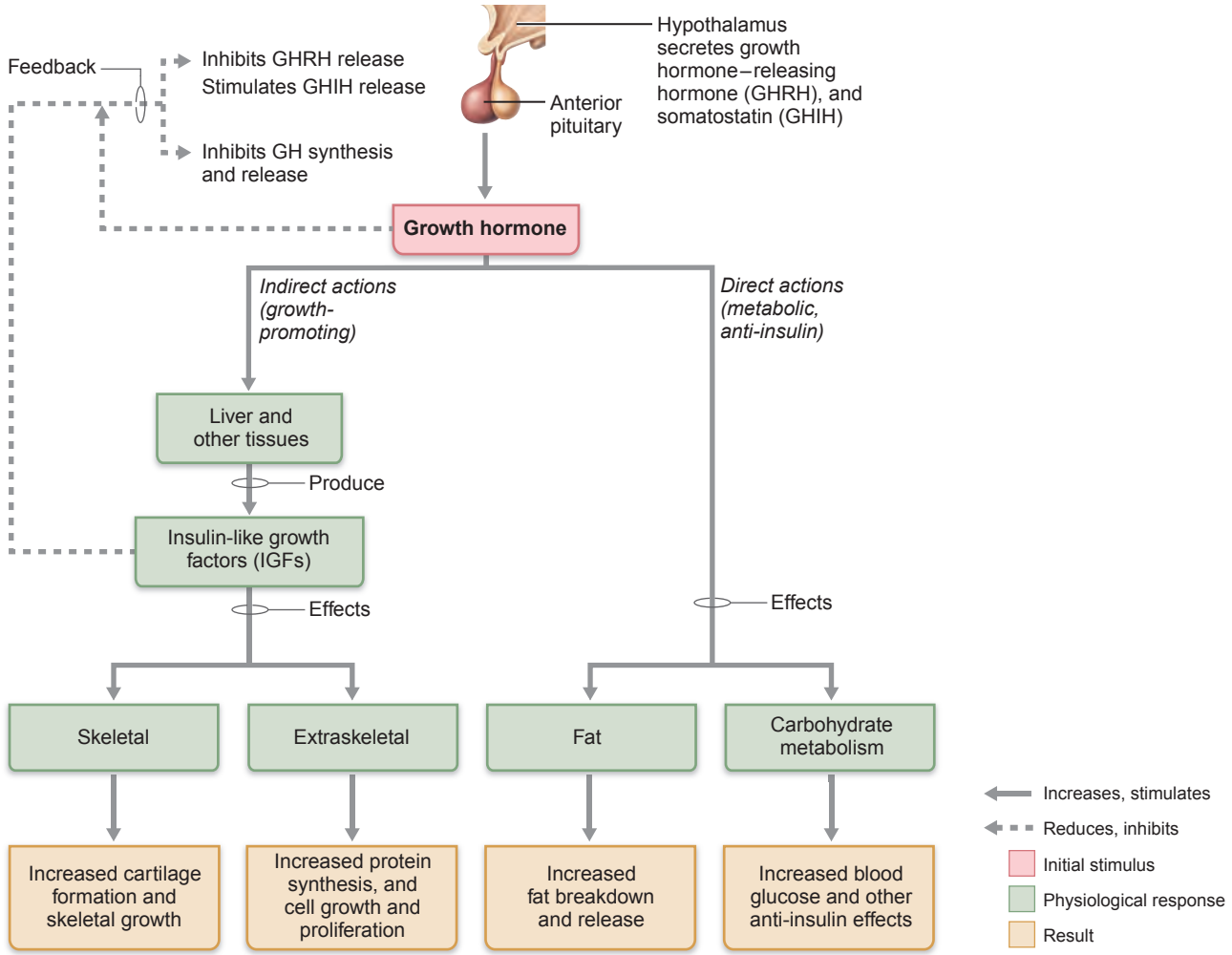


Figure 16.6 **Growth-promoting and metabolic actions of growth hormone (GH).**

levels occurring during evening sleep. The total amount secreted daily peaks during adolescence and then declines with age.

Besides inhibiting growth hormone secretion, GHIH blocks the release of thyroid-stimulating hormone. GHIH is also produced in various locations in the gut, where it inhibits the release of virtually all gastrointestinal and pancreatic secretions—both endocrine and exocrine.

HOMEOSTATIC IMBALANCE

Both hypersecretion and hyposecretion of GH may result in structural abnormalities. Hypersecretion in children results in **gigantism** because GH targets the still-active epiphyseal (growth) plates. The person becomes abnormally tall, often reaching a height of 2.4 m (8 feet), but has relatively normal body proportions. If excessive amounts of GH are secreted after the epiphyseal plates have closed, **acromegaly** (ak″ro-meg′ah-le) results. Literally translated as "enlarged extremities," this condition is characterized by overgrowth of bony areas still responsive to GH, namely bones of the hands, feet, and face. Hypersecretion usually results from an anterior pituitary tumor that churns out excessive amounts of GH. The usual treatment is surgical removal of the tumor, but this surgery does not reverse anatomical changes that have already occurred.

Hyposecretion of GH in adults usually causes no problems. GH deficiency in children results in slowed long bone growth, a condition called **pituitary dwarfism**. Such individuals attain a maximum height of 1.2 m (4 feet), but usually have fairly normal body proportions. Lack of GH is often accompanied by deficiencies of other anterior pituitary hormones, and if thyroid-stimulating hormone and gonadotropins are lacking, the individual will be malproportioned and will fail to mature sexually as well. Fortunately, human GH is produced commercially by genetic engineering techniques. When pituitary dwarfism is diagnosed before puberty, growth hormone replacement therapy can promote nearly normal somatic growth.

The availability of synthetic GH also has a downside. Athletes and the elderly have been tempted to use GH for its bodybuilding properties, and some parents have used GH in an attempt to give their children additional height. However, while muscle mass increases, there is no objective evidence for an increase in muscle strength in either athletes or the elderly, and only minimal increases in stature occur in normal children. Moreover,

taking GH can lead to fluid retention, joint and muscle pain, diabetes, and may promote cancer. ■

Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (**TSH**), or **thyrotropin**, is a tropic hormone that stimulates normal development and secretory activity of the thyroid gland. Its release follows the hypothalamic–pituitary–target endocrine organ feedback loop described earlier and shown in Figure 16.7. TSH release from cells of the anterior pituitary called **thyrotrophs** is triggered by the hypothalamic peptide **thyrotropin-releasing hormone** (**TRH**). Rising blood levels of thyroid hormones act on both the pituitary and the hypothalamus to inhibit TSH secretion.

Adrenocorticotropic Hormone

Adrenocorticotropic hormone (**ACTH**) (ah-dre″no-kor″tĭ-kotrōp′ik), or **corticotropin**, is secreted by the **corticotrophs** of the anterior pituitary. ACTH stimulates the adrenal cortex to release corticosteroid hormones, most importantly glucocorticoids that help the body to resist stressors. ACTH release, elicited by hypothalamic **corticotropin-releasing hormone** (**CRH**), has a daily rhythm, with levels peaking in the morning, shortly before awakening. Rising levels of glucocorticoids feed back and block secretion of CRH and ACTH release. Internal and external factors that alter the normal ACTH rhythm by triggering CRH release include fever, hypoglycemia, and stressors of all types.

Gonadotropins

Follicle-stimulating hormone (**FSH**) and **luteinizing hormone** (**LH**) (lu′te-in-īz″ing) are referred to collectively as **gonadotropins**. They regulate the function of the gonads (ovaries and testes). In both sexes, FSH stimulates gamete (sperm or egg) production and LH promotes production of gonadal hormones. In females, LH works with FSH to cause an egg-containing ovarian follicle to mature. LH then independently triggers ovulation and promotes synthesis and release of ovarian hormones. In males, LH stimulates the interstitial cells of the testes to produce the male hormone testosterone.

Gonadotropins are virtually absent from the blood of prepubertal boys and girls. During puberty, the **gonadotrophs** of the anterior pituitary are activated and gonadotropin levels begin to rise, causing the gonads to mature. In both sexes, gonadotropin release by the anterior pituitary is prompted by **gonadotropin-releasing hormone** (**GnRH**) produced by the hypothalamus. Gonadal hormones, produced in response to the gonadotropins, feed back to suppress FSH and LH release.

Prolactin

Prolactin (**PRL**) is a protein hormone structurally similar to GH. Produced by the **lactotrophs**, PRL stimulates the gonads of some animals (other than humans) and is considered a gonadotropin by some researchers. Its only well-documented effect in humans is to stimulate milk production by the breasts (*pro* = for; *lact* = milk). The role of prolactin in males is not well understood.

Unlike the other anterior pituitary hormones, PRL release is controlled primarily by an inhibitory hormone, **prolactin-inhibiting hormone** (**PIH**), now known to be *dopamine* (*DA*), which prevents prolactin secretion. Decreased PIH secretion leads to a surge in PRL release. There are a number of *prolactin-releasing factors*, including TRH, but their exact roles are not well understood.

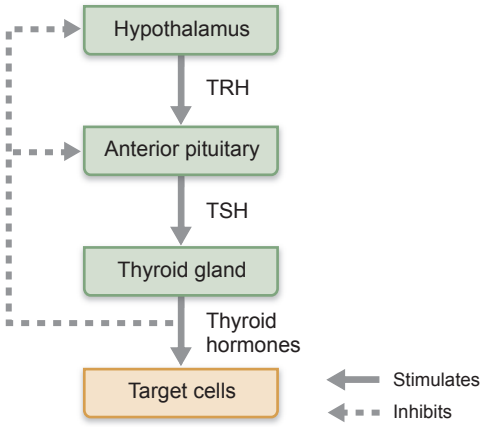


Figure 16.7 Regulation of thyroid hormone secretion. TRH = thyrotropin-releasing hormone, TSH = thyroid-stimulating hormone.

In females, prolactin levels rise and fall in rhythm with estrogen blood levels. Estrogen stimulates prolactin release, both directly and indirectly. A brief rise in prolactin levels just before the menstrual period partially accounts for the breast swelling and tenderness some women experience at that time, but because this PRL stimulation is so brief, the breasts do not produce milk. In pregnant women, PRL blood levels rise dramatically toward the end of pregnancy, and milk production becomes possible. After birth, the infant's suckling stimulates release of prolactin-releasing factors in the mother, encouraging continued milk production and availability.

HOMEOSTATIC IMBALANCE

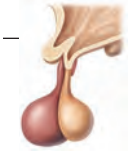
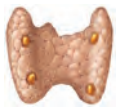
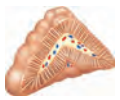
Hypersecretion of prolactin is more common than hyposecretion (which is not a problem in anyone except women who choose to nurse). In fact, hyperprolactinemia is the most frequent abnormality of anterior pituitary tumors. Clinical signs include inappropriate lactation, lack of menses, infertility in females, and impotence in males. ■

The Posterior Pituitary and Hypothalamic Hormones

The posterior pituitary, made largely of the axons of hypothalamic neurons, stores antidiuretic hormone (ADH) and oxytocin that have been synthesized and forwarded by hypothalamic neurons of the supraoptic and paraventricular nuclei. These hormones are later released "on demand" in response to nerve impulses from the same hypothalamic neurons.

ADH and oxytocin, each composed of nine amino acids, are almost identical. They differ in only two amino acids, and yet they have dramatically different physiological effects, summarized in Table 16.1. ADH influences body water balance, and

TABLE 16.1 Pituitary Hormones: Summary of Regulation and Effects

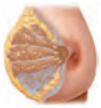
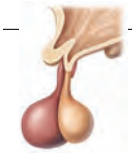
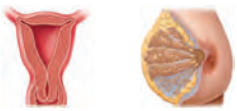
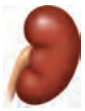
HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
 **Anterior Pituitary Hormones**			
Growth hormone (GH) (Protein, somatotroph)	**Stimulated** by GHRH* release, which is triggered by low blood levels of GH as well as by a number of secondary triggers including hypoglycemia, increases in blood levels of amino acids, low levels of fatty acids, exercise, other types of stressors, and estrogens **Inhibited** by feedback inhibition exerted by GH and IGFs, and by hyperglycemia, hyperlipidemia, obesity, and emotional deprivation via either increased GHIH* (somatostatin) or decreased GHRH* release	 Liver, muscle, bone, cartilage, and other tissues: anabolic hormone; stimulates somatic growth; mobilizes fats; spares glucose Growth-promoting effects mediated indirectly by IGFs	↓ Pituitary dwarfism in children ↑ Gigantism in children; acromegaly in adults
Thyroid-stimulating hormone (TSH) (Glycoprotein, thyrotroph)	**Stimulated** by TRH* and indirectly by pregnancy and (in infants) cold temperature **Inhibited** by feedback inhibition exerted by thyroid hormones on anterior pituitary and hypothalamus and by GHIH*	 Thyroid gland: stimulates thyroid gland to release thyroid hormones	↓ Cretinism in children; myxedema in adults ↑ Hyperthyroidism; effects similar to those of Graves' disease, in which antibodies mimic TSH
Adrenocorticotropic hormone (ACTH) (Polypeptide of 39 amino acids, corticotroph)	**Stimulated** by CRH;* stimuli that increase CRH release include fever, hypoglycemia, and other stressors **Inhibited** by feedback inhibition exerted by glucocorticoids	 Adrenal cortex: promotes release of glucocorticoids and androgens (mineralocorticoids to a lesser extent)	↓ Rare ↑ Cushing's disease
Follicle-stimulating hormone (FSH) (Glycoprotein, gonadotroph)	**Stimulated** by GnRH* **Inhibited** by feedback inhibition exerted by inhibin, and estrogen in females and testosterone in males	 Ovaries and testes: in females, stimulates ovarian follicle maturation and estrogen production; in males, stimulates sperm production	↓ Failure of sexual maturation ↑ No important effects

oxytocin stimulates contraction of smooth muscle, particularly that of the uterus and breasts.

Oxytocin

A strong stimulant of uterine contraction, **oxytocin** is released in significantly higher amounts during childbirth (*oxy* = rapid; *tocia* = childbirth) and in nursing women. The number of oxytocin receptors in the uterus peaks near the end of pregnancy, and uterine smooth muscle becomes more and more sensitive to the hormone's stimulatory effects. Stretching of the uterus and cervix as birth nears dispatches afferent impulses to the hypothalamus, which responds by synthesizing oxytocin and triggering its release from the posterior pituitary. Oxytocin acts via the PIP_2-Ca^{2+} second-messenger system to mobilize Ca^{2+}, allowing stronger contractions. As blood levels of oxytocin rise, the expulsive contractions of labor gain momentum and finally end in birth.

TABLE 16.1 *(continued)*

HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
Luteinizing hormone (LH) (Glycoprotein, gonadotroph)	**Stimulated** by GnRH* **Inhibited** by feedback inhibition exerted by estrogen and progesterone in females and testosterone in males	 Ovaries and testes: in females, triggers ovulation and stimulates ovarian production of estrogen and progesterone; in males, promotes testosterone production	As for FSH
Prolactin (PRL) (Protein, lactotroph)	**Stimulated** by decreased PIH*; release enhanced by estrogens, birth control pills, breast-feeding, and dopamine-blocking drugs **Inhibited** by PIH* (dopamine)	 Breast secretory tissue: promotes lactation	↓ Poor milk production in nursing women ↑ Inappropriate milk production (galactorrhea); cessation of menses in females; impotence in males
 **Posterior Pituitary Hormones (Made by Hypothalamic Neurons and Stored in Posterior Pituitary)**			
Oxytocin (Peptide mostly from neurons in paraventricular nucleus of hypothalamus)	**Stimulated** by impulses from hypothalamic neurons in response to cervical/uterine stretching and suckling of infant at breast **Inhibited** by lack of appropriate neural stimuli	 Uterus: stimulates uterine contractions; initiates labor; breast: initiates milk ejection	Unknown
Antidiuretic hormone (ADH) or **vasopressin** (Peptide, mostly from neurons in supraoptic nucleus of hypothalamus)	**Stimulated** by impulses from hypothalamic neurons in response to increased osmolality of blood or decreased blood volume; also stimulated by pain, some drugs, low blood pressure **Inhibited** by adequate hydration of the body and by alcohol	 Kidneys: stimulates kidney tubule cells to reabsorb water	↓ Diabetes insipidus ↑ Syndrome of inappropriate ADH secretion (SIADH)

*Indicates hypothalamic releasing and inhibiting hormones: GHRH = growth hormone–releasing hormone; GHIH = growth hormone–inhibiting hormone; TRH = thyrotropin-releasing hormone; CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; PIH = prolactin-inhibiting hormone

Oxytocin also acts as the hormonal trigger for milk ejection (the "letdown" reflex) in women whose breasts are producing milk in response to prolactin. Suckling causes a reflex-initiated release of oxytocin, which targets specialized myoepithelial cells surrounding the milk-producing glands. As these cells contract, milk is forced from the breast into the infant's mouth. Both childbirth and milk ejection result from *positive feedback mechanisms* and are described in more detail in Chapter 28.

Both natural and synthetic oxytocic drugs are used to induce labor or to hasten normal labor that is progressing slowly. Less frequently, oxytocic drugs are used to stop postpartum bleeding

(by compressing ruptured blood vessels at the placental site) and to stimulate the milk ejection reflex.

Until recently, oxytocin's role in males and nonpregnant, nonlactating females was unknown, but studies reveal that this potent peptide plays a role in sexual arousal and orgasm when the body is already primed for reproduction by sex hormones. Then, it may be responsible for the feeling of sexual satisfaction that results from that interaction. In nonsexual relationships, it is thought to promote nurturing and affectionate behavior, that is, it acts as a "cuddle hormone."

Antidiuretic Hormone

Diuresis (di″u-re′sis) is urine production, so an *antidiuretic* is a substance that inhibits or prevents urine formation. **Antidiuretic hormone (ADH)** prevents wide swings in water balance, helping the body avoid dehydration and water overload. Hypothalamic neurons called *osmoreceptors* continually monitor the solute concentration (and thus the water concentration) of the blood. When solutes threaten to become too concentrated (as might follow excessive perspiration or inadequate fluid intake), the osmoreceptors transmit excitatory impulses to the hypothalamic neurons, which synthesize and release ADH. Liberated into the blood by the posterior pituitary, ADH targets the kidney tubules via cAMP. The tubule cells respond by reabsorbing more water from the forming urine and returning it to the bloodstream. As a result, less urine is produced and blood solute concentration decreases. As the solute concentration of the blood declines, the osmoreceptors stop depolarizing, effectively ending ADH release. Other stimuli triggering ADH release include pain, low blood pressure, and such drugs as nicotine, morphine, and barbiturates.

Drinking alcoholic beverages inhibits ADH secretion and causes copious urine output. The dry mouth and intense thirst of the "hangover" reflect this dehydrating effect of alcohol. As might be expected, ADH release is also inhibited by drinking excessive amounts of water. *Diuretic drugs* antagonize the effects of ADH and cause water to be flushed from the body. These drugs are used to manage some cases of hypertension and the edema (water retention in tissues) typical of congestive heart failure.

At high blood concentrations, ADH causes vasoconstriction, primarily of the visceral blood vessels. This response targets different ADH receptors found on vascular smooth muscle. Under certain conditions, such as severe blood loss, exceptionally large amounts of ADH are released, causing a rise in blood pressure. The alternative name for this hormone, **vasopressin**, reflects this particular effect.

HOMEOSTATIC IMBALANCE

One result of ADH deficiency is **diabetes insipidus**, a syndrome marked by the output of huge amounts of urine and intense thirst. The name of this condition (*diabetes* = overflow; *insipidus* = tasteless) distinguishes it from diabetes mellitus (*mel* = honey), in which insulin deficiency causes large amounts of blood glucose to be lost in the urine. At one time, urine was tasted to determine which type of diabetes the patient was suffering from.

Diabetes insipidus can be caused by a blow to the head that damages the hypothalamus or the posterior pituitary. In either case, ADH release is deficient. Though inconvenient, the condition is not serious when the thirst center is operating properly and the person drinks enough water to prevent dehydration. However, it can be life threatening in unconscious or comatose patients, so accident victims with head trauma must be carefully monitored.

Hypersecretion of ADH occurs in children with meningitis, may follow neurosurgery or hypothalamic injury, or results from ectopic ADH secretion by cancer cells (particularly pulmonary cancers). It also may occur after general anesthesia or administration of certain drugs. The resulting condition, *syndrome of inappropriate ADH secretion* (*SIADH*), is marked by retention of fluid, headache and disorientation due to brain edema, weight gain, and decreased solute concentration in the blood. SIADH management requires fluid restriction and careful monitoring of blood sodium levels. ■

CHECK YOUR UNDERSTANDING

7. What is the key difference between the way the hypothalamus communicates with the anterior pituitary and the way it communicates with the posterior pituitary?
8. List the four anterior pituitary hormones that are tropic hormones and name their target glands.
9. Anita drank too much alcohol one night and suffered from a headache and nausea the next morning. What caused these "hangover" effects?

For answers, see Appendix G.

The Thyroid Gland

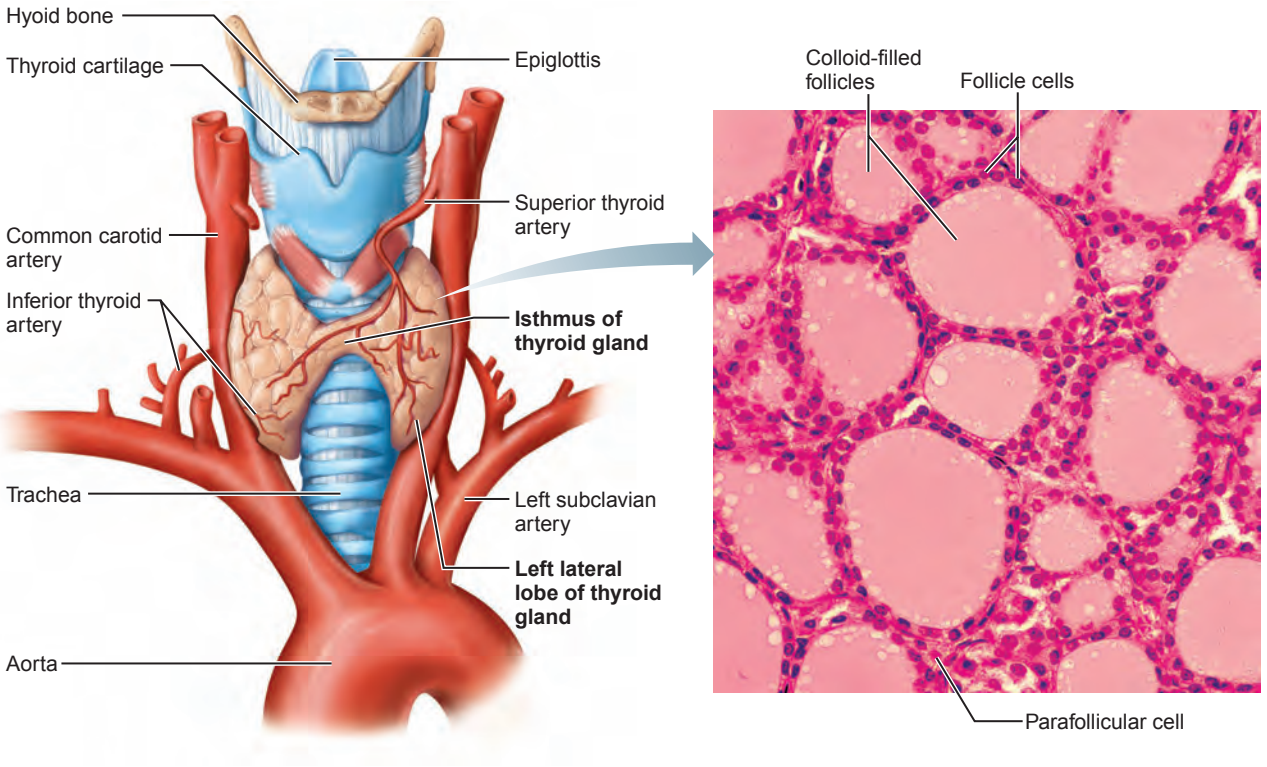
- Describe important effects of the two groups of hormones produced by the thyroid gland.
- Follow the process of thyroxine formation and release.

Location and Structure

The butterfly-shaped **thyroid gland** is located in the anterior neck, on the trachea just inferior to the larynx (Figure 16.1 and Figure 16.8a). Its two lateral *lobes* are connected by a median tissue mass called the *isthmus*. The thyroid gland is the largest pure endocrine gland in the body. Its prodigious blood supply (from the *superior* and *inferior thyroid arteries*) makes thyroid surgery a painstaking (and bloody) endeavor.

Internally, the gland is composed of hollow, spherical **follicles** (Figure 16.8b). The walls of each follicle are formed largely by cuboidal or squamous epithelial cells called *follicle cells*, which produce the glycoprotein **thyroglobulin** (thi″roglob′u-lin). The central cavity, or lumen, of the follicle stores **colloid**, an amber-colored, sticky material consisting of thyroglobulin molecules with attached iodine atoms. *Thyroid hormone* is derived from this iodinated thyroglobulin.

The *parafollicular cells*, another population of endocrine cells in the thyroid gland, produce *calcitonin*, an entirely different hormone. The parafollicular cells lie in the follicular epithelium but protrude into the soft connective tissue that separates and surrounds the thyroid follicles.



(a) Gross anatomy of the thyroid gland, anterior view

(b) Photomicrograph of thyroid gland follicles (125×)

Figure 16.8 The thyroid gland.

Thyroid Hormone

Often referred to as the body's major metabolic hormone, **thyroid hormone** (**TH**) is actually two iodine-containing amine hormones, **thyroxine** (thi-rok′sin), or **T_4**, and **triiodothyronine** (tri″i-o″do-thi′ro-nēn), or **T_3**. T_4 is the major hormone secreted by the thyroid follicles. Most T_3 is formed at the target tissues by conversion of T_4 to T_3. Very much like one another, these hormones are constructed from two linked tyrosine amino acids. The principal difference is that T_4 has four bound iodine atoms, and T_3 has three (thus, T_4 and T_3).

TH affects virtually every cell in the body, as summarized in Table 16.2 (p. 612). Like steroids, TH enters a target cell, binds to intracellular receptors within the cell's nucleus, and initiates transcription of mRNA for protein synthesis. By turning on transcription of genes concerned with glucose oxidation, TH increases basal metabolic rate and body heat production. This effect is known as the hormone's **calorigenic effect** (*calorigenic* = heat producing). Because TH provokes an increase in the number of adrenergic receptors in blood vessels, it plays an important role in maintaining blood pressure. Additionally, it is important in regulating tissue growth and development. It is critical for normal skeletal and nervous system development and maturation and for reproductive capabilities.

Synthesis

The thyroid gland is unique among the endocrine glands in its ability to store its hormone extracellularly and in large quantities. In the normal thyroid gland, the amount of stored colloid remains relatively constant and is sufficient to provide normal levels of hormone release for two to three months.

When TSH from the anterior pituitary binds to receptors on follicle cells, their *first* response is to secrete stored thyroid hormone. Their *second* response is to begin synthesizing more colloid to "restock" the follicle lumen. As a general rule, TSH levels are lower during the day, peak just before sleep, and remain high during the night. Consequently, thyroid hormone release and synthesis follows a similar pattern.

Let's examine how follicle cells synthesize thyroid hormone. The following numbers correspond to steps 1–7 in Figure 16.9:

1. **Thyroglobulin is synthesized and discharged into the follicle lumen.** After being synthesized on the ribosomes of the thyroid's follicle cells, thyroglobulin is transported to the Golgi apparatus, where sugar molecules are attached and the thyroglobulin is packed into transport vesicles. These vesicles move to the apex of the follicle cell, where they discharge their contents into the follicle lumen to become part of the stored colloid.
2. **Iodide is trapped.** To produce the functional iodinated hormones, the follicle cells must accumulate iodides (anions of iodine, I^-) from the blood. Iodide trapping depends on active transport. (The intracellular concentration of I^- is over 30 times higher than that in blood.) Once trapped inside the follicle cell, iodide then moves into the follicle lumen by facilitated diffusion.

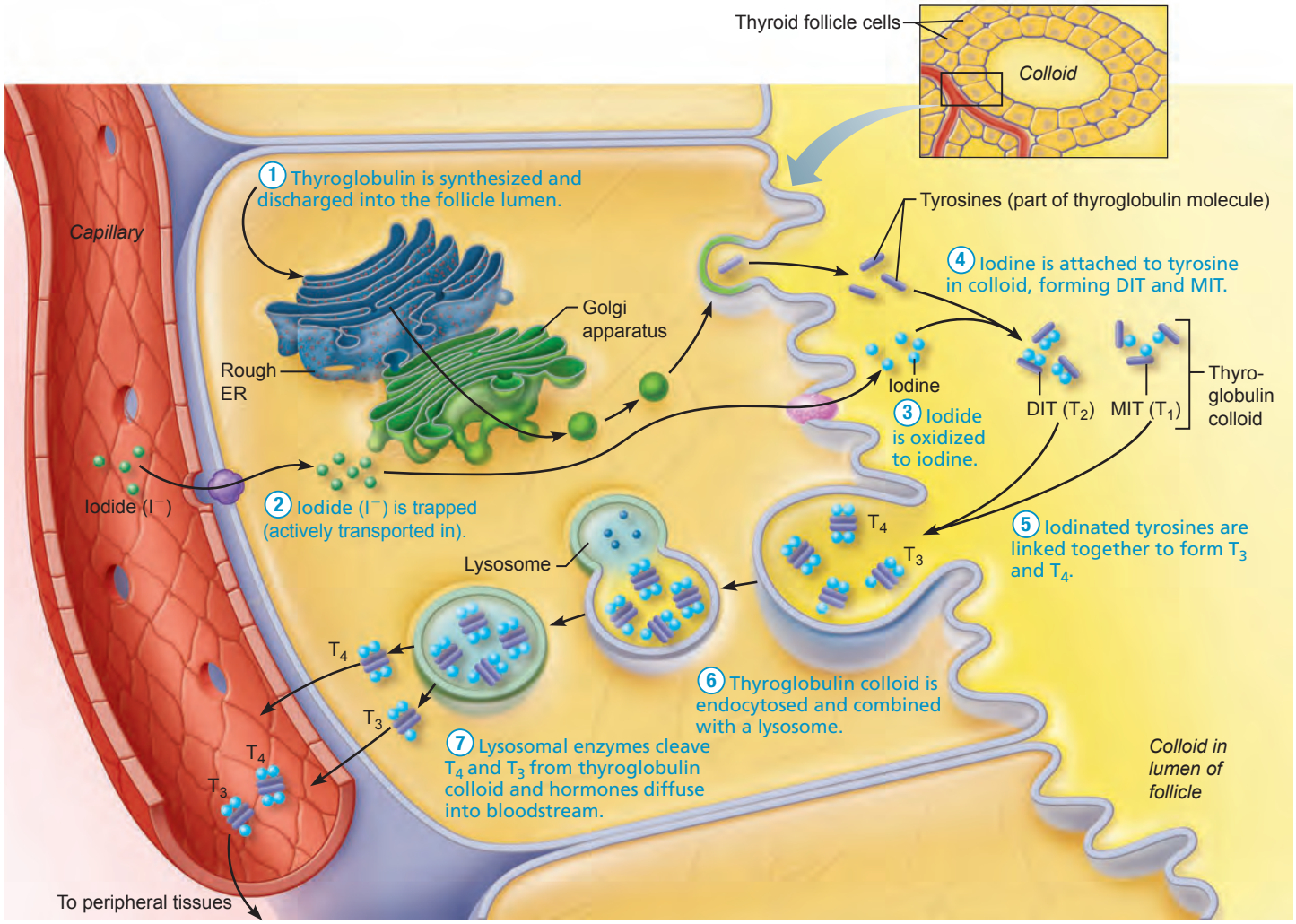


Figure 16.9 Synthesis of thyroid hormone. Only a few tyrosines of the thyroglobulins in the colloid are illustrated. The colloid is represented by the unstructured yellow substance outside of the cells.

16

③ **Iodide is oxidized to iodine.** At the border of the follicle cell and colloid, iodides are oxidized (by removal of electrons) and converted to iodine (I_2).

④ **Iodine is attached to tyrosine.** Once formed, iodine is attached to tyrosine amino acids that form part of the thyroglobulin colloid. This iodination reaction occurs at the junction of the follicle cell apex and the colloid and is mediated by peroxidase enzymes. Attachment of one iodine to a tyrosine produces **monoiodotyrosine (MIT** or **T_1)**, and attachment of two iodines produces **diiodotyrosine (DIT** or **T_2)**.

⑤ **Iodinated tyrosines are linked together to form T_3 and T_4.** Enzymes in the colloid link MIT and DIT together. Two linked DITs result in T_4, and coupling of MIT and DIT produces T_3. At this point, the hormones are still part of the thyroglobulin colloid.

⑥ **Thyroglobulin colloid is endocytosed.** In order to secrete the hormones, the follicle cells must reclaim iodinated thyroglobulin by endocytosis and combine the vesicles with lysosomes.

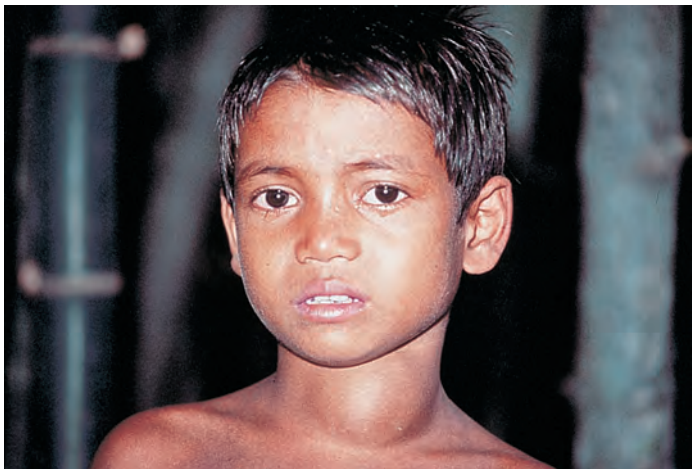
⑦ **Lysosomal enzymes cleave T_4 and T_3 from thyroglobulin and the hormones diffuse from the follicle cell into the bloodstream.** The main hormonal product secreted is T_4. Some T_4 is converted to T_3 before secretion, but most T_3 is generated in the peripheral tissues.

Transport and Regulation

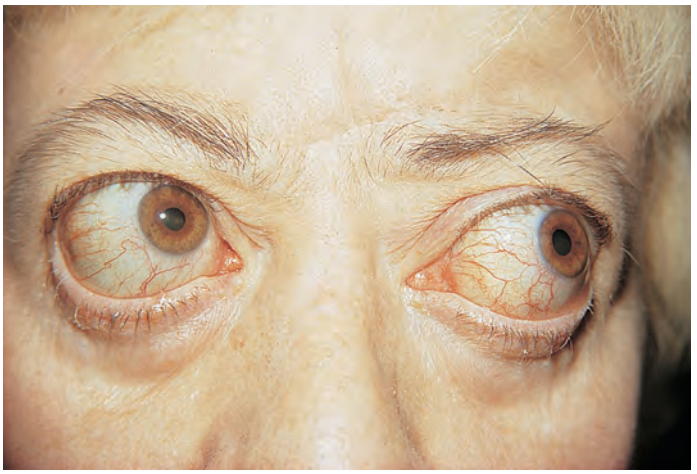
Most released T_4 and T_3 immediately binds to transport proteins, most importantly *thyroxine-binding globulins* (*TBGs*) produced by the liver. Both T_4 and T_3 bind to target tissue receptors, but T_3 binds much more avidly and is about 10 times more active. Most peripheral tissues have the enzymes needed to convert T_4 to T_3 by removing one iodine atom.

The negative feedback loop that regulates blood levels of TH is shown in Figure 16.7. Falling TH blood levels trigger release of *thyroid-stimulating hormone* (*TSH*), and ultimately of more TH. Rising TH levels feed back to inhibit the hypothalamic–anterior pituitary axis, temporarily shutting off the stimulus for TSH release.

Conditions that increase body energy requirements, such as pregnancy and exposure of infants to cold, stimulate the hypothalamus to secrete *thyrotropin-releasing hormone* (*TRH*),



(a)



(b)

Figure 16.10 Thyroid disorders. (a) An enlarged thyroid (goiter) of a Bangladeshi boy. **(b)** Exophthalmos of Graves' disease.

which triggers TSH release, and in such instances, TRH overcomes the negative feedback controls. The thyroid gland then releases larger amounts of thyroid hormones, enhancing body metabolism and heat production.

Factors that inhibit TSH release include GHIH, dopamine, and rising levels of glucocorticoids. Excessively high blood iodide concentrations also inhibit TH release.

HOMEOSTATIC IMBALANCE

Both overactivity and underactivity of the thyroid gland can cause severe metabolic disturbances. Hypothyroid disorders may result from some thyroid gland defect or secondarily from inadequate TSH or TRH release. They also occur when the thyroid gland is removed surgically and when dietary iodine is inadequate.

In adults, the full-blown hypothyroid syndrome is called **myxedema** (mik″sĕ-de′mah; "mucous swelling"). Symptoms include a low metabolic rate; feeling chilled; constipation; thick, dry skin and puffy eyes; edema; lethargy; and mental sluggishness (but not mental retardation). If myxedema results from lack of iodine, the thyroid gland enlarges and protrudes, a condition called **endemic** (en-dem′ik), or *colloidal*, **goiter** (Figure 16.10a). The follicle cells produce colloid but cannot iodinate it and make functional hormones. The pituitary gland secretes increasing amounts of TSH in a futile attempt to stimulate the thyroid to produce TH, but the only result is that the follicles accumulate more and more *unusable* colloid. Untreated, the thyroid cells eventually "burn out" from frantic activity, and the gland atrophies.

Before the marketing of iodized salt, parts of the midwestern United States were called the "goiter belt." Goiters were common there because these areas had iodine-poor soil and no access to iodine-rich seafood. Depending on the cause, myxedema can be reversed by iodine supplements or hormone replacement therapy.

Like many other hormones, the important effects of TH depend on a person's age and development. Severe hypothyroidism in infants is called **cretinism** (kre′tĭ-nizm). The child is mentally retarded and has a short, disproportionately sized body and a thick tongue and neck. Cretinism may reflect a genetic deficiency of the fetal thyroid gland or maternal factors, such as lack of dietary iodine. It is preventable by thyroid hormone replacement therapy if diagnosed early enough, but developmental abnormalities and mental retardation are not reversible once they appear.

The most common hyperthyroid pathology is an autoimmune disease called **Graves' disease**. In this condition, a person makes abnormal antibodies directed against thyroid follicle cells. Rather than destroying these cells, as antibodies normally do, these antibodies paradoxically mimic TSH and continuously stimulate TH release. Typical symptoms include an elevated metabolic rate; sweating; rapid, irregular heartbeat; nervousness; and weight loss despite adequate food intake. *Exophthalmos*, protrusion of the eyeballs, may occur if the tissue behind the eyes becomes edematous and then fibrous (Figure 16.10b). Treatments include surgical removal of the thyroid gland or ingestion of radioactive iodine (^{131}I), which selectively destroys the most active thyroid cells. ■

Calcitonin

Calcitonin is a polypeptide hormone produced by the **parafollicular**, or **C**, **cells** of the thyroid gland. Its effect is to lower blood Ca^{2+} levels, antagonizing the effects of parathyroid hormone produced by the parathyroid glands, which we consider in the next section. Calcitonin targets the skeleton, where it (1) inhibits osteoclast activity, inhibiting bone resorption and release of Ca^{2+} from the bony matrix, and (2) stimulates Ca^{2+} uptake and incorporation into bone matrix. As a result, calcitonin has a bone-sparing effect.

Excessive blood levels of Ca^{2+} (approximately 20% above normal) act as a humoral stimulus for calcitonin release, whereas declining blood Ca^{2+} levels inhibit C cell secretory activity. Calcitonin regulation of blood Ca^{2+} levels is short-lived but extremely rapid.

Calcitonin does not appear to play an important role in calcium homeostasis in humans. For example, calcitonin does not need to be replaced in patients whose thyroid gland has been

TABLE 16.2 Major Effects of Thyroid Hormone (T_4 and T_3) in the Body

PROCESS OR SYSTEM AFFECTED	NORMAL PHYSIOLOGICAL EFFECTS	EFFECTS OF HYPOSECRETION	EFFECTS OF HYPERSECRETION
Basal metabolic rate (BMR)/ temperature regulation	Promotes normal oxygen use and BMR; calorigenesis; enhances effects of sympathetic nervous system	BMR below normal; decreased body temperature and cold intolerance; decreased appetite; weight gain; reduced sensitivity to catecholamines	BMR above normal; increased body temperature and heat intolerance; increased appetite; weight loss
Carbohydrate/lipid/protein metabolism	Promotes glucose catabolism; mobilizes fats; essential for protein synthesis; enhances liver's synthesis of cholesterol	Decreased glucose metabolism; elevated cholesterol/triglyceride levels in blood; decreased protein synthesis; edema	Enhanced catabolism of glucose, proteins, and fats; weight loss; loss of muscle mass
Nervous system	Promotes normal development of nervous system in fetus and infant; promotes normal adult nervous system function	In infant, slowed/deficient brain development, retardation; in adult, mental dulling, depression, paresthesias, memory impairment, hypoactive reflexes	Irritability, restlessness, insomnia, personality changes, exophthalmos (in Graves' disease)
Cardiovascular system	Promotes normal functioning of the heart	Decreased efficiency of pumping action of the heart; low heart rate and blood pressure	Increased sensitivity to catecholamines leads to rapid heart rate and possible palpitations; high blood pressure; if prolonged, heart failure
Muscular system	Promotes normal muscular development and function	Sluggish muscle action; muscle cramps; myalgia	Muscle atrophy and weakness
Skeletal system	Promotes normal growth and maturation of the skeleton	In child, growth retardation, skeletal stunting and retention of child's body proportions; in adult, joint pain	In child, excessive skeletal growth initially, followed by early epiphyseal closure and short stature; in adult, demineralization of skeleton
Gastrointestinal system	Promotes normal GI motility and tone; increases secretion of digestive juices	Depressed GI motility, tone, and secretory activity; constipation	Excessive GI motility; diarrhea; loss of appetite
Reproductive system	Promotes normal female reproductive ability and lactation	Depressed ovarian function; sterility; depressed lactation	In females, depressed ovarian function; in males, impotence
Integumentary system	Promotes normal hydration and secretory activity of skin	Skin pale, thick, and dry; facial edema; hair coarse and thick	Skin flushed, thin, and moist; hair fine and soft; nails soft and thin

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removed. However, calcitonin is given therapeutically to patients to treat Paget's disease (a bone disease described in Chapter 6, p. 191).

The Parathyroid Glands

▶ Indicate general functions of parathyroid hormone.

The tiny, yellow-brown **parathyroid glands** are nearly hidden from view in the posterior aspect of the thyroid gland (Figure 16.11a). There are usually four of these glands, but the number varies from one individual to another—as many as eight have been reported, and some may be located in other regions of the neck or even in the thorax. The parathyroid's glandular cells are arranged in thick, branching cords containing scattered *oxyphil cells* and large numbers of smaller **chief cells** (Figure 16.11b). The chief cells secrete parathyroid hormone. The function of the oxyphil cells is unclear.

Discovery of the parathyroid glands was accidental. Years ago, surgeons were baffled by the observation that most patients recovered uneventfully after partial (or even total) thyroid gland removal, while others suffered uncontrolled muscle spasms and severe pain, and subsequently died. It was only after several such tragic deaths that the parathyroid glands were discovered and their hormonal function, quite different from that of the thyroid gland hormones, became known.

Parathyroid hormone (**PTH**), or *parathormone*, the protein hormone of these glands, is the single most important hormone controlling the calcium balance of the blood. Precise control of calcium levels is critical because Ca^{2+} homeostasis is essential for so many functions, including transmission of nerve impulses, muscle contraction, and blood clotting.

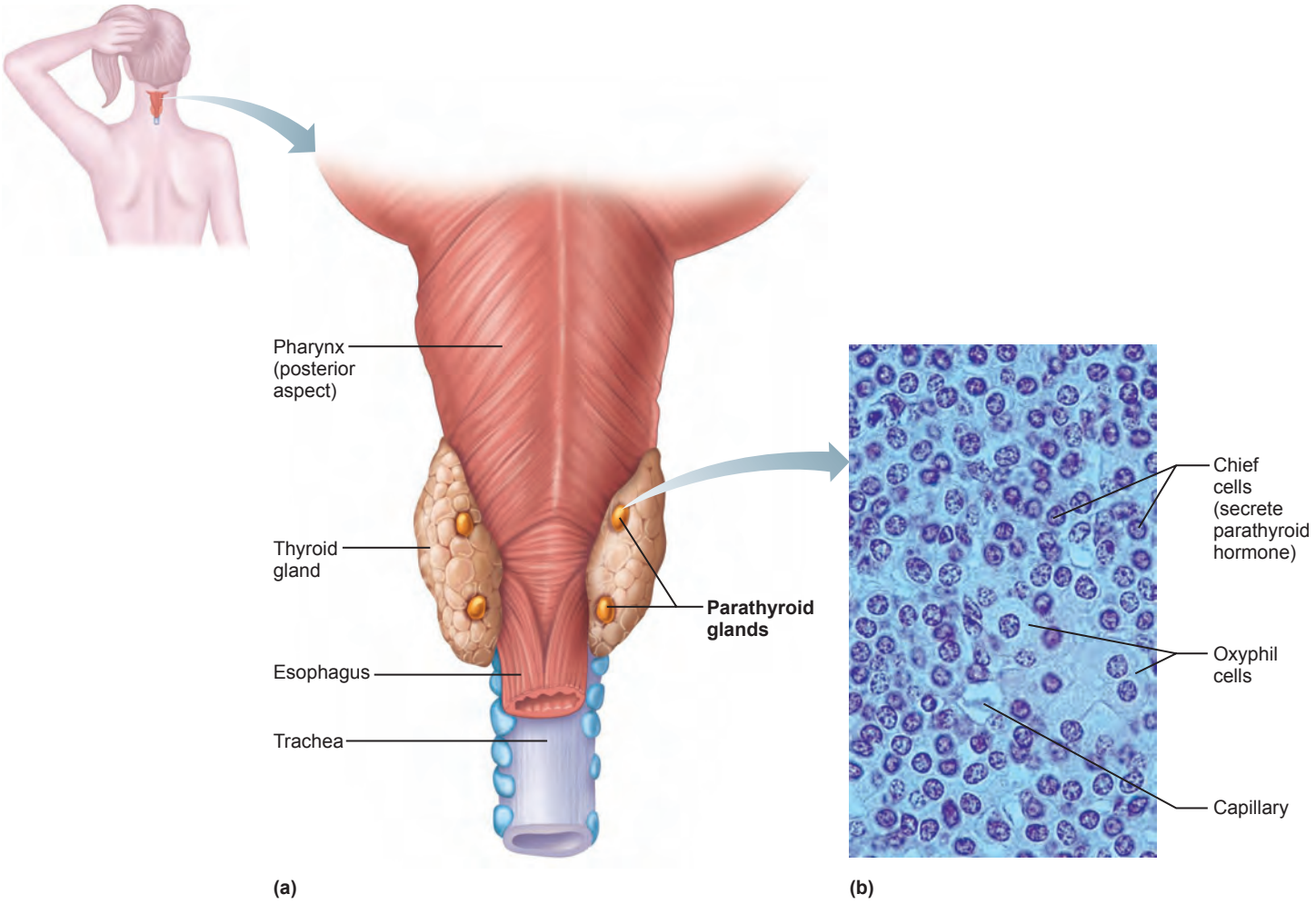

Figure 16.11 The parathyroid glands. (a) The parathyroid glands are located on the posterior aspect of the thyroid gland and may be more inconspicuous than depicted. **(b)** Photomicrograph of parathyroid gland tissue (500×).

PTH release is triggered by falling blood Ca^{2+} levels and inhibited by rising blood Ca^{2+} levels. PTH increases Ca^{2+} levels in blood by stimulating three target organs: the skeleton (which contains considerable amounts of calcium salts in its matrix), the kidneys, and the intestine **(Figure 16.12)**.

PTH release ① stimulates osteoclasts (bone-resorbing cells) to digest some of the bony matrix and release ionic calcium and phosphates to the blood; ② enhances reabsorption of Ca^{2+} [and excretion of phosphate (PO_4^{3-})] by the kidneys; and ③ promotes activation of vitamin D, thereby increasing absorption of Ca^{2+} by the intestinal mucosal cells. Vitamin D is required for absorption of Ca^{2+} from food, but the vitamin is ingested or produced by the skin in an inactive form. For vitamin D to exert its physiological effects, it must first be converted by the kidneys to its active vitamin D_3 form, *calcitriol* (1,25-dihydroxycholecalciferol). PTH stimulates this transformation.

HOMEOSTATIC IMBALANCE

Hyperparathyroidism is rare and usually results from a parathyroid gland tumor. In hyperparathyroidism, calcium is leached from the bones, and the bones soften and deform as their mineral salts are replaced by fibrous connective tissue. In *osteitis fibrosa cystica*, a severe example of this disorder, the bones have a moth-eaten appearance on X rays and tend to fracture spontaneously. The resulting abnormally elevated blood Ca^{2+} level (hypercalcemia) has many outcomes, but the two most notable are (1) depression of the nervous system, which leads to abnormal reflexes and weakness of the skeletal muscles, and (2) formation of kidney stones as excess calcium salts precipitate in the kidney tubules. Calcium deposits may also form in soft tissues throughout the body and severely impair vital organ functioning, a condition called *metastatic calcification*.

Hypoparathyroidism, or PTH deficiency, most often follows parathyroid gland trauma or removal during thyroid surgery. However, an extended deficiency of dietary magnesium (required for PTH secretion) can cause functional hypoparathyroidism. The resulting hypocalcemia (low blood Ca^{2+}) increases the excitability of neurons and accounts for the classical symptoms of *tetany* such as loss of sensation, muscle twitches, and convulsions. Untreated, the symptoms progress to respiratory paralysis and death. ■

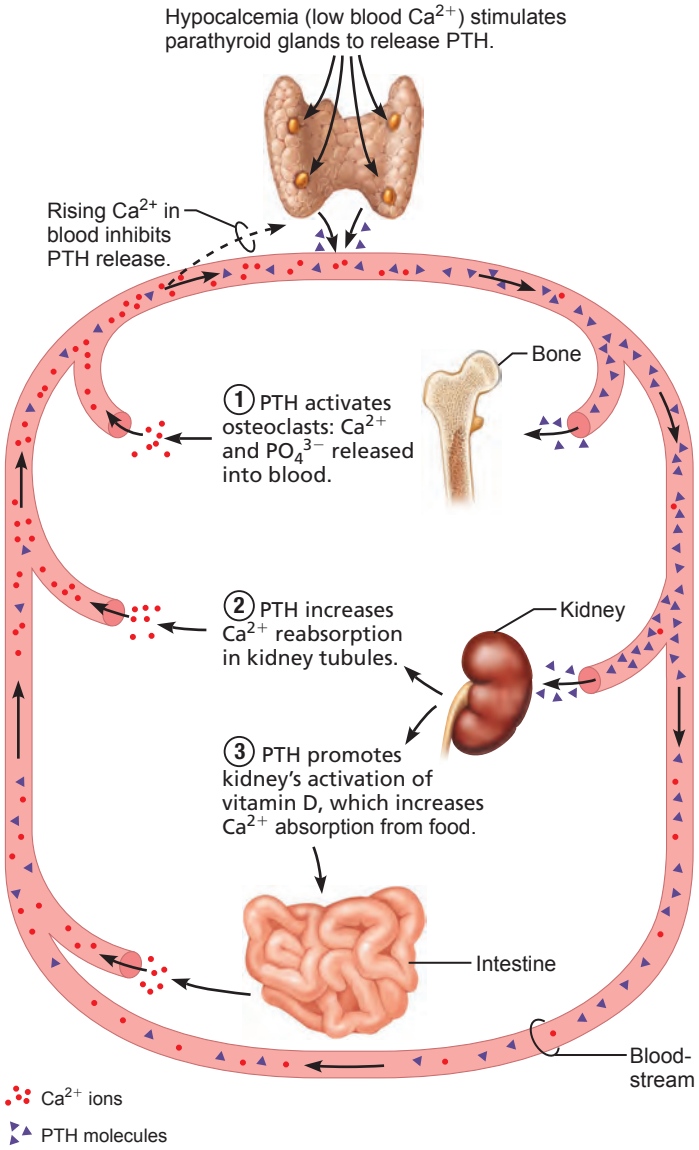

Figure 16.12 Effects of parathyroid hormone on bone, the kidneys, and the intestine. The effect on the intestine is indirect via activated vitamin D.

CHECK YOUR UNDERSTANDING

10. What is the major effect of thyroid hormone? Parathyroid hormone? Calcitonin?

11. Name the cells that release each of the three hormones listed above.

For answers, see Appendix G.

The Adrenal (Suprarenal) Glands

▶ List hormones produced by the adrenal gland, and cite their physiological effects.

The paired **adrenal glands** are pyramid-shaped organs perched atop the kidneys (*ad* = near; *renal* = kidney), where they are enclosed in a fibrous capsule and a cushion of fat (see Figure 16.1 and Figure 16.13). They are also often referred to as the **suprarenal glands** (*supra* = above).

Each adrenal gland is structurally and functionally two endocrine glands. The inner **adrenal medulla**, more like a knot of nervous tissue than a gland, is part of the sympathetic nervous system. The outer **adrenal cortex**, encapsulating the medulla and forming the bulk of the gland, is glandular tissue derived from embryonic mesoderm. Each region produces its own set of hormones summarized in Table 16.3 (p. 617), but all adrenal hormones help us cope with stressful situations.

The Adrenal Cortex

The adrenal cortex synthesizes well over two dozen steroid hormones, collectively called **corticosteroids**. The multistep steroid synthesis pathway begins with cholesterol, and involves varying intermediates depending on the hormone being formed. Unlike the amino acid–based hormones, steroid hormones are not stored in cells. Consequently, their rate of release in response to stimulation depends on their rate of synthesis.

The large, lipid-laden cortical cells are arranged in three layers or zones (Figure 16.13). The cell clusters forming the superficial **zona glomerulosa** (zo′nah glo-mer″u-lo′sah) produce mineralocorticoids, hormones that help control the balance of minerals and water in the blood. The principal products of the middle **zona fasciculata** (fah-sik″u-la′tah) cells, arranged in more or less linear cords, are the metabolic hormones called glucocorticoids. The cells of the innermost **zona reticularis** (rĕ-tik″u-lar′is), abutting the adrenal medulla, have a netlike arrangement. These cells mainly produce small amounts of adrenal sex hormones, or gonadocorticoids. Note, however, that the two innermost layers of the adrenal cortex share production of glucocorticoids and gonadocorticoids, although each layer predominantly produces one type.

Mineralocorticoids

The essential function of **mineralocorticoids** is to regulate the electrolyte (mineral salt) concentrations in extracellular fluids, particularly of Na^+ and K^+. The single most abundant cation in extracellular fluid is Na^+, and the amount of Na^+ in the body largely determines the volume of the extracellular fluid—where Na^+ goes, water follows. Changes in Na^+ concentration lead to changes in blood volume and blood pressure. Moreover, the regulation of a number of other ions, including K^+, H^+, HCO_3^- (bicarbonate), and Cl^- (chloride), is coupled to that of Na^+. The extracellular concentration of K^+ is also critical—it sets the resting membrane potential of all cells and determines how easily action potentials are generated in nerve and muscle. Not surprisingly, Na^+ and K^+ regulation are crucial to overall body homeostasis. Their regulation is the primary job of **aldosterone** (al-dos′ter-ōn), the most potent mineralocorticoid. Aldosterone accounts for more than 95% of the mineralocorticoids produced.

Aldosterone reduces excretion of Na^+ from the body. Its primary target is the distal parts of the kidney tubules, where it stimulates Na^+ reabsorption and water retention accompanied by elimination of K^+ and, in some instances, alterations in the

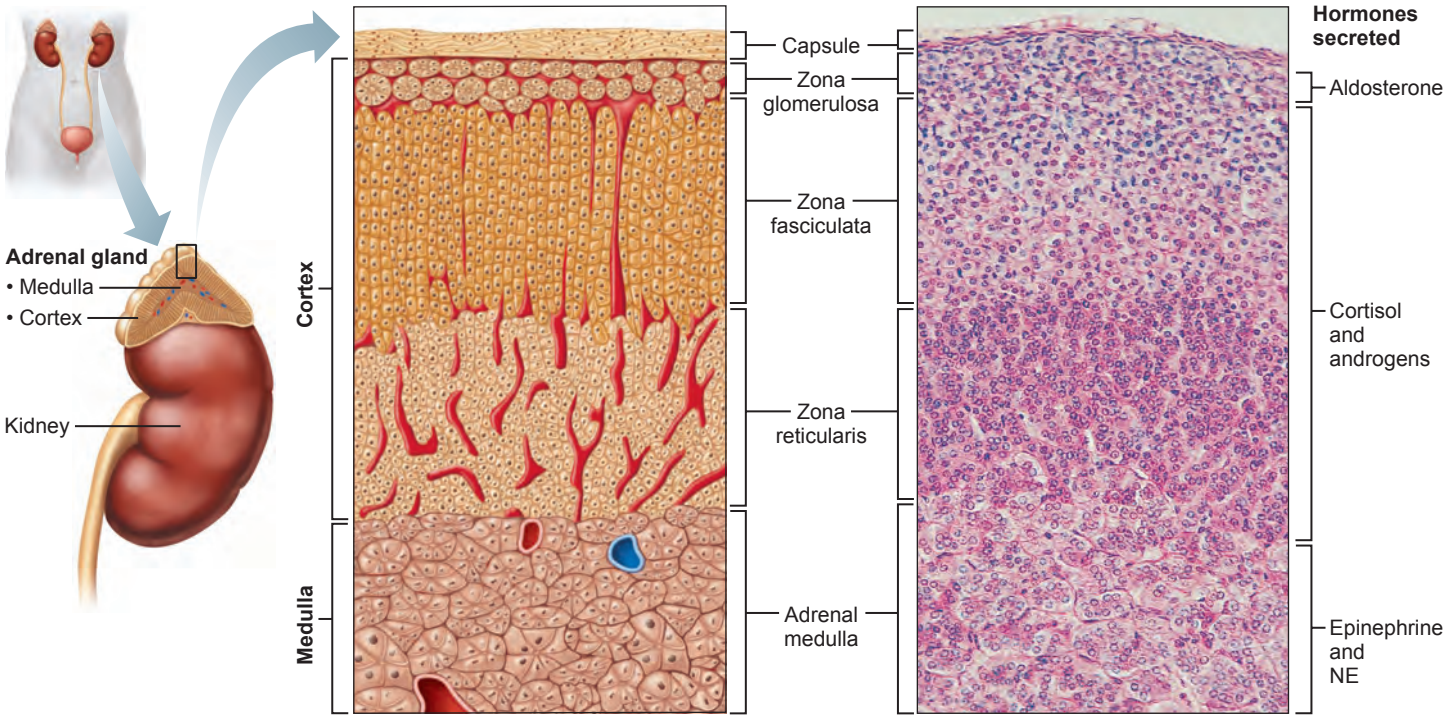

Figure 16.13 **Microscopic structure of the adrenal gland.**

acid-base balance of the blood (by H^+ excretion). Aldosterone also enhances Na^+ reabsorption from perspiration, saliva, and gastric juice. Because aldosterone's regulatory effects are brief (lasting approximately 20 minutes), plasma electrolyte balance can be precisely controlled and modified continuously. The mechanism of aldosterone activity involves the synthesis and activation of proteins required for Na^+ transport such as Na^+-K^+ ATPase, the pump that exchanges Na^+ for K^+.

In this discussion we are focusing on the major roles of bloodborne aldosterone produced by the adrenal cortex, but aldosterone is also secreted by cardiovascular organs. There it is a paracrine and plays a completely different role in cardiac regulation.

Aldosterone secretion is stimulated by decreasing blood volume and blood pressure, and rising blood levels of K^+. The reverse conditions inhibit aldosterone secretion. Four mechanisms regulate aldosterone secretion, but the first two are by far the most important (Figure 16.14 and Table 16.3):

1. **The renin-angiotensin mechanism.** The renin-angiotensin mechanism (re′nin an″je-o-ten′sin) influences both blood volume and blood pressure by regulating the release of aldosterone and therefore Na^+ and water reabsorption by the kidneys. Specialized cells of the *juxtaglomerular apparatus* in the kidneys become excited when blood pressure (or blood volume) declines. These cells respond by releasing **renin** into the blood. Renin cleaves off part of the plasma protein **angiotensinogen** (an″je-o-ten′sin-o-gen), triggering an enzymatic cascade leading to the formation of **angiotensin II**, a potent stimulator of aldosterone release by the glomerulosa cells.

   However, the renin-angiotensin mechanism does much more than trigger aldosterone release, and all of its effects are ultimately involved in raising the blood pressure. We describe these additional effects in detail in Chapters 25 and 26.
2. **Plasma concentrations of potassium.** Fluctuating blood levels of K^+ directly influence the zona glomerulosa cells in the adrenal cortex. Increased K^+ stimulates aldosterone release, whereas decreased K^+ inhibits it.
3. **ACTH.** Under normal circumstances, ACTH released by the anterior pituitary has little or no effect on aldosterone release. However, when a person is severely stressed, the hypothalamus secretes more corticotropin-releasing hormone (CRH), and the resulting rise in ACTH blood levels steps up the rate of aldosterone secretion to a small extent. The increase in blood volume and blood pressure that results helps ensure adequate delivery of nutrients and respiratory gases during the stressful period.
4. **Atrial natriuretic peptide (ANP).** Atrial natriuretic peptide, a hormone secreted by the heart when blood pressure rises, fine-tunes blood pressure and sodium-water balance of the body. One of its major effects is to inhibit the renin-angiotensin mechanism. It blocks renin and aldosterone secretion and inhibits other angiotensin-induced mechanisms that enhance water and Na^+ reabsorption. Consequently, ANP's overall influence is to decrease blood pressure by allowing Na^+ (and water) to flow out of the body in urine (*natriuretic* = producing salty urine).

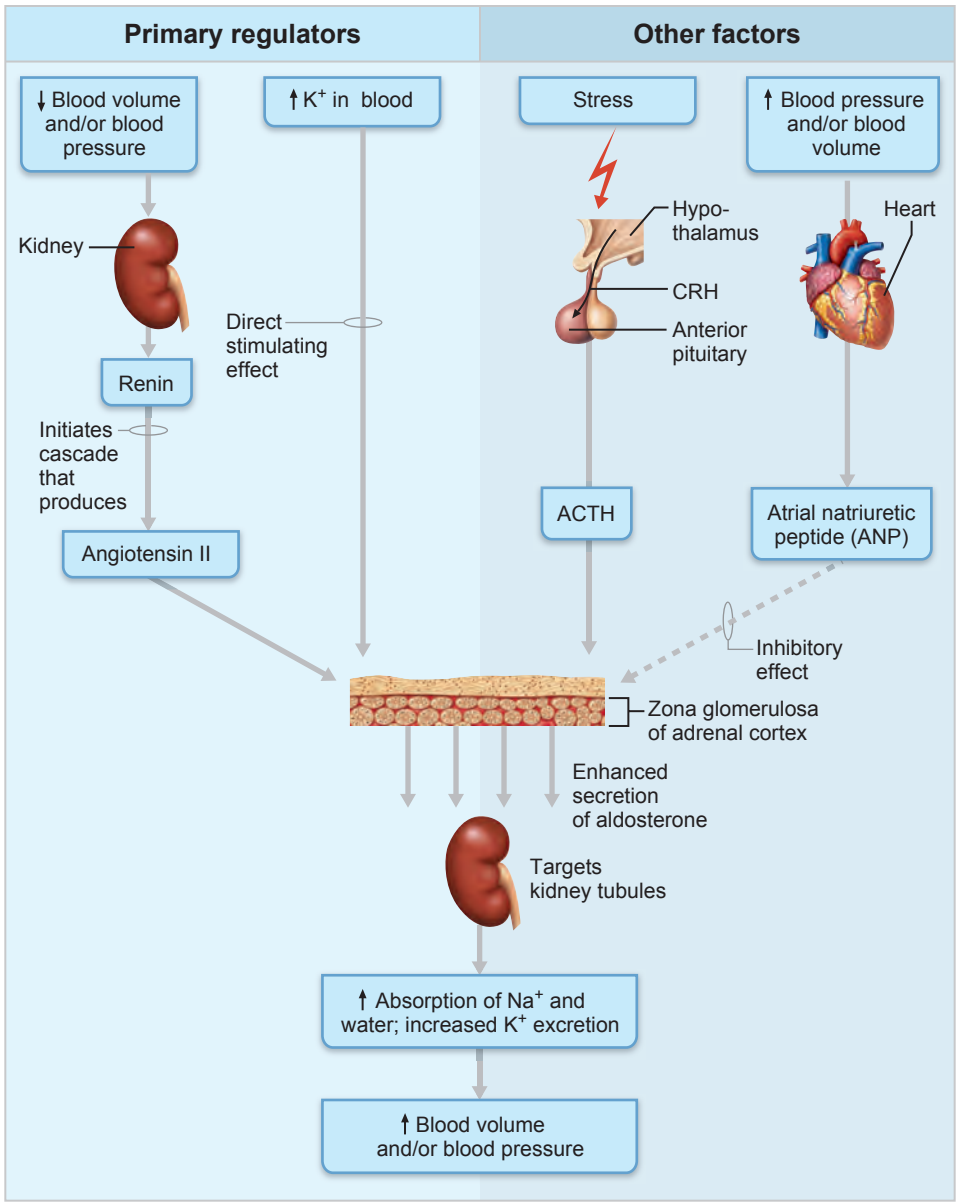

Figure 16.14 **Major mechanisms controlling aldosterone release from the adrenal cortex.**

HOMEOSTATIC IMBALANCE

Hypersecretion of aldosterone, a condition called *aldosteronism*, typically results from adrenal tumors. Two major sets of problems result: (1) hypertension and edema due to excessive Na^+ and water retention, and (2) accelerated excretion of potassium ions. If K^+ loss is extreme, neurons become nonresponsive and muscle weakness (and eventually paralysis) occurs. *Addison's disease*, a hyposecretory disease of the adrenal cortex, generally involves a deficient output of both mineralocorticoids and glucocorticoids, as we will describe shortly. ■

Glucocorticoids

Essential to life, the **glucocorticoids** influence the energy metabolism of most body cells and help us to resist stressors. Under normal circumstances, they help the body adapt to intermittent food intake by keeping blood glucose levels fairly constant, and maintain blood pressure by increasing the action of vasoconstrictors. However, severe stress due to hemorrhage, infection, or physical or emotional trauma evokes a dramatically higher output of glucocorticoids, which helps the body negotiate the crisis. Glucocorticoid hormones include **cortisol (hydrocortisone)**, **cortisone**, and **corticosterone**, but only cortisol is secreted in significant amounts in humans. As for all steroid hormones, the basic mechanism of glucocorticoid action on target cells is to modify gene activity.

Glucocorticoid secretion is regulated by negative feedback. Cortisol release is promoted by ACTH, triggered in turn by the hypothalamic releasing hormone CRH. Rising cortisol levels feed back to act on both the hypothalamus and the anterior pituitary, preventing CRH release and shutting off ACTH and cortisol secretion. Cortisol secretory bursts, driven by patterns of

TABLE 16.3 Adrenal Gland Hormones: Summary of Regulation and Effects

HORMONE	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPERSECRETION ↑ AND HYPOSECRETION ↓
Adrenocortical Hormones			
Mineralocorticoids (chiefly aldosterone)	Stimulated by renin-angiotensin mechanism (activated by decreasing blood volume or blood pressure), elevated blood K^+ levels, and ACTH (minor influence); inhibited by increased blood volume and pressure, and decreased blood K^+ levels	Kidneys: increase blood levels of Na^+ and decrease blood levels of K^+; since water reabsorption accompanies sodium retention, blood volume and blood pressure rise	↑ Aldosteronism ↓ Addison's disease
Glucocorticoids (chiefly cortisol)	Stimulated by ACTH; inhibited by feedback inhibition exerted by cortisol	Body cells: promote gluconeogenesis and hyperglycemia; mobilize fats for energy metabolism; stimulate protein catabolism; assist body to resist stressors; depress inflammatory and immune responses	↑ Cushing's syndrome ↓ Addison's disease
Gonadocorticoids (chiefly androgens, converted to testosterone or estrogens after release)	Stimulated by ACTH; mechanism of inhibition incompletely understood, but feedback inhibition not seen	Insignificant effects in males; responsible for female libido; development of pubic and axillary hair in females; source of estrogen after menopause	↑ Virilization of females (adrenogenital syndrome) ↓ No effects known
Adrenal Medullary Hormones			
Catecholamines (epinephrine and norepinephrine)	Stimulated by preganglionic fibers of the sympathetic nervous system	Sympathetic nervous system target organs: effects mimic sympathetic nervous system activation; increase heart rate and metabolic rate; increase blood pressure by promoting vasoconstriction	↑ Prolonged fight-or-flight response; hypertension ↓ Unimportant

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eating and activity, occur in a definite pattern throughout the day and night. Cortisol blood levels peak shortly before we arise in the morning. The lowest levels occur in the evening just before and shortly after we fall asleep. The normal cortisol rhythm is interrupted by acute stress of any variety as higher CNS centers override the (usually) inhibitory effects of elevated cortisol levels and trigger CRH release. The resulting increase in ACTH blood levels causes an outpouring of cortisol from the adrenal cortex.

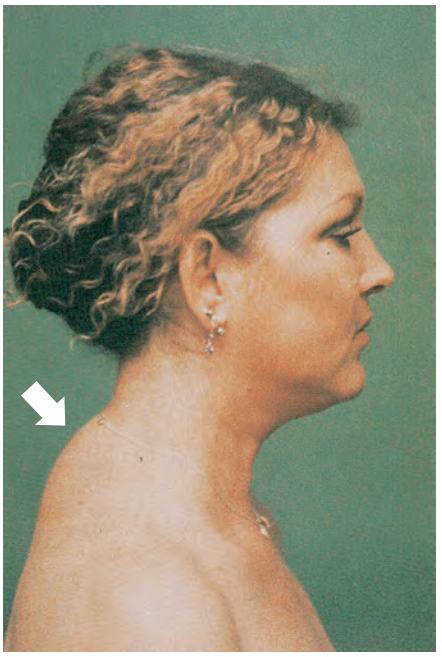
Stress results in a dramatic rise in blood levels of glucose, fatty acids, and amino acids, all provoked by cortisol. Cortisol's prime metabolic effect is to provoke *gluconeogenesis*, that is, the formation of glucose from fats and proteins. In order to "save" glucose for the brain, cortisol mobilizes fatty acids from adipose tissue and encourages their increased use for energy. Under cortisol's influence, stored proteins are broken down to provide building blocks for repair or for making enzymes to be used in metabolic processes. Cortisol enhances the sympathetic nervous system's vasoconstrictive effects, and the rise in blood pressure and circulatory efficiency that results helps ensure that these nutrients are quickly distributed to the cells.

Note that *ideal amounts of glucocorticoids promote normal function*, but cortisol excess is associated with significant anti-inflammatory and anti-immune effects. Excessive levels of glucocorticoids (1) depress cartilage and bone formation, (2) inhibit inflammation by decreasing the release of inflammatory chemicals, (3) depress the immune system, and (4) promote changes in cardiovascular, neural, and gastrointestinal function. Recognition of the effects of glucocorticoid hypersecretion has led to widespread use of glucocorticoid drugs to control symptoms of many chronic inflammatory disorders, such as rheumatoid arthritis or allergic responses. However, these potent drugs are a double-edged sword. Although they relieve some of the symptoms of these disorders, they also cause the undesirable effects of excessive levels of these hormones.

HOMEOSTATIC IMBALANCE

The pathology of glucocorticoid excess, **Cushing's syndrome**, may be caused by an ACTH-releasing pituitary tumor (in which case, it is called **Cushing's disease**); by an ACTH-releasing malignancy of the lungs, pancreas, or kidneys; or by a tumor of the adrenal cortex. However, it most often results from the clinical administration of pharmacological doses (doses higher than those found in the body) of glucocorticoid drugs. The syndrome is characterized by persistent elevated blood glucose levels

(a) Patient before onset.



(b) **Same patient with Cushing's syndrome.** The white arrow shows the characteristic "buffalo hump" of fat on the upper back.

Figure 16.15 The effects of excess glucocorticoid.

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(*steroid diabetes*), dramatic losses in muscle and bone protein, and water and salt retention, leading to hypertension and edema. The so-called *cushingoid signs* (Figure 16.15) include a swollen "moon" face, redistribution of fat to the abdomen and the posterior neck (causing a "buffalo hump"), a tendency to bruise, and poor wound healing. Because of enhanced anti-inflammatory effects, infections may become overwhelmingly severe before producing recognizable symptoms. Eventually, muscles weaken and spontaneous fractures force the person to become bedridden. The only treatment is removal of the cause—be it surgical removal of the offending tumor or discontinuation of the drug.

Addison's disease, the major hyposecretory disorder of the adrenal cortex, usually involves deficits in both glucocorticoids and mineralocorticoids. Its victims tend to lose weight; their plasma glucose and sodium levels drop, and potassium levels rise. Severe dehydration and hypotension are common. Corticosteroid replacement therapy at physiological doses (doses typical of those normally found in the body) is the usual treatment. ■

Gonadocorticoids (Sex Hormones)

The bulk of the **gonadocorticoids** secreted by the adrenal cortex are weak **androgens**, or male sex hormones, such as *androstenedione* and *dehydroepiandrosterone* (*DHEA*). These are converted to the more potent male hormone, *testosterone*, in the tissue cells or to estrogens (female sex homones) in females. The adrenal cortex also makes small amounts of female hormones (estradiol and other estrogens). The amount of gonadocorticoids produced by the adrenal cortex is insignificant compared with the amounts made by the gonads during late puberty and adulthood.

The exact role of the adrenal sex hormones is still in question, but because adrenal androgen levels rise continuously between the ages of 7 and 13 in both boys and girls, it is assumed that these hormones contribute to the onset of puberty and the appearance of axillary and pubic hair during that time. In adult women adrenal androgens are thought to be responsible for the sex drive, and they may account for the estrogens produced after menopause when ovarian estrogens are no longer produced. Control of gonadocorticoid secretion is not completely understood. Release seems to be stimulated by ACTH, but the gonadocorticoids do not appear to exert feedback inhibition on ACTH release.

HOMEOSTATIC IMBALANCE

Since androgens predominate, hypersecretion of gonadocorticoids causes *adrenogenital syndrome* (masculinization). In adult males, these effects of elevated gonadocorticoid levels may be obscured, since testicular testosterone has already produced virilization, but in prepubertal males and in females, the results can be dramatic. In the young man, maturation of the reproductive organs and appearance of the secondary sex characteristics occur rapidly, and the sex drive emerges with a vengeance. Females develop a beard and a masculine pattern of body hair distribution, and the clitoris grows to resemble a small penis. ■

The Adrenal Medulla

We discussed the adrenal medulla in Chapter 14 as part of the autonomic nervous system, so our coverage here is brief. The spherical **chromaffin cells** (kro′maf-in), which crowd around

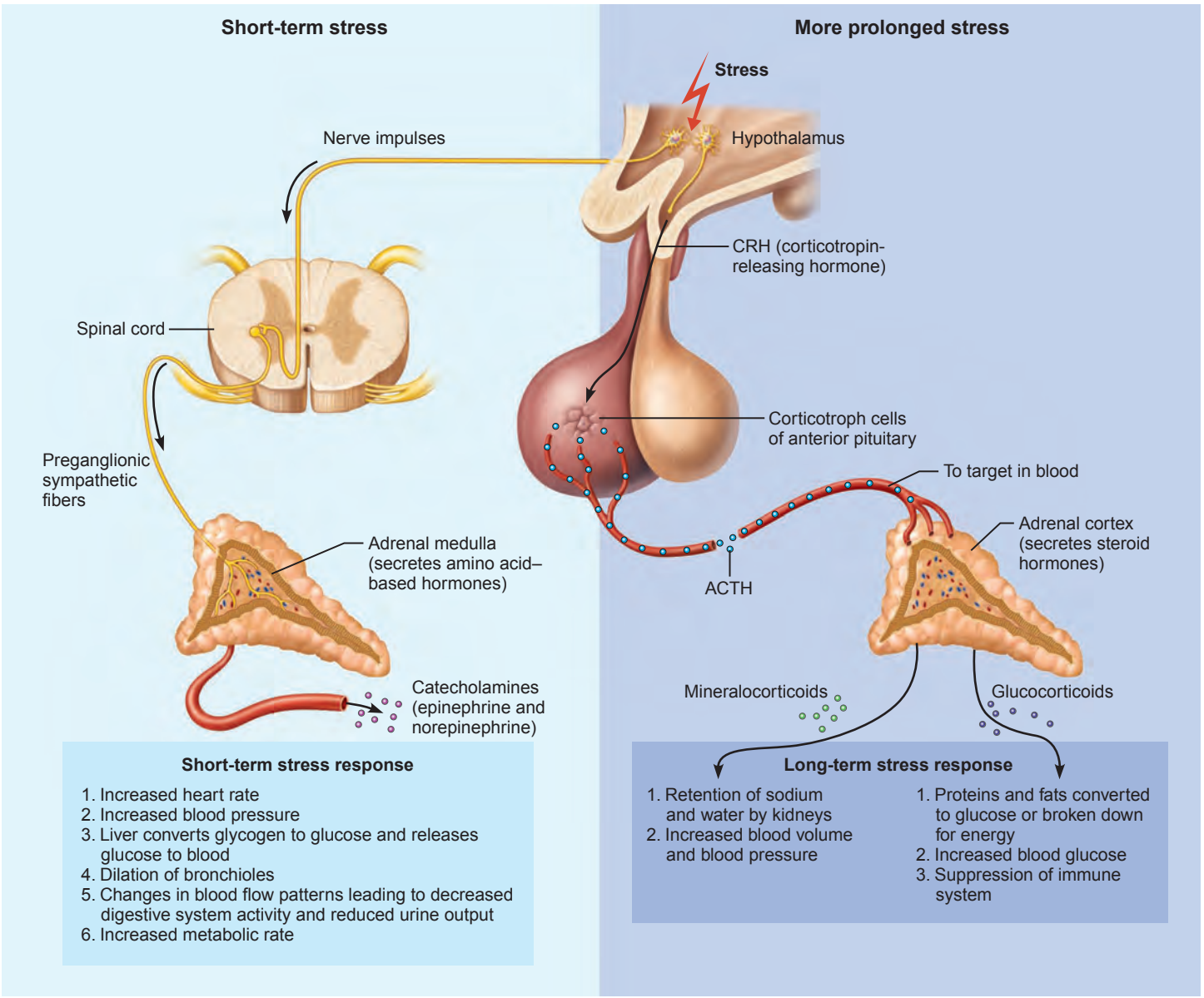


Figure 16.16 Stress and the adrenal gland. Stressful stimuli cause the hypothalamus to activate the adrenal medulla via sympathetic nerve impulses and the adrenal cortex via hormonal signals.

blood-filled capillaries and sinusoids, are modified ganglionic sympathetic neurons that synthesize the *catecholamines* **epinephrine** and **norepinephrine (NE)** via a molecular sequence from tyrosine to dopamine to NE to epinephrine.

When the body is activated to fight-or-flight status by some short-term stressor, the sympathetic nervous system is mobilized. Blood glucose levels rise, blood vessels constrict and the heart beats faster (together raising the blood pressure), blood is diverted from temporarily nonessential organs to the heart and skeletal muscles, and preganglionic sympathetic nerve endings weaving through the adrenal medulla signal for release of catecholamines, which reinforce and prolong the fight-or-flight response.

Unequal amounts of the two hormones are stored and released. Approximately 80% is epinephrine and 20% norepinephrine. With a few exceptions, the two hormones exert the same effects (see Table 14.2, p. 536). Epinephrine is the more potent stimulator of metabolic activities, bronchial dilation, and increased blood flow to skeletal muscles and the heart, but norepinephrine has the greater influence on peripheral vasoconstriction and blood pressure. Epinephrine is used clinically as a heart stimulant and to dilate the bronchioles during acute asthmatic attacks.

Unlike the adrenocortical hormones, which promote long-lasting body responses to stressors, catecholamines cause fairly brief responses. The interrelationships of the adrenal hormones and the hypothalamus, the "director" of the stress response, are depicted in Figure 16.16.

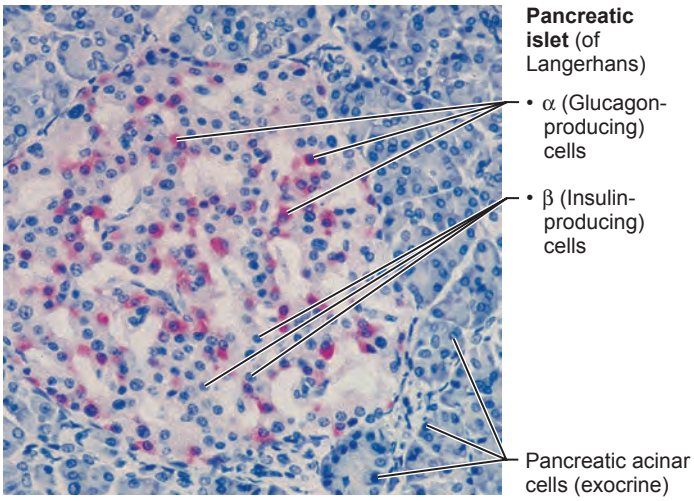


Figure 16.17 Photomicrograph of differentially stained pancreatic tissue. A pancreatic islet is surrounded by acinar cells (stained blue-gray), which produce the exocrine product (enzyme-rich pancreatic juice). The β cells of the islets that produce insulin are stained pale pink, and the α cells that produce glucagon are bright pink (230×).

HOMEOSTATIC IMBALANCE

A deficiency of hormones of the adrenal medulla is not a problem because these hormones merely intensify activities set into motion by the sympathetic nervous system neurons. Unlike glucocorticoids and mineralocorticoids, adrenal catecholamines are not essential for life. On the other hand, hypersecretion of catecholamines, sometimes arising from a chromaffin cell tumor called a *pheochromocytoma* (fe-o-kro″mo-si-to′mah), produces symptoms of uncontrolled sympathetic nervous system activity—**hyperglycemia** (elevated blood glucose), increased metabolic rate, rapid heartbeat and palpitations, hypertension, intense nervousness, and sweating. ■

CHECK YOUR UNDERSTANDING

12. List the three classes of hormones released from the adrenal cortex and for each briefly state its major effect(s).

For answers, see Appendix G.

The Pineal Gland

▶ Briefly describe the importance of melatonin.

The tiny, pine cone–shaped **pineal gland** hangs from the roof of the third ventricle in the diencephalon (see Figure 16.1). Its secretory cells, called **pinealocytes**, are arranged in compact cords and clusters. Lying between pinealocytes in adults are dense particles containing calcium salts ("brain-sand" or "pineal sand"). These salts are radiopaque, making the pineal gland a handy landmark for determining brain orientation in X rays.

The endocrine function of the pineal gland is still somewhat of a mystery. Although many peptides and amines have been isolated from this minute gland, its only major secretory product is **melatonin** (mel″ah-to′nin), a powerful antioxidant and amine hormone derived from serotonin. Melatonin concentrations in the blood rise and fall in a diurnal (daily) cycle. Peak levels occur during the night and make us drowsy, and lowest levels occur around noon.

The pineal gland indirectly receives input from the visual pathways (retina → suprachiasmatic nucleus of hypothalamus → superior cervical ganglion → pineal gland) concerning the intensity and duration of daylight. In some animals, mating behavior and gonadal size vary with changes in the relative lengths of light and dark periods, and melatonin mediates these effects. In children, melatonin may have an antigonadotropic effect. In other words, it may inhibit precocious (too early) sexual maturation and affect the timing of puberty.

The *suprachiasmatic nucleus* of the hypothalamus, an area referred to as our "biological clock," is richly supplied with melatonin receptors, and exposure to bright light (known to suppress melatonin secretion) can reset the clock timing. For this reason, changing melatonin levels may also be a means by which the day/night cycles influence physiological processes that show rhythmic variations, such as body temperature, sleep, and appetite.

CHECK YOUR UNDERSTANDING

13. Synthetic melatonin supplements are available, although their safety and efficacy have not been proved. What do you think they might be used for?

For answers, see Appendix G.

Other Endocrine Glands and Tissues

So far, we've examined the endocrine role of the hypothalamus and of glands dedicated solely to endocrine function. We will now consider a set of organs that contain endocrine tissue but also have other major functions. These include the pancreas, gonads, and placenta.

The Pancreas

▶ Compare and contrast the effects of the two major pancreatic hormones.

Located partially behind the stomach in the abdomen, the soft, triangular **pancreas** is a mixed gland composed of both endocrine and exocrine gland cells (see Figure 16.1). Along with the thyroid and parathyroids, it develops as an outpocketing of the epithelial lining of the gastrointestinal tract. *Acinar cells*, forming the bulk of the gland, produce an enzyme-rich juice that is carried by ducts to the small intestine during digestion.

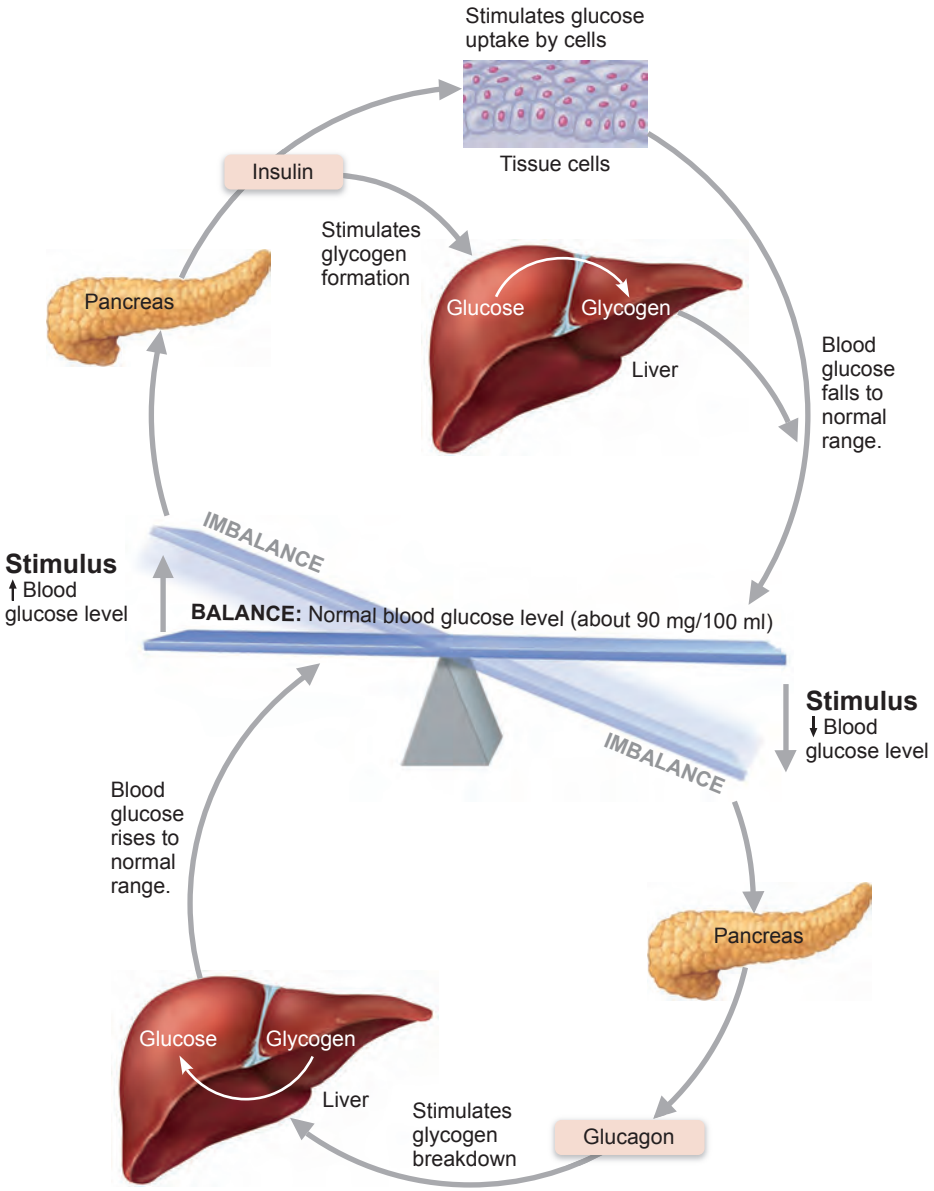


Figure 16.18 Regulation of blood glucose levels by insulin and glucagon from the pancreas.

Scattered among the acinar cells are approximately a million **pancreatic islets** (also called **islets of Langerhans**), tiny cell clusters that produce pancreatic hormones (Figure 16.17). The islets contain two major populations of hormone-producing cells, the glucagon-synthesizing **alpha (α) cells** and the more numerous insulin-producing **beta (β) cells**. These cells act as tiny fuel sensors, secreting glucagon and insulin appropriately during the fasting and fed states. In this way insulin and glucagon are intimately but independently involved in the regulation of blood glucose levels. Their effects are antagonistic: Insulin is a *hypoglycemic* hormone, whereas glucagon is a *hyperglycemic* hormone (Figure 16.18). Some islet cells also synthesize other peptides in small amounts. These include *somatostatin*, *pancreatic polypeptide* (*PP*), and others. However, we will not deal with these here.

Glucagon

Glucagon (gloo′kah-gon), a 29-amino-acid polypeptide, is an extremely potent hyperglycemic agent. One molecule of this hormone can cause the release of 100 million molecules of glucose into the blood! The major target of glucagon is the liver, where it promotes the following actions:

1. Breakdown of glycogen to glucose (*glycogenolysis*) (Figure 16.18)
2. Synthesis of glucose from lactic acid and from noncarbohydrate molecules (*gluconeogenesis*)
3. Release of glucose to the blood by liver cells, causing blood glucose levels to rise

A secondary effect is a fall in the amino acid concentration in the blood as the liver cells sequester these molecules to make new glucose molecules.

Humoral stimuli, mainly falling blood glucose levels, prompt the alpha cells to secrete glucagon. However, sympathetic nervous system stimulation and rising amino acid levels (as might follow a protein-rich meal) are also stimulatory. Glucagon release is suppressed by rising blood glucose levels, insulin, and somatostatin.

Insulin

Insulin is a small (51-amino-acid) protein consisting of two amino acid chains linked by disulfide (–S–S–) bonds. It is synthesized as part of a larger polypeptide chain called **proinsulin**. The middle portion of this chain is then excised by enzymes, releasing functional insulin. This "clipping" process occurs in the secretory vesicles just before insulin is released from the beta cell.

Insulin's effects are most obvious when we have just eaten. Its main effect is to lower blood glucose levels (Figure 16.18), but it also influences protein and fat metabolism. Circulating insulin lowers blood glucose levels in three main ways. (1) Insulin enhances membrane transport of glucose (and other simple sugars) into body cells, especially muscle and fat cells. (It does *not* accelerate glucose entry into liver, kidney, and brain tissue, all of which have easy access to blood glucose regardless of insulin levels. However, insulin does have important roles in the brain—it participates in neuronal development, feeding behavior, and learning and memory.) (2) Insulin inhibits the breakdown of glycogen to glucose, and (3) it inhibits the conversion of amino acids or fats to glucose. These inhibiting effects counter any metabolic activity that would increase plasma levels of glucose.

How does insulin act at the cellular level? Insulin activates its receptor (a tyrosine kinase enzyme), which phosphorylates specific proteins, beginning the cascade that leads to increased glucose uptake and insulin's other effects. After glucose enters a target cell, insulin binding triggers enzymatic activities that

1. Catalyze the oxidation of glucose for ATP production
2. Join glucose molecules together to form glycogen
3. Convert glucose to fat (particularly in adipose tissue)

As a rule, energy needs are met first, followed by glycogen formation. Finally, if excess glucose is still available, it is converted to fat. Insulin also stimulates amino acid uptake and protein synthesis in muscle tissue. In summary, insulin sweeps glucose out of the blood, causing it to be used for energy or converted to other forms (glycogen or fats), and it promotes protein synthesis and fat storage.

Pancreatic beta cells are stimulated to secrete insulin chiefly by elevated blood glucose levels, but also by rising plasma levels of amino acids and fatty acids, and release of acetylcholine by parasympathetic nerve fibers. As body cells take up glucose and other nutrients, and plasma levels of these substances drop, insulin secretion is suppressed.

Other hormones also influence insulin release. For example, any hyperglycemic hormone (such as glucagon, epinephrine, growth hormone, thyroxine, or glucocorticoids) called into action as blood glucose levels drop indirectly stimulates insulin release by promoting glucose entry into the bloodstream. Somatostatin and sympathetic nervous system activation depress insulin release. As you can see, blood glucose levels represent a balance of humoral, neural, and hormonal influences. Insulin is the major hypoglycemic factor that counterbalances the many hyperglycemic hormones.

HOMEOSTATIC IMBALANCE

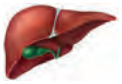
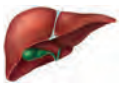
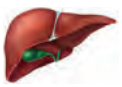
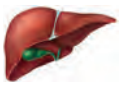
Diabetes mellitus (DM) results from either hyposecretion or hypoactivity of insulin. When insulin is absent or deficient, blood glucose levels remain high after a meal because glucose is unable to enter most tissue cells. Ordinarily, when blood glucose levels rise, hyperglycemic hormones are not released, but when hyperglycemia becomes excessive, the person begins to feel nauseated, which precipitates the fight-or-flight response. This response results, inappropriately, in all the reactions that normally occur in the hypoglycemic (fasting) state to make glucose available—that is, glycogenolysis, lipolysis (breakdown of fat), and gluconeogenesis. Consequently, the already high blood glucose levels soar even higher, and excesses of glucose begin to be lost from the body in the urine (*glycosuria*).

When sugars cannot be used as cellular fuel, more fats are mobilized, resulting in high fatty acid levels in the blood, a condition called lipidemia or lipemia. In severe cases of diabetes mellitus, blood levels of fatty acids and their metabolites (acetoacetic acid, acetone, and others) rise dramatically. The fatty acid metabolites, collectively called **ketones** (ke′tōnz) or **ketone bodies**, are organic acids. When they accumulate in the blood, the blood pH drops, resulting in **ketoacidosis**, and ketone bodies begin to spill into the urine (*ketonuria*). Severe ketoacidosis is life threatening. The nervous system responds by initiating rapid deep breathing (hyperpnea) to blow off carbon dioxide from the blood and increase blood pH. (We will explain the physiological basis of this mechanism in Chapter 22.) If untreated, ketoacidosis disrupts heart activity and oxygen transport, and severe depression of the nervous system leads to coma and death.

The three cardinal signs of diabetes mellitus are polyuria, polydipsia, and polyphagia. The excessive glucose in the kidney filtrate acts as an osmotic diuretic (that is, it inhibits water reabsorption by the kidney tubules), resulting in **polyuria**, a huge urine output that leads to decreased blood volume and dehydration. Serious electrolyte losses also occur as the body rids itself of excess ketone bodies. Ketone bodies are negatively charged and carry positive ions out with them, and as a result, sodium and potassium ions are also lost from the body. Because of the electrolyte imbalance, the person gets abdominal pains and may vomit, and the stress reaction spirals even higher. Dehydration stimulates hypothalamic thirst centers, causing **polydipsia**, or excessive thirst. The final sign, **polyphagia**, refers to excessive hunger and food consumption, a sign that the person is "starving in the land of plenty." Although plenty of glucose is available, it cannot be used, and the body starts to utilize its fat and protein stores for energy metabolism. **Table 16.4** summarizes the consequences of insulin deficiency. DM is the focus of *A Closer Look* on pp. 626–627.

Hyperinsulinism, or excessive insulin secretion, results in low blood glucose levels, or **hypoglycemia**. This condition triggers the release of hyperglycemic hormones, which cause anxiety, nervousness, tremors, and weakness. Insufficient glucose delivery to the brain causes disorientation, progressing to convulsions, unconsciousness, and even death. In rare cases, hyperinsulinism re-

TABLE 16.4 Symptoms of Insulin Deficit (Diabetes Mellitus)

ORGANS/TISSUES INVOLVED	ORGAN/TISSUE RESPONSES TO INSULIN DEFICIENCY	*RESULTING CONDITIONS* IN BLOOD	*RESULTING CONDITIONS* IN URINE	SIGNS AND SYMPTOMS
 Liver  Adipose tissue  Muscle	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria Osmotic diuresis	Polyuria (and dehydration, soft eyeballs) Polydipsia (and fatigue, weight loss) Polyphagia
	Glycogenolysis			
 	Protein catabolism and gluconeogenesis			
 	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea, vomiting, abdominal pain Cardiac irregularities Central nervous system depression; coma

sults from an islet cell tumor. More commonly, it is caused by an overdose of insulin and is easily treated by ingesting some sugar. ■

CHECK YOUR UNDERSTANDING

14. You've just attended a football game with your friend, Sharon, who is diabetic. While you aren't aware of Sharon having had more than one beer during the game, she is having trouble walking straight, her speech is slurred, and she is not making sense. What does it mean when we say Sharon is diabetic? What is the most likely explanation for Sharon's current behavior?

15. Diabetes mellitus and diabetes insipidus are both due to lack of a hormone. Which hormone causes which? What symptom do they have in common? What would you find in the urine of a patient with one but not the other?

For answers, see Appendix G.

The Gonads and Placenta

▶ Describe the functional roles of hormones of the testes, ovaries, and placenta.

The male and female **gonads** produce steroid sex hormones, identical to those produced by adrenal cortical cells (see Figure 16.1). The major distinction is the source and relative amounts produced. The release of gonadal hormones is regulated by gonadotropins, as described earlier.

The paired *ovaries* are small, oval organs located in the female's abdominopelvic cavity. Besides producing ova, or eggs, the ovaries produce several hormones, most importantly **estrogens** and **progesterone** (pro-jes′tĕ-rōn). Alone, the estrogens are responsible for maturation of the reproductive organs and the appearance of the secondary sex characteristics of females at puberty. Acting with progesterone, estrogens promote breast development and cyclic changes in the uterine mucosa (the menstrual cycle).

The male *testes*, located in an extra-abdominal skin pouch called the scrotum, produce sperm and male sex hormones, primarily **testosterone** (tes-tos′tĕ-rōn). During puberty, testosterone initiates the maturation of the male reproductive organs and the appearance of secondary sex characteristics and sex drive. In addition, testosterone is necessary for normal sperm production and maintains the reproductive organs in their mature functional state in adult males.

The *placenta* is a temporary endocrine organ. Besides sustaining the fetus during pregnancy, it secretes several steroid and protein hormones that influence the course of pregnancy. Placental hormones include estrogens and progesterone (hormones more often associated with the ovary), and human chorionic gonadotropin (hCG).

We will discuss the roles of the gonadal, placental, and gonadotropic hormones in detail in Chapters 27 and 28, where we consider the reproductive system and pregnancy.

CHECK YOUR UNDERSTANDING

16. Which of the two chemical classes of hormones introduced at the beginning of this chapter do the gonadal hormones belong to? Which major endocrine gland secretes hormones of this same chemical class?

For answers, see Appendix G.

Hormone Secretion by Other Organs

- Name a hormone produced by the heart.
- State the location of enteroendocrine cells.
- Briefly explain the hormonal functions of the kidney, skin, adipose tissue, bone, and thymus.

Other hormone-producing cells occur in various organs of the body, including the following, summarized in **Table 16.5**:

1. **Heart.** The atria contain some specialized cardiac muscle cells that secrete **atrial natriuretic peptide**. ANP prompts the kidneys to increase their production of salty urine and inhibits aldosterone release by the adrenal cortex. In this way, ANP decreases the amount of sodium in the extracellular fluid, thereby reducing blood volume and blood pressure (see Figure 16.14).
2. **Gastrointestinal tract.** *Enteroendocrine cells* are hormone-secreting cells sprinkled in the mucosa of the gastrointestinal (GI) tract. These scattered cells release several peptide hormones that help regulate a wide variety of digestive functions, some of which are summarized in Table 16.5. Enteroendocrine cells also release amines such as serotonin, which act as paracrines, diffusing to and influencing nearby target cells without first entering the bloodstream. Enteroendocrine cells are sometimes referred to as *paraneurons* because they are similar in certain ways to neurons and many of their hormones and paracrines are chemically identical to neurotransmitters.
3. **Kidneys.** Interstitial cells in the kidneys secrete **erythropoietin** (ĕ-rith″ro-poi′ĕ-tin; "red-maker"), a protein hormone that signals the bone marrow to increase production of red blood cells. The kidneys also release **renin**, the hormone that acts as an enzyme to initiate the renin-angiotensin mechanism of aldosterone release described earlier.
4. **Skin.** The skin produces **cholecalciferol**, an inactive form of vitamin D_3, when modified cholesterol molecules in epidermal cells are exposed to ultraviolet radiation. This compound then enters the blood via the dermal capillaries, is modified in the liver, and becomes fully activated in the kidneys. The active form of vitamin D_3, **calcitriol**, is an essential regulator of the carrier system that intestinal cells use to absorb Ca^{2+} from ingested food. Without this vitamin, the bones become soft and weak.
5. **Adipose tissue.** Adipose cells release **leptin**, which serves to tell your body how much stored energy (as fat) you have. The more fat you have, the more leptin there will be in your blood. As we describe in Chapter 24, leptin binds to CNS neurons concerned with appetite control, producing a sensation of satiety. It also appears to stimulate increased energy expenditure. Two other hormones released by adipose cells both affect the sensitivity of cells to insulin. *Resistin* is an insulin antagonist, while *adiponectin* enhances sensitivity to insulin.
6. **Skeleton.** Osteoblasts in bone secrete *osteocalcin*, a hormone that prods pancreatic beta cells to divide and secrete more insulin. It also restricts fat storage by adipocytes, and triggers the release of adiponectin. As a result, glucose handling is improved and body fat is reduced. Osteocalcin levels are low in type 2 diabetes, and increasing its level may offer a new treatment approach.
7. **Thymus.** Located deep to the sternum in the thorax is the lobulated **thymus** (see Figure 16.1). Large and conspicuous in infants and children, the thymus diminishes in size throughout adulthood. By old age, it is composed largely of adipose and fibrous connective tissues.

   Thymic epithelial cells secrete several different families of peptide hormones, including **thymulin, thymopoietins,** and **thymosins** (thi′mo-sinz). These hormones are thought to be involved in the normal development of *T lymphocytes* and the immune response, but their roles are not well understood. Although still called hormones, they mainly act locally as paracrines. We describe the thymus in Chapter 20 in our discussion of the lymphoid organs and tissues.

CHECK YOUR UNDERSTANDING

17. What hormone does the heart produce and what is its function?

18. What is the function of the hormone produced by the skin?

For answers, see Appendix G.

16

Developmental Aspects of the Endocrine System

- Describe the effects of aging on endocrine system functioning.

Hormone-producing glands arise from all three embryonic germ layers. Endocrine glands derived from mesoderm produce steroid hormones. All others produce amines, peptides, or protein hormones.

Though not usually considered important when describing hormone effectiveness, exposure to many environmental pollutants has been shown to disrupt endocrine function. These pollutants include many pesticides, industrial chemicals, arsenic, dioxin, and other soil and water pollutants. So far, sex hormones, thyroid hormone, and glucocorticoids have proved vulnerable to the effects of such pollutants. Interference with glucocorticoids, which turn on many genes that may suppress cancer, may help to explain the high cancer rates in certain areas of the country.

Barring exposure to environmental pollutants, and hypersecretory and hyposecretory disorders, most endocrine organs operate smoothly throughout life until old age. Aging may bring about changes in the rates of hormone secretion, breakdown, and excretion, or in the sensitivity of target cell receptors. Endocrine functioning in the elderly is difficult to research, however, because it is frequently altered by the chronic illnesses common in that age group.

TABLE 16.5 Selected Examples of Hormones Produced by Organs Other Than the Major Endocrine Organs

SOURCE	HORMONE	CHEMICAL COMPOSITION	TRIGGER	TARGET ORGAN AND EFFECTS
Adipose tissue	Leptin	Peptide	Secretion proportional to fat stores; increased by nutrient uptake	Brain: suppresses appetite; increases energy expenditure
Adipose tissue	Resistin, adiponectin	Peptides	Unknown	Fat, muscle, liver: resistin antagonizes insulin's action and adiponectin enhances it
GI tract mucosa				
▪ Stomach	Gastrin	Peptide	Secreted in response to food	Stomach: stimulates glands to release hydrochloric acid (HCl)
▪ Duodenum (of small intestine)	Intestinal gastrin	Peptide	Secreted in response to food, especially fats	Stomach: stimulates HCl secretion and gastrointestinal tract motility
▪ Duodenum	Secretin	Peptide	Secreted in response to food	Pancreas and liver: stimulates release of bicarbonate-rich juice; Stomach: inhibits secretory activity
▪ Duodenum	Cholecystokinin (CCK)	Peptide	Secreted in response to food	Pancreas: stimulates release of enzyme-rich juice; Gallbladder: stimulates expulsion of stored bile; Hepatopancreatic sphincter: causes sphincter to relax, allowing bile and pancreatic juice to enter duodenum
▪ Duodenum (and other gut regions)	Incretins [glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)]	Peptide	Secreted in response to glucose in intestinal lumen	Pancreas: enhances insulin release and inhibits glucagon release caused by increased blood glucose
Heart (atria)	Atrial natriuretic peptide	Peptide	Secreted in response to stretching of atria (by rising blood pressure)	Kidney: inhibits sodium ion reabsorption and renin release; adrenal cortex: inhibits secretion of aldosterone; decreases blood pressure
Kidney	Erythropoietin (EPO)	Glycoprotein	Secreted in response to hypoxia	Red bone marrow: stimulates production of red blood cells
Kidney	Renin	Peptide	Secreted in response to low blood pressure or plasma volume, or sympathetic stimulation	Acts as an enzyme to initiate renin-angiotensin mechanism of aldosterone release; returns blood pressure to normal
Skeleton	Osteocalcin	Peptide	Unknown	Increases insulin production and insulin sensitivity
Skin (epidermal cells)	Cholecalciferol (provitamin D_3)	Steroid	Activated by the kidneys to active vitamin D_3 (calcitriol) in response to parathyroid hormone	Intestine: stimulates active transport of dietary calcium across intestinal cell membranes
Thymus	Thymulin, thymopoietins, thymosins	Peptides	Unknown	Mostly act locally as paracrines; involved in T lymphocyte development and in immune responses

A CLOSER LOOK

Sweet Revenge: Taming the DM Monster?

Few medical breakthroughs have been as electrifying as the discovery of insulin in 1921, an event that changed diabetes mellitus from a death sentence to a survivable disease. Nonetheless, DM is still a huge health problem: Determining blood glucose levels accurately and maintaining desirable levels sorely challenge our present biotechnology. Let's take a closer look at the characteristics and challenges of type 1 and type 2, the major forms of diabetes mellitus.

More than 1 million Americans have **type 1 diabetes mellitus**, formerly called *insulin-dependent diabetes mellitus* (*IDDM*). Symptoms appear suddenly, usually before age 15, following a long asymptomatic period during which the beta cells are destroyed by the immune system. Consequently, type 1 diabetics effectively lack insulin.

Type 1 diabetes susceptibility genes have been localized on several chromosomes, indicating that type 1 diabetes is an example of a multigene autoimmune response. However, some investigators believe that *molecular mimicry* is at least part of the problem: Some foreign substance (for example, a virus) has entered the body and is so similar to certain self (beta cell) proteins that the immune system attacks the beta cells as well as the invader.

Indeed, elegant studies on certain strains of diabetic mice, stressed by infections or other irritants, demonstrated that they produced increasing amounts of a particular stress protein (heat shock protein 60) and also churned out antibodies against that stress protein. When fragments of the stress protein called p277 were injected into other mice showing early signs of diabetes, the beta cells were spared from the autoimmune attack. Recent clinical trials in which newly diagnosed diabetics were given the fragment as a drug (called DiaPep277) have yielded conflicting results, with some studies showing less need for insulin and others showing no effect.

Type 1 diabetes is difficult to control and patients typically develop long-term vascular and neural problems. The lipidemia and high blood cholesterol levels typical of the disease can lead to severe vascular complications including atherosclerosis, strokes, heart attacks, renal shutdown, gangrene, and blindness. Nerve damage leads to loss of sensation, impaired bladder function, and impotence. Female type 1 diabetics also tend to have lumpy breasts and to undergo premature menopause, which increases their risk for cardiac problems.

Hyperglycemia is the culprit behind these complications, and the closer to normal blood glucose levels are held, the less likely complications are. Continuous glucose monitors make this much easier than relying upon finger pricks. Currently, frequent insulin injections (up to four times daily, or better yet, by a continuous infusion pump) are recommended to reduce vascular and renal complications. While some glucose sensors can talk directly to insulin pumps, problems with automatically calculating the amount of insulin to dispense mean patients must still make these decisions. In this way, such combined devices still fall short of being a true "artificial pancreas." A number of alternative insulin delivery methods exist—insulin inhalers are now approved for use and insulin patches may be on the horizon.

Pancreatic islet cell transplants have become increasingly successful in helping type 1 diabetics. Still, only 33% of patients

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Structural changes in the anterior pituitary occur with age. The amount of connective tissue increases, vascularization decreases, and the number of hormone-secreting cells declines. These changes may or may not affect hormone production. In women, for example, blood levels and the release rhythm of ACTH remain constant, but levels of gonadotropins increase with age. GH levels decline in both sexes, which partially explains muscle atrophy in old age.

The adrenal glands also show structural changes with age, but normal controls of cortisol appear to persist as long as a person is healthy and not stressed. Chronic stress, on the other hand, drives up blood levels of cortisol and appears to contribute to hippocampal (and memory) deterioration. Plasma levels of aldosterone are reduced by half in old age, but this change may reflect a decline in renin release by the kidneys, which become less responsive to renin-evoking stimuli. No age-related differences have been found in the release of catecholamines by the adrenal medulla.

The gonads, particularly the ovaries, undergo significant changes with age. In late middle age, the ovaries decrease in size and weight, and they become unresponsive to gonadotropins. As female hormone production declines dramatically, the ability to bear children ends, and problems associated with estrogen deficiency, such as arteriosclerosis and osteoporosis, begin to occur. Testosterone production by the testes also wanes with age, but this effect usually is not seen until very old age.

Glucose tolerance (the ability to dispose of a glucose load effectively) begins to deteriorate as early as the fourth decade of life. Blood glucose levels rise higher and return to resting levels more slowly in the elderly than in young adults. The fact that the islet cells continue to secrete near-normal amounts of insulin leads researchers to conclude that decreasing glucose tolerance with age may reflect declining receptor sensitivity to insulin (pre–type 2 diabetes).

Thyroid hormone synthesis and release diminish somewhat with age. Typically, the follicles are loaded with colloid in the elderly, and fibrosis of the gland occurs. Basal metabolic rate declines with age. Mild hypothyroidism is only one cause of this decline. The increase in body fat relative to muscle is equally important, because muscle tissue is more active metabolically than fat.

The parathyroid glands change little with age, and PTH levels remain fairly normal throughout life. Estrogens protect women

A CLOSER LOOK
(continued)

need no injected insulin after two years. The need for long-term immunosuppression limits this treatment to only those diabetics who cannot control their blood glucose by any other means.

Over 90% of known DM cases are **type 2 diabetes mellitus**, formerly called *non-insulin-dependent diabetes mellitus* (*NIDDM*), which grows increasingly common with age and with the increasing size of our waistlines. About 12 million people in the U.S. have been diagnosed with type 2 diabetes, and roughly half as many are believed to be undiagnosed victims. Type 2 diabetics are at risk for the same complications as type 1 diabetics—heart disease, amputations, kidney failure, and blindness.

A hereditary predisposition is particularly striking in this diabetic group. About 25–30% of Americans carry a gene that predisposes them to type 2 diabetes, with nonwhites affected to a much greater extent. If an identical twin has type 2 diabetes mellitus, the probability that the other twin will have the disease is virtually 100%. Most type 2 diabetics produce insulin, but the insulin receptors are unable to respond to it, a phenomenon called **insulin resistance**. Mutations in any one of several genes could lead to insulin resistance.

Lifestyle factors also play a role: Type 2 diabetics are almost always overweight and sedentary. Adipose cells of obese people overproduce a number of signaling chemicals including *tumor necrosis factor alpha* and *resistin*, which may alter the enzymatic cascade triggered by insulin binding. The Diabetes Prevention Program, a major clinical trial, showed that weight loss and regular exercise can lower the risk of type 2 diabetes dramatically, even for people at high risk.

In many cases type 2 diabetes can be managed solely by exercise, weight loss, and a healthy diet. Some type 2 diabetics also benefit from oral medications that lower blood glucose or reduce insulin resistance. A promising new class of drugs targets the incretin hormones normally secreted by the gut, enhancing glucose-dependent insulin release from pancreatic beta cells using a normal physiological pathway. However, most type 2 diabetics must eventually inject insulin.

While we cannot yet cure diabetes, biotechnology promises to continue to improve control of blood glucose levels and thereby tame the monster that is diabetes.

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against the demineralizing effects of PTH, but estrogen production wanes after menopause, leaving older women vulnerable to the bone-demineralizing effects of PTH and osteoporosis.

CHECK YOUR UNDERSTANDING

19. In the elderly, the decline in levels of which hormone is associated with muscle atrophy? With osteoporosis in women?

For answers, see Appendix G.

In this chapter, we have covered the general mechanisms of hormone action and have provided an overview of the major endocrine organs, their chief targets, and their most important physiological effects, as summarized in *Making Connections* on p. 628. However, every one of the hormones discussed here comes up in at least one other chapter, where its actions are described as part of the functional framework of a particular organ system. For example, we described the effects of PTH and calcitonin on bone mineralization in Chapter 6 along with the discussion of bone remodeling.

RELATED CLINICAL TERMS

Hirsutism (her′soot-izm; *hirsut* = hairy, rough) Excessive hair growth; usually refers to this phenomenon in women and reflects excessive androgen production.

Hypophysectomy (hi-pof″ĭ-sek′to-me) Surgical removal of the pituitary gland.

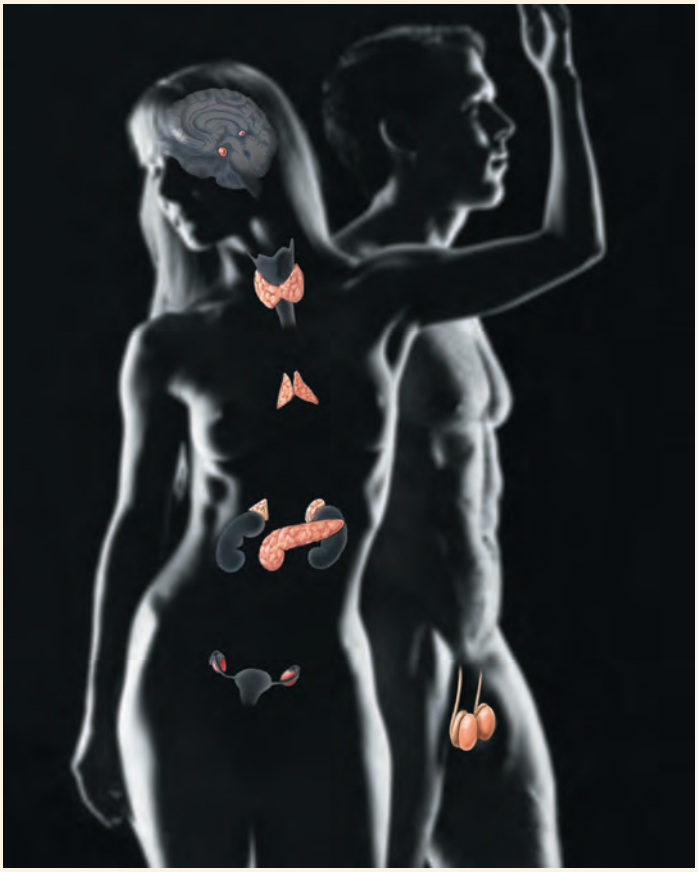
Prolactinoma (pro-lak″tĭ-no′mah; *oma* = tumor) The most common type (30–40% or more) of pituitary gland tumor; evidenced by hypersecretion of prolactin and menstrual disturbances in women.

Psychosocial dwarfism Dwarfism (and failure to thrive) resulting from stress and emotional disorders that suppress hypothalamic release of growth hormone–releasing hormone and thus anterior pituitary secretion of growth hormone.

Thyroid storm (thyroid crisis) A sudden and dangerous increase in all of the symptoms of hyperthyroidism due to excessive amounts of circulating TH. Symptoms of this hypermetabolic state include fever, rapid heart rate, high blood pressure, dehydration, nervousness, and tremors. Precipitating factors include severe infection, excessive intake of TH supplements, and trauma.

System Connections

Homeostatic Interrelationships Between the Endocrine System and Other Body Systems



Integumentary System

- Androgens cause activation of sebaceous glands; estrogen increases skin hydration
- Skin produces cholecalciferol (provitamin D)

Skeletal System

- PTH regulates calcium blood levels; growth hormone, T_3, T_4, and sex hormones are necessary for normal skeletal development
- The skeleton provides some protection to endocrine organs, especially to those in the brain, chest, and pelvis

Muscular System

- Growth hormone is essential for normal muscular development; other hormones (thyroxine and catecholamines) influence muscle metabolism
- Muscular system mechanically protects some endocrine glands; muscular activity elicits catecholamine release

Nervous System

- Many hormones (growth hormone, thyroxine, sex hormones) influence normal maturation and function of the nervous system
- Hypothalamus controls anterior pituitary function and produces two hormones

Cardiovascular System

- Several hormones influence blood volume, blood pressure, and heart contractility; erythropoietin stimulates red blood cell production
- Blood is the main transport medium of hormones; heart produces atrial natriuretic peptide

Lymphatic System/Immunity

- Lymphocytes "programmed" by thymic hormones seed the lymph nodes; glucocorticoids depress the immune response and inflammation
- Chemical messengers of the immune system stimulate the release of cortisol and ACTH; lymph provides a route for transport of hormones

Respiratory System

- Epinephrine influences ventilation (dilates bronchioles)
- Respiratory system provides oxygen; disposes of carbon dioxide; converting enzyme in lungs converts angiotensin I to angiotensin II

Digestive System

- GI hormones and paracrines influence GI function; activated vitamin D necessary for absorption of calcium from diet; catecholamines influence digestive motility and secretory activity
- Digestive system provides nutrients to endocrine organs

Urinary System

- Aldosterone and ADH influence renal function; erythropoietin released by kidneys influences red blood cell formation
- Kidneys activate vitamin D (considered a hormone)

Reproductive System

- Hypothalamic, anterior pituitary, and gonadal hormones direct reproductive system development and function; oxytocin and prolactin involved in birth and breast-feeding
- Gonadal hormones feed back to influence endocrine system function

Closer Connections

THE ENDOCRINE SYSTEM and Interrelationships with the Nervous and Reproductive Systems

Like most body systems, the endocrine system performs many functions that benefit the body as a whole. For example, without insulin, thyroxine, and various other metabolic hormones, body cells would be unable to get or use glucose, and would die. Likewise, total body growth is beholden to the endocrine system, which coordinates the growth spurts with increases in skeletal and muscular mass so that we don't look out of proportion most of the time. But the interactions that are most noticeable and crucial are those that the endocrine system has with the nervous and the reproductive systems, and they begin before birth.

Nervous System

The influence of hormones on behavior is striking. While we are still in the wet darkness of our mother's uterus, testosterone—or lack of it—is determining the "sex" of our brain. If testosterone is produced by the exceedingly tiny male testes, then certain areas of the brain enlarge, develop large numbers of androgen receptors, and thereafter determine the so-called masculine aspects of behavior (aggressiveness, etc.). Conversely, in the absence of testosterone, the brain is feminized. At puberty, Mom and Dad's "little angels," driven by raging hormones, turn into strangers. The surge of androgens—produced first by the adrenal cortices, and then by the maturing gonads—produces an often thoughtless aggressiveness and galloping sex drive, typically long before the cognitive abilities of the brain can rein them in.

Neural involvement in hormonal affairs is no less striking. Not only is the hypothalamus an endocrine organ in its own right, but it also effectively regulates the bulk of hormonal activity via its hormonal or neural controls of the pituitary and adrenal medulla. And that's just on a normal day. The effects of trauma on the hypothalamic-pituitary axis can be far-reaching. Lack of loving care to a newborn baby results in failure to thrive; exceptionally vigorous athletic training in the pubertal female can result in bone wasting and infertility. The shadow the nervous system casts over the endocrine system is long indeed.

Reproductive System

The reproductive system is totally dependent on hormones to "order up the right organs" to match our genetic sex. Testosterone secretion by the testes of male embryos directs formation of the male reproductive tract and external genitalia. Without testosterone, female structures develop—regardless of gonadal sex. The next crucial period is puberty, when gonadal sex hormone production rises and steers maturation of the reproductive organs, bringing them to their adult structure and function. Without these hormonal signals, the reproductive organs remain childlike and the person cannot produce offspring.

Pregnancy invites more endocrine system interactions with the reproductive system. The placenta, a temporary endocrine organ, churns out estrogens and progesterone, which help maintain the pregnancy and prepare the mother's breasts for lactation, as well as a number of other hormones that influence maternal metabolism. During and after birth, oxytocin and prolactin take center stage to promote labor and delivery, and then milk production and ejection. Other than feedback inhibition exerted by its sex hormones on the hypothalamic-pituitary axis, the influence of reproductive organs on the endocrine system is negligible.

Clinical Connections

Endocrine System

Case study: We have a new patient to consider today. Mr. Gutteman, a 70-year-old male, was brought into the ER in a comatose state and has yet to come out of it. It is obvious that he suffered severe head trauma—his scalp was badly lacerated, and he has an impacted skull fracture. His initial lab tests (blood and urine) were within normal limits. His fracture was repaired and the following orders (and others) were given:

- Check qh (every hour) and record: spontaneous behavior, level of responsiveness to stimulation, movements, pupil size and reaction to light, speech, and vital signs.
- Turn patient q4h and maintain meticulous skin care and dryness.

1. Explain the rationale behind these orders.

On the second day of his hospitalization, the aide reports that Mr. Gutteman is breathing irregularly, his skin is dry and flaccid, and that she has emptied his urine reservoir several times during the day. Upon receiving this information, the physician ordered

- Blood and urine tests for presence of glucose and ketones
- Strict I&O (fluid intake and output recording)

Mr. Gutteman is found to be losing huge amounts of water in urine and the volume lost is being routinely replaced (via IV line). Mr. Gutteman's blood and urine tests are negative for glucose and ketones.

Relative to these findings:

2. What would you say Mr. Gutteman's hormonal problem is and what do you think caused it?

3. Is it life threatening? (Explain your answer.)

(Answers in Appendix G)