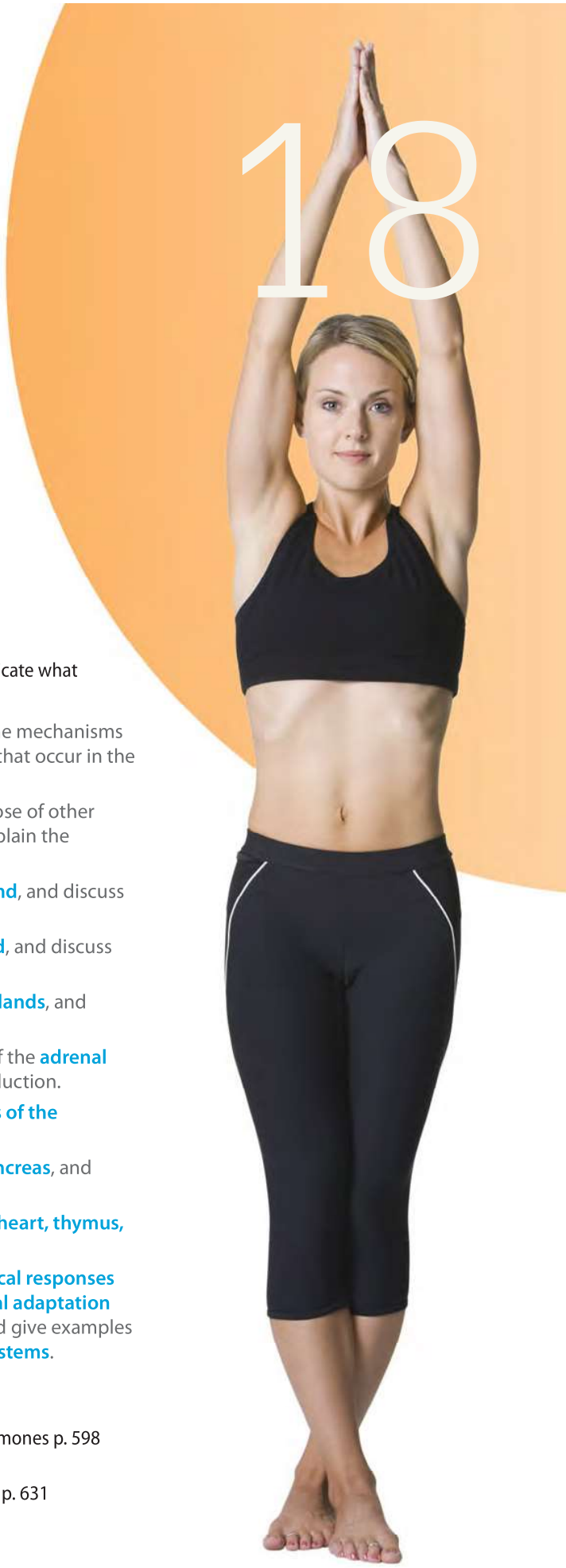
18 The Endocrine System



Learning Outcomes

These Learning Outcomes correspond by number to this chapter's sections and indicate what you should be able to do after completing this chapter.

18-1 Explain the importance of **intercellular communication**, describe the mechanisms involved, and compare the **modes of intercellular communication** that occur in the endocrine and nervous systems.

18-2 Compare the cellular components of the **endocrine system** with those of other systems, contrast the major **structural classes of hormones**, and explain the **general mechanisms of hormonal action** on target organs.

18-3 Describe the location, hormones, and functions of the **pituitary gland**, and discuss the **effects of abnormal pituitary hormone** production.

18-4 Describe the location, hormones, and functions of the **thyroid gland**, and discuss the **effects of abnormal thyroid hormone** production.

18-5 Describe the location, hormone, and functions of the **parathyroid glands**, and discuss the **effects of abnormal parathyroid hormone** production.

18-6 Describe the location, structure, hormones, and general functions of the **adrenal glands**, and discuss the **effects of abnormal adrenal hormone** production.

18-7 Describe the location of the **pineal gland**, and discuss the **functions of the hormone** it produces.

18-8 Describe the location, structure, hormones, and functions of the **pancreas**, and discuss the **effects of abnormal pancreatic hormone production**.

18-9 Describe the functions of the **hormones produced by the kidneys, heart, thymus, testes, ovaries, and adipose tissue**.

18-10 Explain how hormones interact to produce **coordinated physiological responses** and influence behavior, describe the role of hormones in the **general adaptation syndrome**, and discuss how **aging affects hormone production** and give examples of **interactions between the endocrine system and other organ systems**.

Clinical Notes

Spotlights

An Introduction to the Endocrine System

The human body contains roughly 30 chemical messengers known as hormones, which regulate activities such as sleep, body temperature, hunger, and stress management. These hormones are products of the endocrine system, which along with the nervous system controls and coordinates our body processes.

In this chapter we examine the structural and functional organization of the endocrine system and compare it to the nervous system. After an overview of the endocrine system and the characteristics of the hormones it produces, we consider the structure and function of the body's various endocrine glands. Finally, we look at the ways in which hormones modify metabolic operations, and the interactions between the endocrine system and other body systems. Let's begin by considering the role of intercellular communication in maintaining homeostasis.

18-1 Homeostasis is preserved through intercellular communication

To preserve homeostasis, cellular activities must be coordinated throughout the body. Neurons monitor or control specific cells or groups of cells. Only a small fraction of all the cells in the body are innervated, however, and the commands from the nervous system are very specific and relatively short-lived. Yet many life processes are not short-lived. For example, your body takes decades to reach adult stature. The body continually controls and maintains its reproductive capabilities for at least 30 years in a typical female, and even longer in males. Long-term processes, such as growth, development, or reproduction, involve or affect metabolic activities in virtually every cell and tissue. There is no way that the nervous system can regulate such processes. Instead, the endocrine system provides this type of regulation. It uses chemical messengers to relay information and instructions between cells. To understand how these messages are generated and interpreted, let's take a closer look at how cells communicate with one another.

In a few specialized cases, adjacent cells coordinate cellular activities by exchanging ions and molecules across gap junctions. This **direct communication** occurs between two cells of the same type, and the cells must be in extensive physical contact. The two cells communicate so closely that they function as a single entity. Gap junctions (1) coordinate ciliary movement among epithelial cells, (2) coordinate the contractions of cardiac muscle cells, and (3) facilitate the propagation of action potentials from one neuron to the next at electrical synapses.

Most communication between cells involves the release and receipt of chemical messages. Each cell continuously "talks" to its neighbors by releasing chemicals into the extracellular fluid. These chemicals tell cells what their neighbors are doing at any moment. The result is the coordination of tissue function at the local level. The use of chemical messengers to transfer information from cell to cell within a single tissue is called **paracrine communication.** The chemicals involved are called *paracrine factors*, also known as *local hormones*. Examples of paracrine factors include the prostaglandins, introduced in Chapter 2, and the various growth factors, discussed in Chapter 3. pp. 46, 100

Paracrine factors enter the bloodstream, but their concentrations are usually so low that distant cells and tissues are not affected. However, some paracrine factors, including several of the prostaglandins and related chemicals, have primary effects in their tissues of origin and secondary effects in other tissues and organs. When these secondary effects occur, the paracrine factors are also acting as **hormones**—chemical messengers that are released in one tissue and transported in the bloodstream to alter the activities of specific cells in other tissues. Most cells release paracrine factors, but typical hormones are produced only by specialized cells.

Nevertheless, the difference between paracrine factors and hormones is mostly a matter of degree. Paracrine factors can diffuse out of their tissue of origin and have widespread effects, and hormones can affect their tissues of origin as well as distant cells. By convention, a substance with effects outside its tissue of origin is called a *hormone* if its chemical structure is known, and a *factor* if that structure remains to be determined.

In intercellular communication, hormones are like messages and the cardiovascular system is e-mail. A hormone released into the bloodstream is distributed throughout the body. Each hormone has **target cells,** specific cells that have the receptors needed to bind and "read" the hormonal message when it arrives. But hormones are really like e-mail spam—cells throughout the body are exposed to them whether or not they have the necessary receptors. At any moment, each individual cell can respond to only a few of the hormones present. The cell ignores other hormones, because it lacks the receptors to read the messages they contain. The activity of hormones in coordinating cellular activities in tissues in distant portions of the body is called **endocrine communication.**

How do hormones work? They alter the operations of target cells by changing the types, quantities, or activities of important enzymes and structural proteins. A hormone may

- stimulate the synthesis of an enzyme or a structural protein not already present in the cytoplasm by activating appropriate genes in the cell nucleus;
- increase or decrease the rate of synthesis of a particular enzyme or other protein by changing the rate of transcription or translation; or
- turn an existing enzyme or membrane channel "on" or "off" by changing its shape or structure.

Through one or more of these mechanisms, a hormone can modify the physical structure or biochemical properties of its target cells. Because the target cells can be anywhere in the body, a single hormone can alter the metabolic activities of multiple tissues and organs at the same time. These effects may be slow to appear, but they typically persist for days. Consequently, hormones are effective in coordinating cell, tissue, and organ activities on a sustained, long-term basis. For example, circulating hormones keep body water content and levels of electrolytes and organic nutrients within normal limits 24 hours a day throughout our entire lives.

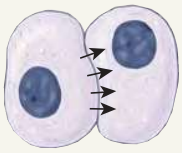
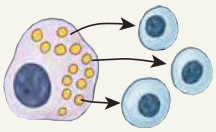
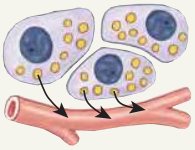
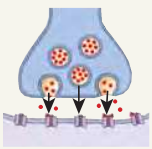
Cells can respond to several different hormones simultaneously. Gradual changes in the quantities and identities of circulating hormones can produce complex changes in the body's physical structure and physiological capabilities. Examples include the processes of embryological and fetal development, growth, and puberty. Hormonal regulation is quite suitable for directing gradual, coordinated processes, but it is totally unable to handle situations requiring split-second responses. That kind of crisis management is the job of the nervous system.

The nervous system too relies primarily on chemical communication, but it does not send messages through the bloodstream. Instead, as we have seen, neurons release a neurotransmitter at a synapse very close to target cells that bear the appropriate receptors. The command to release the neurotransmitter rapidly travels from one location to another in the form of action potentials propagated along axons. The nervous system thus acts like a telecommunications company, with a cable network carrying high-speed "messages" to specific destinations throughout the body. The effects of neural stimulation are generally short-lived, and they tend to be restricted to specific target cells—primarily because the neurotransmitter is rapidly broken down or recycled. This **synaptic communication** is ideal for crisis management: If you are in danger of being hit by a speeding bus, the nervous system can coordinate and direct your leap to safety. Once the crisis is over and the neural circuits quiet down, things soon return to normal.

Table 18–1 summarizes the four ways cells and tissues communicate with one another. Viewed from a general perspective, the differences between the nervous system and endocrine system seem relatively clear. In fact, these broad organizational and functional distinctions are the basis for treating them as two separate systems. Yet when we consider them in detail, we see that the two systems are similarly organized:

- Both systems rely on the release of chemicals that bind to specific receptors on their target cells.

Table 18–1 Mechanisms of Intercellular Communication

Mechanism	Transmission	Chemical Mediators	Distribution of Effects
Direct communication 	Through gap junctions	Ions, small solutes, lipid-soluble materials	Usually limited to adjacent cells of the same type that are interconnected by connexons
Paracrine communication 	Through extracellular fluid	Paracrine factors	Primarily limited to a local area, where paracrine factor concentrations are relatively high Target cells must have appropriate receptors
Endocrine communication 	Through the bloodstream	Hormones	Target cells are primarily in other tissues and organs and must have appropriate receptors
Synaptic communication 	Across synaptic clefts	Neurotransmitters	Limited to very specific area; target cells must have appropriate receptors

- The two systems share many chemical messengers. For example, norepinephrine and epinephrine are called *hormones* when released into the bloodstream, but *neurotransmitters* when released across synapses.
- Both systems are regulated mainly by negative feedback control mechanisms.
- The two systems share a common goal: to preserve homeostasis by coordinating and regulating the activities of other cells, tissues, organs, and systems.

Next we introduce the components and functions of the endocrine system and further explore the interactions between the nervous and endocrine systems. We consider specific endocrine organs, hormones, and functions in detail in later sections.

Checkpoint

1. **Define hormone.**
2. **Describe paracrine communication.**
3. **Identify four mechanisms of intercellular communication.**

See the blue Answers tab at the back of the book.

18-2 The endocrine system regulates physiological processes through the binding of hormones to receptors

The **endocrine system** includes all the endocrine cells and tissues of the body that produce hormones or paracrine factors with effects beyond their tissues of origin. As noted in Chapter 4, *endocrine cells* are glandular secretory cells that release their secretions into the extracellular fluid. This characteristic distinguishes them from *exocrine cells*, which secrete their products onto epithelial surfaces, generally by way of ducts. p. 118 The chemicals released by endocrine cells may affect only nearby cells, as in the case of most paracrine factors, or they may affect cells throughout the body.

Figure 18–1 introduces the tissues, organs, and hormones of the endocrine system. Some of these organs, such as the pituitary gland, have endocrine secretion as a primary function. Others, such as the pancreas, have many other functions in addition to endocrine secretion. We consider such endocrine organs in more detail in chapters on other systems.

Classes of Hormones

We can divide hormones into three groups on the basis of their chemical structure: (1) *amino acid derivatives*, (2) *peptide hormones*, and (3) *lipid derivatives*.

Amino acid derivatives, sometimes known as *biogenic amines*, are relatively small molecules that are structurally related to amino acids, the building blocks of proteins. p. 50 These hormones are synthesized from the amino acids *tyrosine* (TĪ-rō-sēn) and *tryptophan* (TRIP-tō-fan). Those made from tyrosine include (1) thyroid hormones, produced by the thyroid gland, and (2) the compounds epinephrine (E), norepinephrine (NE), and dopamine, which are sometimes called *catecholamines* (kat-e-KŌ-la-mēnz). The primary hormone made from tryptophan is melatonin (mel-a-TŌ-nin), produced by the pineal gland.

We can divide peptide hormones into two groups. One group consists of glycoproteins, and the other group is made up of short polypeptides and small proteins.

There are two classes of lipid derivatives: (1) *eicosanoids* and (2) *steroid hormones*. Eicosanoids are signaling molecules and include leukotrienes, prostaglandins, thromboxanes, and prostacyclins. Steroid hormones are lipids structurally similar to cholesterol (**Figure 2–17a**, p. 48). The individual hormones differ in the side chains attached to the basic ring structure. Over time, the liver gradually absorbs these steroids and converts them to a soluble form that can be excreted in the bile or urine (**Spotlight Figure 18–2**).

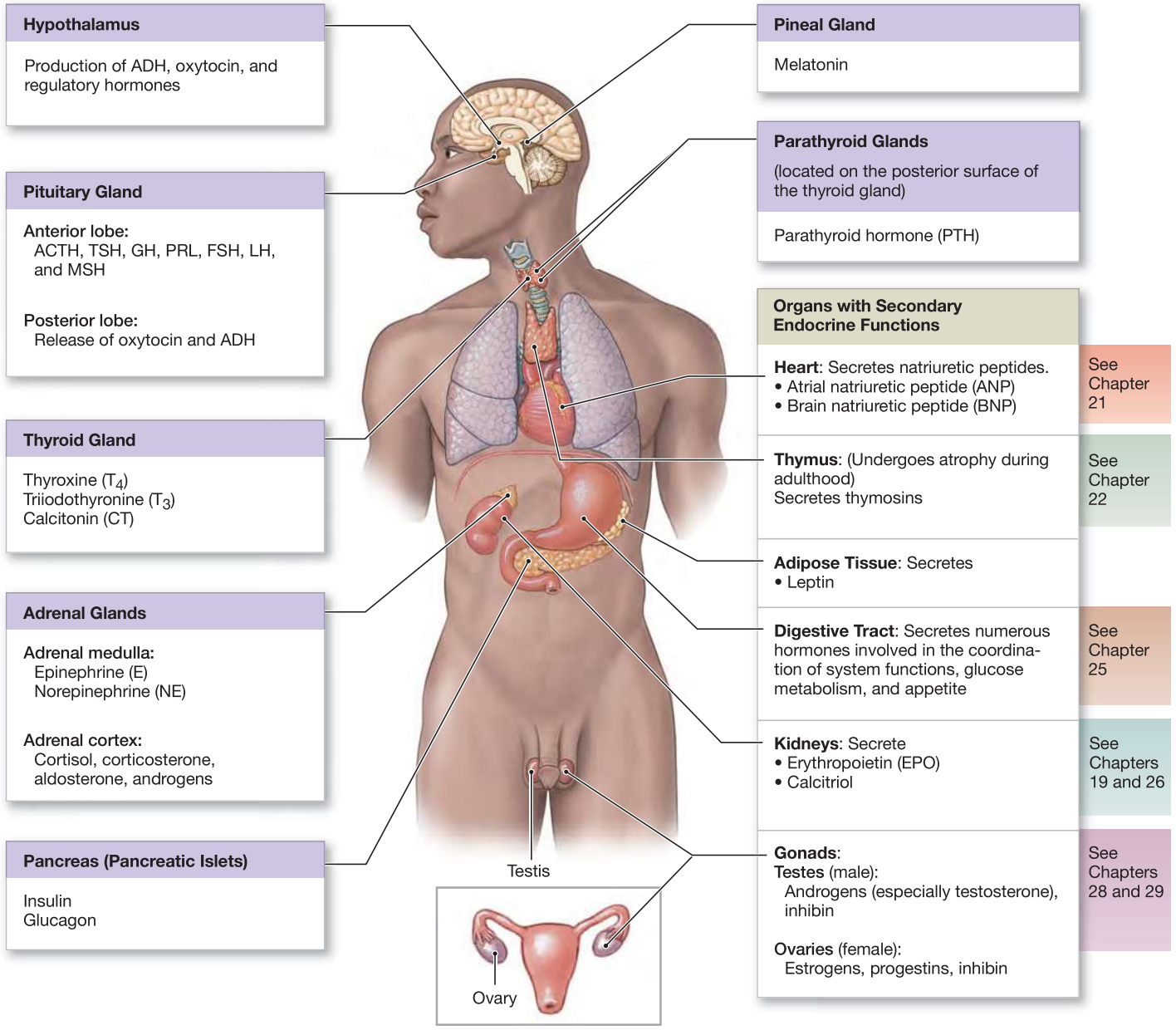
In this chapter we focus on circulating hormones that function primarily to coordinate activities in many tissues and organs. We consider eicosanoids in chapters that discuss individual tissues and organs, including Chapters 19 (the blood), 22 (the lymphatic system), and 28 (the reproductive system).

Secretion and Distribution of Hormones

Hormones are typically released where capillaries are abundant, and the hormones quickly enter the bloodstream for distribution throughout the body. Within the blood, hormones may circulate freely or travel bound to special carrier proteins. A freely circulating hormone remains functional for less than one hour, and sometimes for as little as two minutes. It is inactivated when (1) it diffuses out of the bloodstream and binds to receptors on target cells, (2) it is absorbed and broken down by cells of the liver or kidneys, or (3) it is broken down by enzymes in the plasma or interstitial fluids.

Thyroid hormones and steroid hormones remain in circulation much longer, because when these hormones enter the bloodstream, more than 99 percent of them become attached to special transport proteins. For each hormone an equilibrium state exists between its free and bound forms. As the free hormones are removed and inactivated, bound hormones are released to replace them. At any given time, the bloodstream contains a substantial reserve (several weeks' supply) of bound hormones.

Figure 18–1 Organs and Tissues of the Endocrine System.



Mechanisms of Hormone Action

Hormones coordinate cell, tissue, and organ activities on a sustained basis. They circulate in the extracellular fluid and bind to specific receptors on or in target cells. They then modify cellular activities by altering membrane permeability, activating or inactivating key enzymes, or changing genetic activity.

To affect a target cell, a hormone must first interact with an appropriate receptor. A hormone receptor, like a neurotransmitter receptor, is a protein molecule to which a particular molecule binds strongly. Each cell has receptors for several different hormones, but cells in different tissues have different combinations of receptors. This arrangement is one reason hormones have different effects on different tissues. For every cell, the presence or absence of a specific receptor determines the cell's hormonal sensitivities. If a cell has a receptor that can bind a particular hormone, that cell responds to the hormone. If a cell lacks the receptor for that hormone, the hormone has no effect on that cell.

Hormone receptors are located either on the plasma membrane or inside the cell. Using a few specific examples, let's consider the basic mechanisms involved.

Spotlight

Figure 18–2
Structural Classification of Hormones

HORMONES

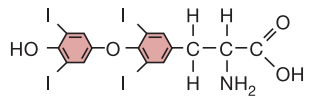
The hormones of the body can be divided into three groups on the basis of their chemical structure.

Amino Acid Derivatives

Amino acid derivatives are small molecules that are structurally related to amino acids, the building blocks of proteins.

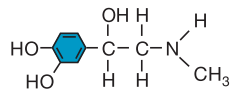
Derivatives of Tyrosine

Thyroid Hormones



Thyroxine (T_4)

Catecholamines

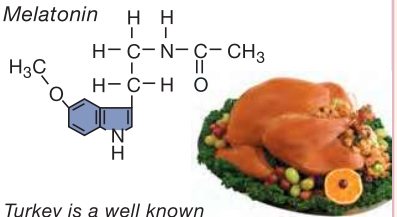


Epinephrine

Sources of tyrosine include meat, dairy, and fish.

Derivative of Tryptophan

Melatonin



Turkey is a well known source of tryptophan. Other sources include chocolate, oats, bananas, dried dates, milk, cottage cheese, and peanuts.

Peptide Hormones

Peptide hormones are chains of amino acids. Most peptide hormones are synthesized as **prohormones**—inactive molecules that are converted to active hormones before or after they are secreted.

Glycoproteins

These proteins are more than 200 amino acids long and have carbohydrate side chains. The glycoproteins include *thyroid-stimulating hormone* (TSH), *luteinizing hormone* (LH), and *follicle-stimulating hormone* (FSH) from the anterior lobe of the pituitary gland, as well as several hormones produced in other organs.

Short Polypeptides/Small Proteins

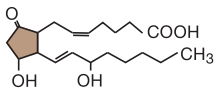
This group of peptide hormones is large and diverse. It includes hormones that range from **short chain polypeptides**, such as *antidiuretic hormone* (ADH) and *oxytocin* (OXT) (each 9 amino acids long), to **small proteins**, such as *growth hormone* (GH; 191 amino acids) and *prolactin* (PRL; 198 amino acids). This group includes all the hormones secreted by the hypothalamus, heart, thymus, digestive tract, pancreas, and posterior lobe of the pituitary gland, as well as several hormones produced in other organs.

Lipid Derivatives

There are two classes of lipid derivatives: **eicosanoids**, derived from arachidonic acid, a 20-carbon fatty acid; and **steroid hormones**, derived from cholesterol.

Eicosanoids

Eicosanoids (ī-kō-sa-noydz) are important paracrine factors that coordinate cellular activities and affect enzymatic processes (such as blood clotting) in extracellular fluids. Some eicosanoids, such as **leukotrienes** (loo-kō-TRĪ-ēns), have secondary roles as hormones. A second group of eicosanoids—**prostaglandins**—are involved primarily in coordinating local cellular activities. In some tissues, prostaglandins are converted to **thromboxanes** (throm-BOX-ānz) and **prostacyclins** (pros-ta-SĪ-klinz), which also have strong paracrine effects.

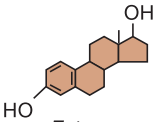


Prostaglandin E

Aspirin suppresses the production of prostaglandins.

Steroid Hormones

Steroid hormones are released by the reproductive organs (androgens by the testes in males, estrogens and progestins by the ovaries in females), by the cortex of the adrenal glands (corticosteroids), and by the kidneys (calcitriol). Because circulating steroid hormones are bound to specific transport proteins in the plasma, they remain in circulation longer than do secreted peptide hormones.



Estrogen

Hormones and Plasma Membrane Receptors

The receptors for catecholamines (E, NE, and dopamine), peptide hormones, and eicosanoids are in the plasma membranes of their target cells. Catecholamines and peptide hormones cannot penetrate a plasma membrane because they are not lipid soluble. Instead, these hormones bind to receptor proteins at the *outer* surface of the plasma membrane (extracellular receptors). Eicosanoids *are* lipid soluble. They diffuse across the plasma membrane to reach receptor proteins on the *inner* surface of the membrane (intracellular receptors).

First and Second Messengers. A hormone that binds to receptors in the plasma membrane cannot directly affect the activities inside the target cell. For example, it cannot begin building a protein or catalyzing a specific reaction. Instead, the hormone uses an intracellular intermediary to bring about its effects. The hormone, or **first messenger,** does something that leads to the appearance of a **second messenger** in the cytoplasm. The second messenger may act as an enzyme activator, inhibitor, or cofactor. The net result is a change in the rates of various metabolic reactions. The most important second messengers are (1) *cyclic-AMP (cAMP)*, a derivative of ATP; (2) *cyclic-GMP (cGMP)*, a derivative of GTP, another high-energy compound; and (3) calcium ions.

When a small number of hormone molecules binds to membrane receptors, thousands of second messengers may appear in a cell. This process, called *amplification,* magnifies the effect of a hormone on the target cell. Moreover, the arrival of a single hormone may promote the release of more than one type of second messenger, or the production of a linked sequence of enzymatic reactions known as a *receptor cascade*. Through such mechanisms, the hormone can alter many aspects of cell function at the same time.

The presence or absence of a hormone can also affect the nature and number of hormone receptor proteins in the plasma membrane. **Down-regulation** is a process in which the presence of a hormone triggers a decrease in the number of hormone receptors. In down-regulation, when levels of a particular hormone are high, cells become *less* sensitive to it. Conversely, **up-regulation** is a process in which the absence of a hormone triggers an increase in the number of hormone receptors. In up-regulation, when levels of a particular hormone are low, cells become *more* sensitive to it.

The link between the first messenger and the second messenger generally involves a **G protein,** an enzyme complex coupled to a membrane receptor. The name *G protein* refers to the fact that these proteins bind GTP. ↩ p. 405 A G protein is activated when a hormone binds to its receptor at the membrane surface. What happens next depends on the nature of the G protein and its effects on second messengers in the cytoplasm. **Figure 18–3** diagrams three major patterns of response to G protein activation. Roughly eighty percent of prescription drugs target receptors coupled to G proteins.

G Proteins and cAMP. **Figure 18–3** (left) shows the steps involved in *increasing* cAMP levels:

- The activated G protein activates the enzyme **adenylate cyclase.**
- Adenylate cyclase converts ATP to the ring-shaped molecule *cyclic-AMP*.
- Cyclic-AMP then functions as a second messenger, typically by activating a *kinase* (KĪ-nās). A kinase is an enzyme that attaches a high-energy phosphate group ($\sim PO_4^{3-}$) to another molecule in a process called *phosphorylation*.
- Generally, cyclic-AMP activates kinases that phosphorylate proteins. The effect on the target cell depends on the nature of these proteins. The phosphorylation of plasma membrane proteins, for example, can open ion channels. In the cytoplasm, many important enzymes can be activated only by phosphorylation. One important example is the enzyme that releases glucose from glycogen reserves in skeletal muscles and the liver.

Many hormones, including calcitonin, parathyroid hormone, ADH, ACTH, epinephrine, FSH, LH, TSH, and glucagon, produce their effects by this mechanism. The increase in cAMP levels is usually short-lived, because the cytoplasm contains another enzyme, **phosphodiesterase (PDE),** which inactivates cyclic-AMP by converting it to AMP (adenosine monophosphate).

Figure 18–3 (center) depicts one way the activation of a G protein can *lower* the concentration of cAMP within the cell. In this case, the activated G protein stimulates PDE activity and inhibits adenylate cyclase activity. Levels of cAMP then decline, because cAMP breakdown accelerates while cAMP synthesis is prevented. The decline has an inhibitory effect on the cell, because without phosphorylation, key enzymes remain inactive. This mechanism is responsible for the inhibitory effects that follow when epinephrine and norepinephrine stimulate α_2 adrenergic receptors, as discussed in Chapter 16. ↩ p. 525

G Proteins and Calcium Ions. An activated G protein can trigger either the opening of calcium ion channels in the plasma membrane or the release of calcium ions from intracellular compartments. **Figure 18–3** (right panel) diagrams the steps involved. The G protein first activates the enzyme *phospholipase C (PLC)*. This enzyme triggers a receptor cascade that begins with the production of **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)** from membrane phospholipids. The cascade then proceeds as follows:

- IP_3 diffuses into the cytoplasm and triggers the release of Ca^{2+} from intracellular reserves, such as those in the smooth endoplasmic reticulum of many cells.
- The combination of DAG and intracellular calcium ions activates another membrane protein: **protein kinase C**

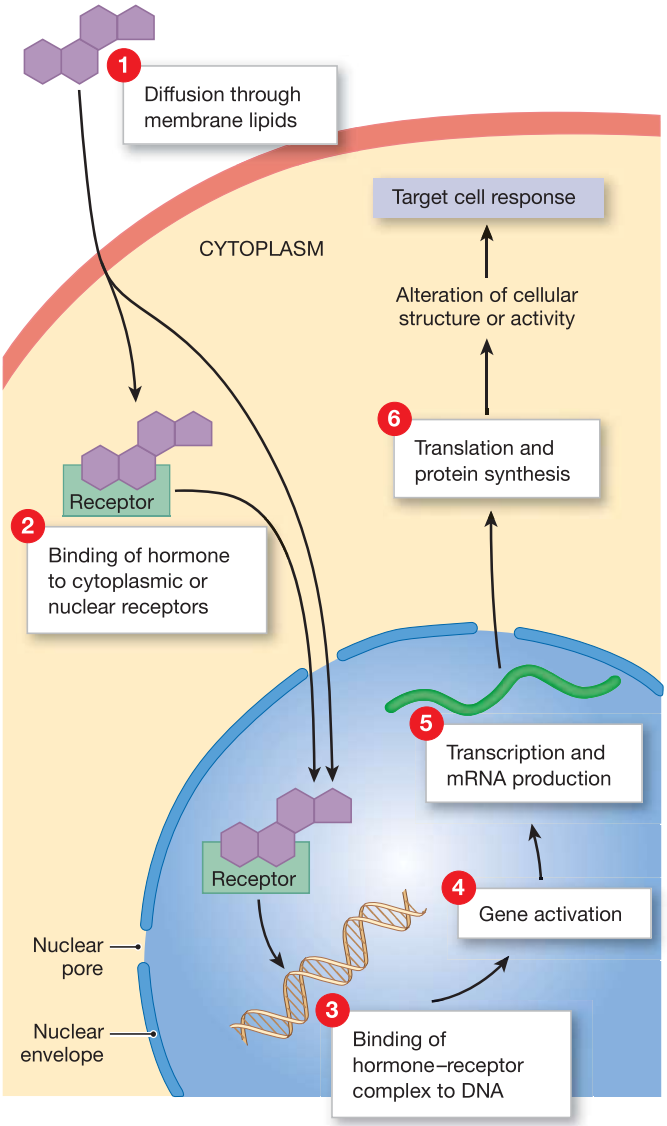
The hormone–receptor complexes then activate or deactivate specific genes (**Figure 18–4a**). By this mechanism, steroid hormones can alter the rate of DNA transcription in the nucleus. In this way, they change the pattern of protein synthesis. Alterations in the synthesis of enzymes or structural proteins directly affect both the metabolic activity and the structure of the target cell. For example, the sex hormone *testosterone* stimulates the production of enzymes and structural proteins in skeletal muscle fibers, causing muscle size and strength to increase.

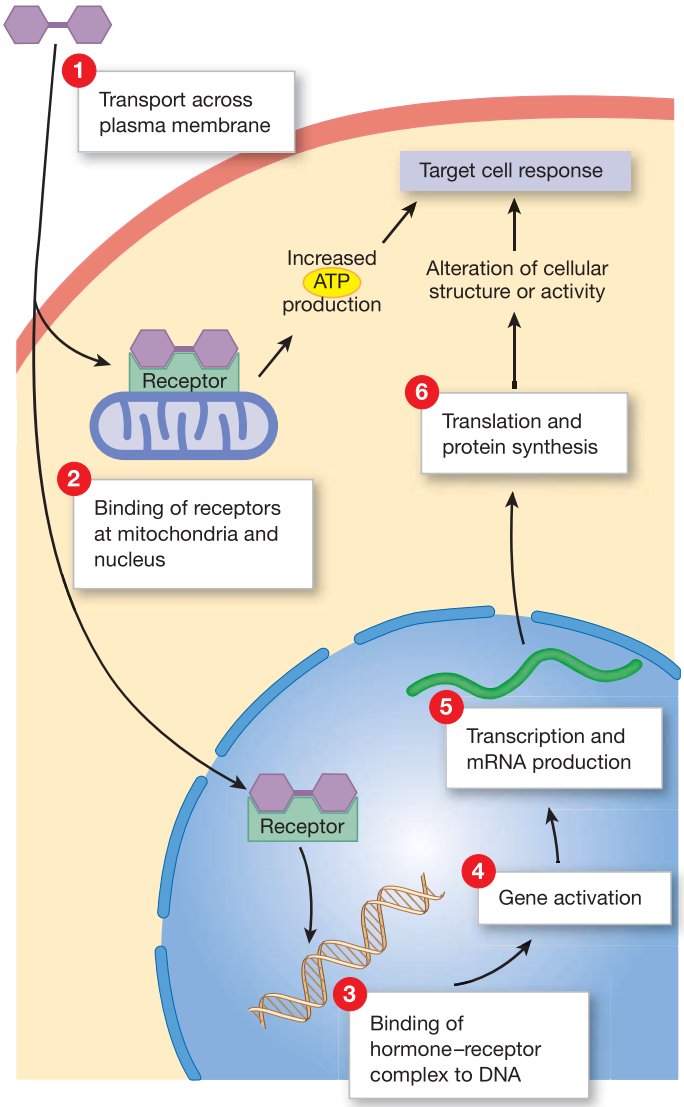
Thyroid hormones cross the plasma membrane primarily by a transport mechanism. Once in the cytoplasm, these hormones bind to receptors within the nucleus and on mitochondria (**Figure 18–4b**). The hormone–receptor complexes in the nucleus activate specific genes or change the rate of transcription. The change in transcription rate affects the metabolic activities of the cell by increasing or decreasing the concentration of specific enzymes. Thyroid hormones bound to mitochondria increase the mitochondrial rates of ATP production.

Figure 18–4 **Effects of Intracellular Hormone Binding.**

a Steroid hormones diffuse through the plasma membrane and bind to receptors in the cytoplasm or nucleus. The complex then binds to DNA in the nucleus, activating specific genes.

b Thyroid hormones enter the cytoplasm and bind to receptors in the nucleus to activate specific genes. They also bind to receptors on mitochondria and accelerate ATP production.





Control of Endocrine Activity by Endocrine Reflexes

As noted earlier, the functional organization of the nervous system parallels that of the endocrine system in many ways. In Chapter 13, we considered the basic operation of neural reflex arcs, the simplest organizational units in the nervous system. ↩ p. 436 The most direct arrangement was a monosynaptic reflex, such as the stretch reflex. Polysynaptic reflexes provide more complex and variable responses to stimuli. Higher centers, which integrate multiple inputs, can facilitate or inhibit these reflexes as needed.

Endocrine reflexes are the functional counterparts of neural reflexes. Endocrine reflexes can be triggered by (1) *humoral stimuli* (changes in the composition of the extracellular fluid), (2) *hormonal stimuli* (the arrival or removal of a specific hormone), or (3) *neural stimuli* (the arrival of neurotransmitters at neuroglandular junctions). In most cases, negative feedback controls endocrine reflexes: A stimulus triggers the production of a hormone, and the direct or indirect effects of the hormone reduce the intensity of the stimulus.

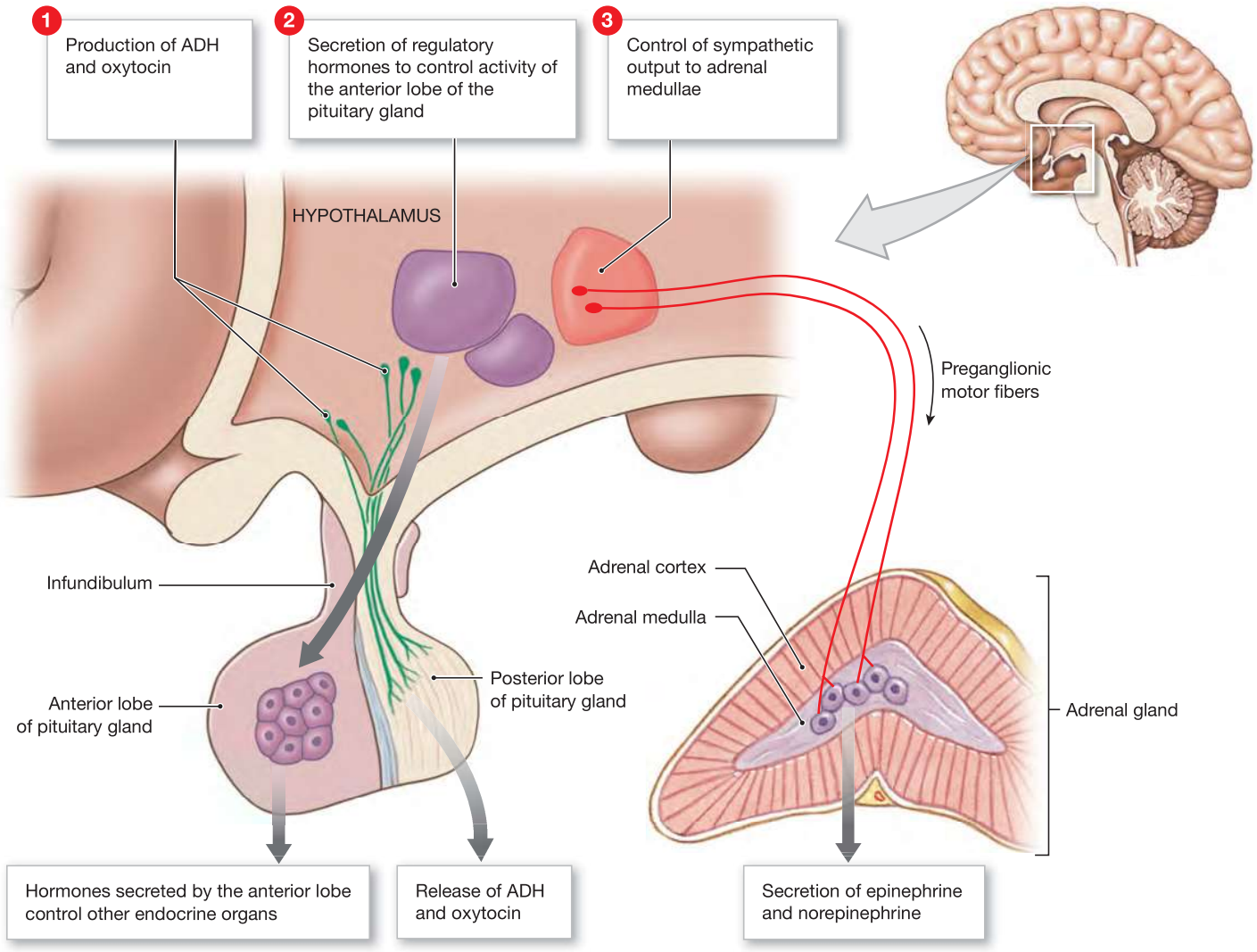
A simple endocrine reflex involves only one hormone. The endocrine cells involved respond directly to changes in the composition of the extracellular fluid. The secreted hormone adjusts the activities of target cells and restores homeostasis. Simple endocrine reflexes control hormone secretion by the heart, pancreas, parathyroid glands, and digestive tract.

More complex endocrine reflexes involve one or more intermediary steps and two or more hormones.

The hypothalamus provides the highest level of endocrine control. It integrates the activities of the nervous and endocrine systems in three ways (**Figure 18–5**):

1. The hypothalamus itself acts as an endocrine organ. Hypothalamic neurons synthesize hormones and transport them along axons to the posterior lobe of the pituitary gland, where

Figure 18–5 Three Mechanisms of Hypothalamic Control over Endocrine Function.



they are released into the circulation. We introduced two of these hormones, ADH and oxytocin, in Chapter 14. ↩ p. 465

2. The hypothalamus secretes **regulatory hormones,** special hormones that control endocrine cells in the pituitary gland. The hypothalamic regulatory hormones control the secretory activities of endocrine cells in the anterior lobe of the pituitary gland. In turn, the hormones from the anterior lobe control the activities of endocrine cells in the thyroid, adrenal cortex, and reproductive organs.
3. The hypothalamus contains autonomic centers that exert direct neural control over the endocrine cells of the adrenal medullae. When the sympathetic division is activated, the adrenal medullae release hormones into the bloodstream.

The hypothalamus secretes regulatory hormones and ADH in response to changes in the composition of the circulating blood. The secretion of oxytocin (OXT), E, and NE involves both neural and hormonal mechanisms. For example, the adrenal medullae secrete E and NE in response to action potentials rather than to circulating hormones. Such pathways are called *neuroendocrine reflexes*, because they include both neural and endocrine components. We will consider these reflex patterns in more detail as we examine specific endocrine tissues and organs.

In Chapter 15, we noted that sensory receptors provide complex information by varying the frequency and pattern of action potentials in a sensory neuron. In a similar way, the endocrine system sends complex commands by changing the amount of hormone secreted and the pattern of hormone release. In a simple endocrine reflex, hormones are released continuously, but the rate of secretion rises and falls in response to humoral stimuli. For example, when blood glucose levels climb, the pancreas increases its secretion of *insulin*, a hormone that stimulates glucose uptake and utilization. As insulin levels rise, glucose levels decline, reducing the stimulation of the insulin-secreting cells. As glucose levels return to normal, the rate of insulin secretion returns to resting levels. (We introduced this regulatory pattern, called *negative feedback*, in Chapter 1 when we considered the control of body temperature. ↩ p. 12)

In this example, the responses of the target cells change over time, because the effect of insulin is proportional to its concentration. However, the relationship between hormone concentration and target cell response is not always predictable. For instance, a hormone can have one effect at low concentrations and more exaggerated effects—or even different effects—at high concentrations. (We consider specific examples later in the chapter.)

Several hypothalamic and pituitary hormones are released in sudden bursts called *pulses*, rather than continuously. When hormones arrive in pulses, target cells may vary their response with the frequency of the pulses. For example, the target cell response to one pulse every three hours can differ from the response when pulses arrive every 30 minutes. The most complicated hormonal instructions from the hypothalamus involve changes in the frequency of pulses *and* in the amount secreted in each pulse.

Checkpoint

4. **How could you distinguish between a neural response and an endocrine response on the basis of response time and duration?**
5. **How would the presence of a substance that inhibits the enzyme adenylate cyclase affect the activity of a hormone that produces its cellular effects by way of the second messenger cAMP?**
6. **What primary factor determines each cell's hormonal sensitivities?**

See the blue Answers tab at the back of the book.

18-3 The bilobed pituitary gland is an endocrine organ that releases nine peptide hormones

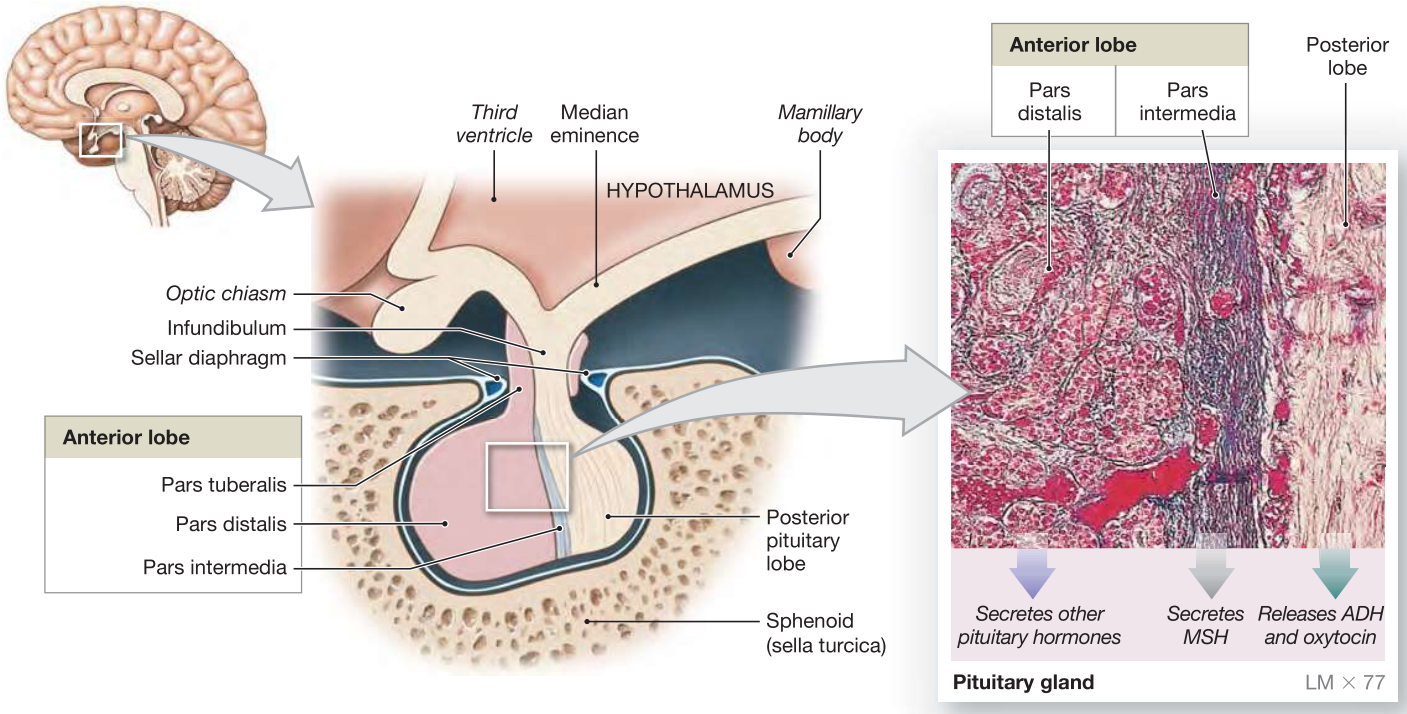
Figure 18–6 shows the anatomical organization of the **pituitary gland,** or **hypophysis** (hī-POF-i-sis). This small, oval gland lies nestled within the *sella turcica*, a depression in the sphenoid (**Figure 7–8**, p. 207). The pituitary gland hangs inferior to the hypothalamus. It is connected by the slender, funnel-shaped structure called the **infundibulum** (in-fun-DIB-ū-lum; funnel). The base of the infundibulum lies between the optic chiasm and the mamillary bodies. Cradled by the sella turcica, the pituitary gland is held in position by the *sellar diaphragm*, a dural sheet that encircles the infundibulum. The sellar diaphragm locks the pituitary gland in position and isolates it from the cranial cavity.

The pituitary gland has anterior and posterior lobes that differ in function and developmental anatomy. It releases nine important peptide hormones. Seven come from the anterior lobe and two from the posterior lobe. All nine hormones bind to membrane receptors, and all nine use cAMP as a second messenger. ATLAS: Embryology Summary 14: The Development of the Endocrine System

The Anterior Lobe of the Pituitary Gland

The **anterior lobe** of the pituitary gland, also called the **adenohypophysis** (ad-e-no-hī-POF-i-sis), contains a variety of endocrine cells. The anterior lobe has three regions: (1) the **pars distalis** (dis-TAL-is; distal part), the largest and most anterior portion of the pituitary gland; (2) an extension called the **pars tuberalis,** which wraps around the adjacent portion of the infundibulum; and (3) the slender **pars intermedia,** a narrow band bordering the posterior lobe (**Figure 18–6**). An extensive capillary network radiates through these regions, giving every endocrine cell immediate access to the bloodstream.

Figure 18–6 The Anatomy and Orientation of the Pituitary Gland.



a Relationship of the pituitary gland to the hypothalamus

b Histological organization of pituitary gland showing the anterior and posterior lobes of the pituitary gland

The Hypophyseal Portal System

The hypothalamus controls the production of hormones in the anterior lobe of the pituitary gland by secreting specific regulatory hormones. At the *median eminence*, a swelling near the attachment of the infundibulum, hypothalamic neurons release regulatory factors into the surrounding interstitial fluids. Their secretions enter the bloodstream quite easily, because the endothelial cells lining the capillaries in this region are unusually permeable. These **fenestrated** (FEN-es-trā-ted; *fenestra*, window) **capillaries** allow relatively large molecules to enter or leave the bloodstream.

The capillary networks in the median eminence are supplied by the *superior hypophyseal artery* (**Figure 18–7**). Before leaving the hypothalamus, the capillary networks unite to form a series of larger vessels that spiral around the infundibulum to reach the anterior lobe. In the anterior lobe, these vessels form a second capillary network that branches among the endocrine cells.

This vascular arrangement is unusual because it carries blood from one capillary network to another. In contrast, a typical artery conducts blood from the heart to a capillary network, and a typical vein carries blood from a capillary network back to the heart. Blood vessels that link two capillary networks are called **portal vessels.** In this case, they have the histological structure of veins, so they are also called portal veins. The entire complex is a **portal system.** Portal systems are named for their destinations. This particular network is the **hypophyseal** (hī-po-FI-sē-al) **portal system**.

Portal systems are an efficient means of chemical communication. This one ensures that all the hypothalamic hormones entering the portal vessels reach the target cells in the anterior lobe before being diluted through mixing with the general circulation. The communication is strictly one way, however. Any chemicals released by the cells "downstream" must do a complete circuit of the cardiovascular system before they reach the capillaries of the portal system.

Hypothalamic Control of the Anterior Lobe

Two classes of hypothalamic regulatory hormones exist: releasing hormones and inhibiting hormones. A **releasing hormone (RH)** stimulates the synthesis and secretion of one or more hormones at the anterior lobe. In contrast, an **inhibiting hormone (IH)** prevents the synthesis and secretion of hormones from the anterior lobe. Releasing hormones, inhibiting hormones, or some combination of the two may control an endocrine cell in the anterior lobe. The regulatory hormones released at the hypothalamus travel directly to the anterior lobe by the hypophyseal portal system.

Negative feedback controls the rate at which the hypothalamus secretes regulatory hormones. The primary regulatory patterns are diagrammed in **Figure 18–8**, and we will refer to them as we examine specific pituitary hormones.

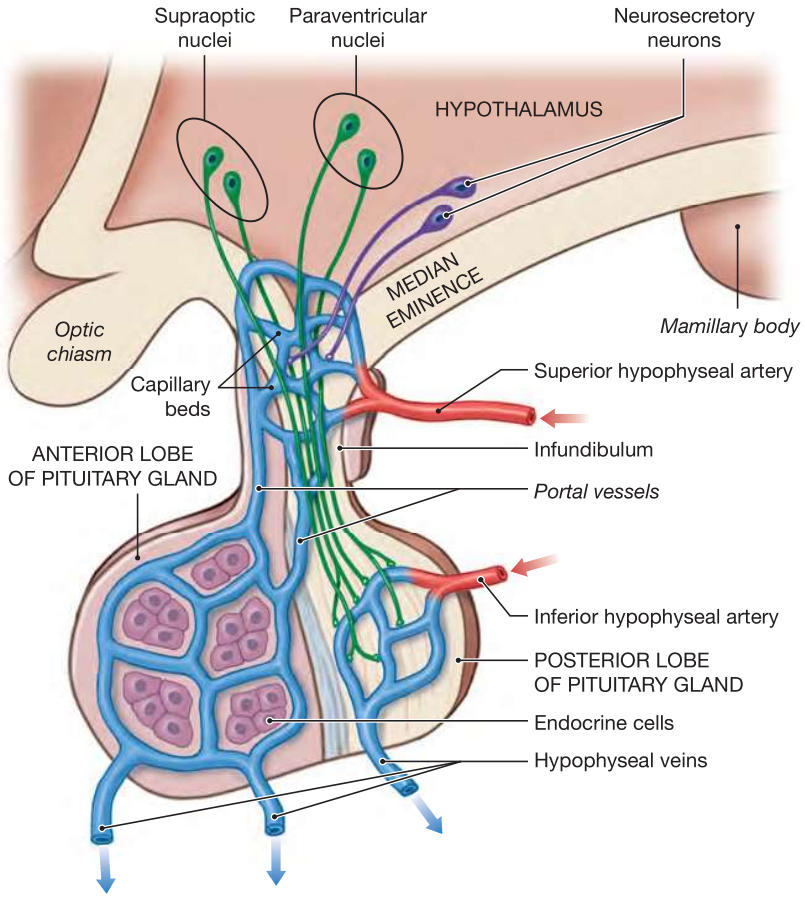
Hormones of the Anterior Lobe

The functions and control mechanisms of seven hormones from the anterior lobe are reasonably well understood: *thyroid-stimulating hormone*; *adrenocorticotropic hormone*; two gonadotropins called *follicle-stimulating hormone* and *luteinizing hormone*; *prolactin*; *growth hormone*; and *melanocyte-stimulating hormone*. Of the six hormones produced by the pars distalis, four regulate the production of hormones by other endocrine glands. The names of these hormones indicate their activities, but many of the phrases are so long that we often use abbreviations instead.

The hormones of the anterior lobe are also called *tropic hormones* (*trope*, a turning). They "turn on" endocrine glands or support the functions of other organs. (Some sources call them *trophic hormones* [*trophe*, nourishment] instead.)

Thyroid-Stimulating Hormone. Thyroid-stimulating hormone (TSH), or *thyrotropin*, targets the thyroid gland and triggers the release of thyroid hormones. TSH is released in response to *thyrotropin-releasing hormone (TRH)* from the hypothalamus. Then as circulating concentrations of thyroid hormones rise, the rates of TRH and TSH production decline (**Figure 18–8a**).

Figure 18–7 The Hypophyseal Portal System and the Blood Supply to the Pituitary Gland.

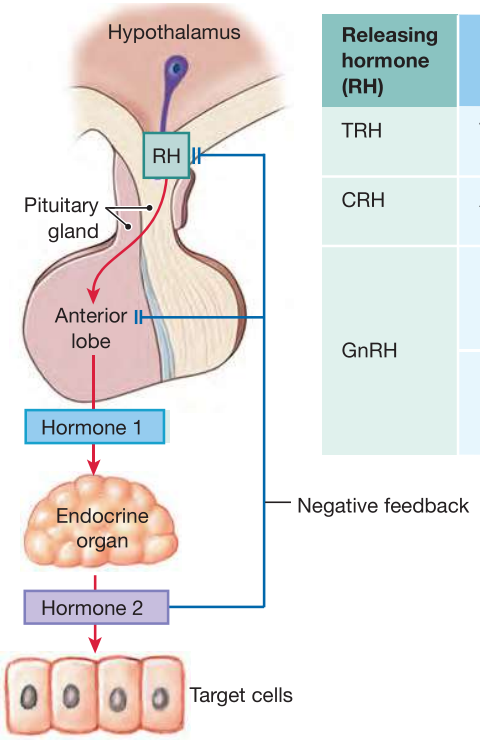


Adrenocorticotropic Hormone. Adrenocorticotropic hormone (ACTH), also known as *corticotropin*, stimulates the release of steroid hormones by the *adrenal cortex*, the outer portion of the adrenal gland. ACTH specifically targets cells that produce *glucocorticoids* (gloo-kō-KOR-ti-koydz), hormones that affect glucose metabolism. ACTH release occurs under the stimulation of **corticotropin-releasing hormone (CRH)** from the hypothalamus. As glucocorticoid levels increase, the rates of CRH release and ACTH release decline (**Figure 18–8a**).

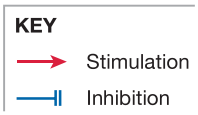
Gonadotropins. The hormones called **gonadotropins** (gō-nad-ō-TRŌ-pinz) regulate the activities of the *gonads*. (These organs—the testes in males and the ovaries in females—produce reproductive cells as well as hormones.) Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates production of gonadotropins. An abnormally low production of gonadotropins produces **hypogonadism.** Children with this condition do not mature sexually, and adults with hypogonadism cannot produce functional sperm (males) or oocytes (females). The two gonadotropins are follicle-stimulating hormone and luteinizing hormone.

- **Follicle-stimulating hormone (FSH),** or *follitropin*, promotes follicle development in females and, in combination with luteinizing hormone, stimulates the secretion of *estrogens* (ES-trō-jenz) by ovarian cells. *Estradiol* is the most important estrogen. In males, FSH stimulates *nurse cells*, specialized cells in the seminiferous tubules where sperm differentiate. In response, the nurse cells promote the physical maturation of developing sperm. FSH production is inhibited by *inhibin*, a peptide hormone released by cells in the testes and ovaries (**Figure 18–8a**). (The role of inhibin in suppressing the release of GnRH as well as FSH is under debate.)
- **Luteinizing** (LOO-tē-in-ī-zing) **hormone (LH),** or *lutropin*, induces *ovulation*, the production of reproductive cells in females. It also promotes the secretion, by the ovaries, of estrogens and the *progestins* (such as *progesterone*), which prepare the body for possible pregnancy. In males, this gonadotropin is sometimes called *interstitial cell–stimulating hormone (ICSH)*, because it stimulates the production of sex hormones by the *interstitial cells* of the testes. These male sex hormones are called **androgens** (AN-drō-jenz; *andros*, man). The most important one is *testosterone*. LH production, like FSH production, is stimulated by GnRH from the hypothalamus. Estrogens, progestins, and androgens inhibit GnRH production (**Figure 18–8a**).

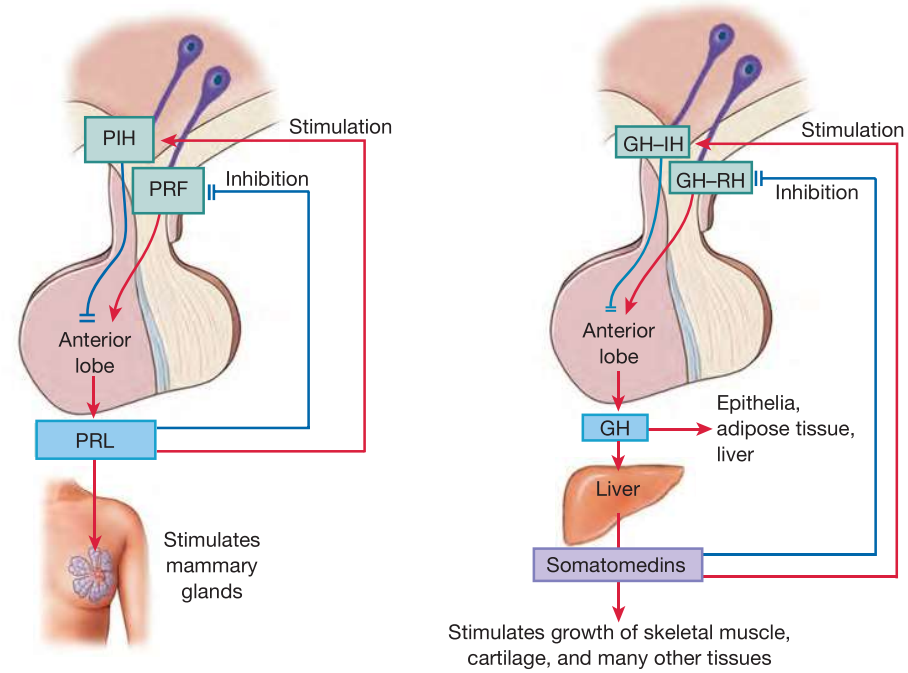
Figure 18–8 Feedback Control of Endocrine Secretion.



Releasing hormone (RH)	Hormone 1 (from pituitary)	Endocrine target organ	Hormone 2 (from target organ)
TRH	TSH	Thyroid gland	Thyroid hormones
CRH	ACTH	Adrenal cortex	Gluco-corticoids
GnRH	FSH	Testes	Inhibin
		Ovaries	Inhibin, Estrogens
	LH	Ovaries	Progestins, Estrogens
		Testes	Androgens



a A typical pattern of regulation when multiple endocrine organs are involved. The hypothalamus produces a releasing hormone (RH) to stimulate hormone production by other glands; control occurs via negative feedback.



b Variations on the theme outlined in part (a). Left: The regulation of prolactin (PRL) production by the anterior lobe. In this case, the hypothalamus produces both a releasing factor (PRF) and an inhibiting hormone (PIH); when one is stimulated, the other is inhibited. Right: the regulation of growth hormone (GH) production by the anterior lobe; when GH–RH release is inhibited, GH–IH release is stimulated.

Prolactin. Prolactin (*pro-*, before + *lac*, milk) **(PRL),** or *mammotropin*, works with other hormones to stimulate mammary gland development. In pregnancy and during the nursing period that follows delivery, PRL also stimulates milk production by the mammary glands. The functions of PRL in males are poorly understood, but evidence indicates that PRL helps regulate androgen production by making interstitial cells more sensitive to LH.

Prolactin production is inhibited by the neurotransmitter dopamine, also known as **prolactin-inhibiting hormone (PIH).** The hypothalamus also secretes several *prolactin-releasing factors (PRF)*. Few of these have been identified. Circulating PRL stimulates PIH release and inhibits the secretion of PRF (**Figure 18–8b**).

Although PRL exerts the dominant effect on the glandular cells, normal development of the mammary glands is regulated by the interaction of several hormones. Prolactin, estrogens, progesterone, glucocorticoids, pancreatic hormones, and hormones produced by the placenta cooperate in preparing the mammary glands for secretion. Milk ejection occurs only in response to oxytocin release at the posterior lobe of the pituitary gland. We describe the functional development of the mammary glands in Chapter 28.

Growth Hormone. Growth hormone (GH), or **somatotropin,** stimulates cell growth and replication by accelerating the rate of protein synthesis. Skeletal muscle cells and chondrocytes (cartilage cells) are particularly sensitive to GH, although virtually every tissue responds to some degree.

The stimulation of growth by GH involves two mechanisms. The primary mechanism, which is indirect, is best understood. Liver cells respond to GH by synthesizing and releasing **somatomedins** (compounds that stimulate tissue growth), or **insulin-like growth factors (IGFs).** These peptide hormones bind to receptors on a variety of plasma membranes (**Figure 18–8b**). In skeletal muscle fibers, cartilage cells, and other target cells, somatomedins increase the uptake of amino acids and their incorporation into new proteins. These effects develop almost immediately after GH is released. They are particularly important after a meal, when the blood contains high concentrations of glucose and amino acids. In functional terms, cells can now obtain ATP easily through the aerobic metabolism of glucose, and amino acids are readily available for protein synthesis. Under these conditions, GH, acting through the somatomedins, stimulates protein synthesis and cell growth.

The direct actions of GH are more selective. They tend to appear after blood glucose and amino acid concentrations have returned to normal levels:

- In epithelia and connective tissues, GH stimulates stem cell divisions and the differentiation of daughter cells. (Somatomedins then stimulate the growth of these daughter cells.)
- In adipose tissue, GH stimulates the breakdown of stored triglycerides by adipocytes (fat cells), which then release fatty acids into the blood. As circulating fatty acid levels rise, many tissues stop breaking down glucose to generate ATP and instead start breaking down fatty acids. This process is termed a **glucose-sparing effect.**
- In the liver, GH stimulates the breakdown of glycogen reserves by liver cells, which then release glucose into the bloodstream. Because most other tissues are now metabolizing fatty acids rather than glucose, blood glucose concentrations begin to climb to levels significantly higher than normal. The elevation of blood glucose levels by GH has been called a **diabetogenic effect,** because *diabetes mellitus*, an endocrine disorder we consider later in the chapter, is characterized by abnormally high blood glucose concentrations.

The production of GH is regulated by **growth hormone–releasing hormone (GH–RH,** or *somatocrinin*) and **growth hormone–inhibiting hormone (GH–IH,** or *somatostatin*) from the hypothalamus. Somatomedins inhibit GH–RH and stimulate GH–IH (**Figure 18–8b**).

Melanocyte-Stimulating Hormone. The pars intermedia may secrete two forms of **melanocyte-stimulating hormone (MSH),** or *melanotropin*. As the name indicates, MSH stimulates the melanocytes of the skin, increasing their production of melanin, a brown, black, or yellow-brown pigment. ↩ p. 149 Dopamine inhibits the release of MSH.

Melanocyte-stimulating hormone from the pituitary gland is important in the control of skin pigmentation in fishes, amphibians, reptiles, and many mammals other than primates. In humans, MSH is produced locally, within sun-exposed skin. The pars intermedia in adult humans is virtually nonfunctional, and the circulating blood usually does not contain MSH. However, the human pars intermedia secretes MSH (1) during fetal development, (2) in very young children, (3) in pregnant women, and (4) in the course of some diseases. The functional significance of MSH secretion under these circumstances is not known. The administration of a synthetic form of MSH causes the skin to darken, so MSH has been suggested as a means of obtaining a "sunless tan."

The Posterior Lobe of the Pituitary Gland

The **posterior lobe** of the pituitary gland, also called the **neurohypophysis** (noo-rō-hī-POF-i-sis), contains the axons of hypothalamic neurons. Neurons of the **supraoptic** and **paraventricular nuclei** manufacture antidiuretic hormone (ADH) and oxytocin (OXT), respectively. These hormones move along axons in the infundibulum to axon terminals, which end on the basal membranes of capillaries in the posterior lobe. They travel by means of axoplasmic transport. ↩ p. 378

Antidiuretic Hormone

Antidiuretic hormone (ADH), also known as *vasopressin (VP)*, is released in response to a variety of stimuli, most notably a rise in the solute concentration in the blood or a fall in blood volume or blood pressure. A rise in the solute concentration stimulates specialized neurons in the hypothalamus. These neurons are called *osmoreceptors* because they respond to a change in the osmotic concentration of body fluids. The osmoreceptors then stimulate the neurosecretory neurons that release ADH.

The primary function of ADH is to decrease the amount of water lost at the kidneys. With losses minimized, any water absorbed from the digestive tract will be retained, reducing the concentrations of electrolytes in the extracellular fluid. In high concentrations, ADH also causes *vasoconstriction*, a narrowing of peripheral blood vessels that helps elevate blood pressure. Alcohol inhibits ADH release, which explains why people find themselves making frequent trips to the bathroom after consuming alcoholic beverages.

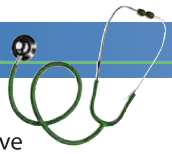
Oxytocin

In women, **oxytocin** (*oxy-*, quick + *tokos*, childbirth) **(OXT)** stimulates smooth muscle contraction in the wall of the uterus, promoting labor and delivery. After delivery, oxytocin promotes the ejection of milk by stimulating the contraction of myoepithelial cells around the secretory alveoli and the ducts of the mammary glands.

Until the last stages of pregnancy, the uterine smooth muscles are relatively insensitive to oxytocin, but they become more sensitive as the time of delivery approaches. The trigger for normal labor and delivery is probably a sudden rise in oxytocin levels at the uterus. There is good evidence, however, that the uterus and fetus secrete most of the oxytocin involved. Oxytocin from the posterior lobe plays only a supporting role.

Oxytocin secretion and milk ejection are part of a neuroendocrine reflex called the *milk let-down reflex*. The normal stimulus is an infant suckling at the breast, and sensory nerves innervating the nipples relay the information to the hypothalamus. Oxytocin is then released into the circulation at the posterior lobe, and the myoepithelial cells respond by squeezing milk from the secretory alveoli into large collecting ducts. Any factor that affects the hypothalamus can modify this reflex. For example, anxiety, stress, and other factors can prevent the flow of milk, even when the mammary glands are fully functional. In contrast, nursing mothers can become conditioned to associate a baby's crying with suckling. In these women, milk let-down may begin as soon as they hear a baby cry.

The functions of oxytocin in sexual activity remain uncertain, but it is known that circulating concentrations of oxytocin rise during sexual arousal and peak at orgasm in both sexes. Evidence indicates that in men, oxytocin stimulates smooth muscle contractions in the walls of the *ductus deferens* (sperm duct) and prostate gland. These actions may be important in *emission*—the ejection of sperm, secretions of the prostate gland, and the secretions of other glands into the male reproductive tract before ejaculation. Studies suggest that the oxytocin released in females during intercourse may stimulate smooth muscle contractions in the uterus and vagina that promote the transport of sperm toward the uterine tubes.



Clinical Note

Diabetes Insipidus *Diabetes* occurs in several forms, all characterized by excessive urine production (polyuria). Most forms result from endocrine abnormalities, although physical damage to the kidneys can cause diabetes. The two most prevalent forms are diabetes insipidus and diabetes mellitus. (We describe diabetes mellitus in the Spotlight on page 623.) **Diabetes insipidus** generally develops because the posterior lobe of the pituitary gland no longer releases adequate amounts of ADH. Water conservation at the kidneys is impaired, and excessive amounts of water are lost in the urine. As a result, the individual is constantly thirsty, but the body does not retain the fluids consumed.

Mild cases of diabetes insipidus may not require treatment if fluid and electrolyte intake keeps pace with urinary losses. In severe cases, the fluid losses can reach 10 liters per day, and dehydration and electrolyte imbalances are fatal without treatment. This condition can be effectively treated with desmopressin, a synthetic form of ADH.

Summary: The Hormones of the Pituitary Gland

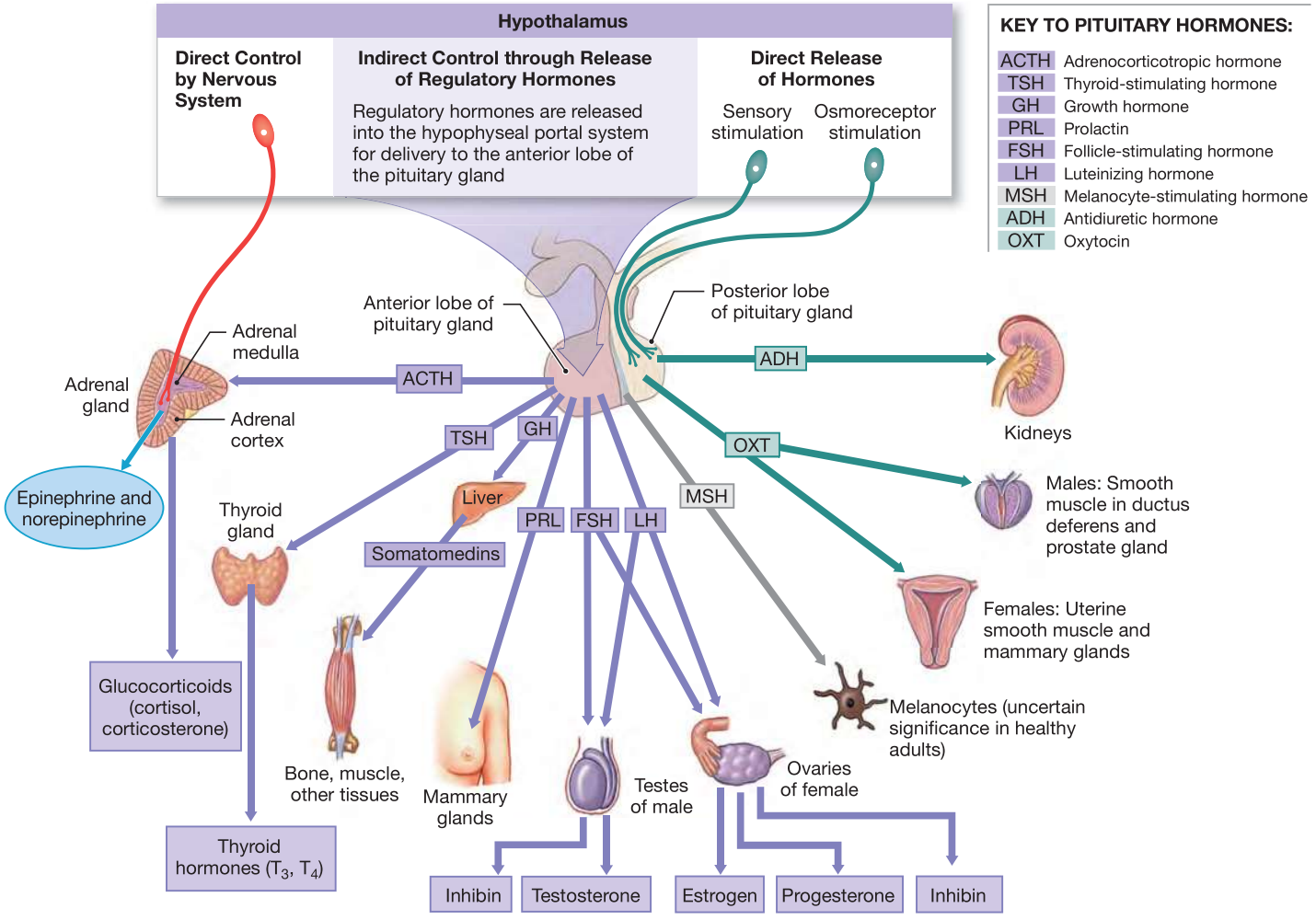
Figure 18–9 and **Table 18–2** summarize important information about the hormones of the pituitary gland. Review them carefully before considering the structure and function of other endocrine organs.

Checkpoint

7. **Identify the two lobes of the pituitary gland.**
8. **If a person were dehydrated, how would the amount of ADH released by the posterior lobe change?**
9. **A blood sample contains elevated levels of somatomedins. Which pituitary hormone would you also expect to be elevated?**
10. **What effect would elevated circulating levels of cortisol, a steroid hormone from the adrenal cortex, have on the pituitary secretion of ACTH?**

See the blue Answers tab at the back of the book.

Figure 18–9 Pituitary Hormones and Their Targets.



18-4 The thyroid gland lies inferior to the larynx and requires iodine for hormone synthesis

The **thyroid gland** curves across the anterior surface of the trachea just inferior to the *thyroid* ("shield-shaped") *cartilage*, which forms most of the anterior surface of the larynx (**Figure 18–10a**). The two **lobes** of the thyroid gland are united by a slender connection, the **isthmus** (IS-mus). You can feel the gland with your fingers. When something goes wrong with it, the thyroid gland typically becomes visible as it enlarges and distorts the surface of the neck. The size of the gland varies, depending on heredity and environmental and nutritional factors, but its average weight is about 34 g (1.2 oz). An extensive blood supply gives the thyroid gland a deep red color.

Thyroid Follicles and Thyroid Hormones

The thyroid gland contains large numbers of **thyroid follicles,** hollow spheres lined by a simple cuboidal epithelium (**Figure 18–10b,c**). The follicle cells surround a **follicle cavity** that holds a viscous *colloid*, a fluid containing large quantities of dissolved proteins. A network of capillaries surrounds each follicle, delivering nutrients and regulatory hormones to the glandular cells and accepting their secretory products and metabolic wastes.

Tips & Tricks

The structure of a thyroid follicle is similar to that of a gel capsule: The simple cuboidal epithelium is comparable to the capsule itself, and the colloid to the capsule's viscous contents.

Follicle cells synthesize a globular protein called **thyroglobulin** (thī-rō-GLOB-ū-lin) and secrete it into the

Table 18–2 The Pituitary Hormones

Region/Area	Hormone	Target	Hormonal Effect	Hypothalamic Regulatory Hormone
ANTERIOR LOBE				
Pars distalis	**Thyroid-stimulating hormone (TSH)**	Thyroid gland	Secretion of thyroid hormones	Thyrotropin-releasing hormone (TRH)
	Adrenocorticotropic hormone (ACTH)	Adrenal cortex (zona fasciculata)	Secretion of glucocorticoids (cortisol, corticosterone)	Corticotropin-releasing hormone (CRH)
	Gonadotropins:			
	Follicle-stimulating hormone (FSH)	Follicle cells of ovaries	Secretion of estrogen, follicle development	Gonadotropin-releasing hormone (GnRH)
		Nurse cells of testes	Stimulation of sperm maturation	Gonadotropin-releasing hormone (GnRH)
	Luteinizing hormone (LH)	Follicle cells of ovaries	Ovulation, formation of corpus luteum, secretion of progesterone	Gonadotropin-releasing hormone (GnRH)
		Interstitial cells of testes	Secretion of testosterone	Gonadotropin-releasing hormone (GnRH)
	Prolactin (PRL)	Mammary glands	Production of milk	Prolactin-releasing factor (PRF)
				Prolactin-inhibiting hormone (PIH)
	Growth hormone (GH)	All cells	Growth, protein synthesis, lipid mobilization and catabolism	Growth hormone–releasing hormone (GH–RH)
				Growth hormone–inhibiting hormone (GH–IH)
Pars intermedia (not active in normal adults)	**Melanocyte-stimulating hormone (MSH)**	Melanocytes	Increased melanin synthesis in epidermis	Melanocyte-stimulating hormone–inhibiting hormone (MSH–IH)
POSTERIOR LOBE				
	Antidiuretic hormone (ADH)	Kidneys	Reabsorption of water, elevation of blood volume and pressure	None: Transported along axons from supraoptic nucleus to the posterior lobe of the pituitary gland
	Oxytocin (OXT)	Uterus, mammary glands (females) Ductus deferens and prostate gland (males)	Labor contractions, milk ejection Contractions of ductus deferens and prostate gland	None: Transported along axons from paraventricular nucleus to the posterior lobe of the pituitary gland

colloid of the thyroid follicles (**Figure 18–10c**). Thyroglobulin molecules contain the amino acid *tyrosine*, the building block of thyroid hormones. The formation of thyroid hormones involves the following basic steps (**Figure 18–11a**):

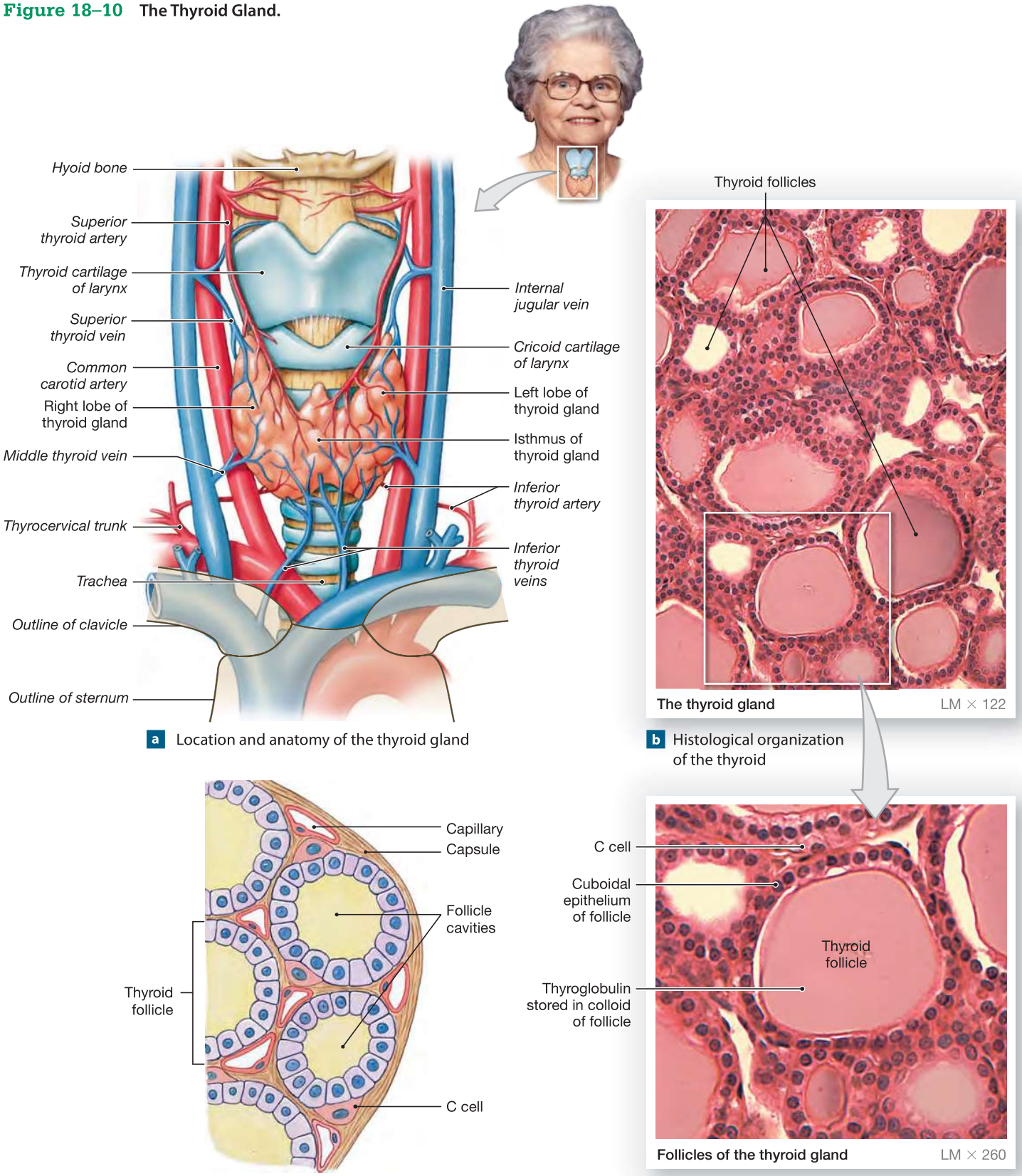
1 Iodide ions are absorbed from the diet at the digestive tract, and the bloodstream delivers them to the thyroid gland. TSH-sensitive carrier proteins in the basement membrane of the follicle cells actively transport iodide ions (I^-) into the cytoplasm. Normally, the follicle cells maintain intracellular concentrations of iodide that are many times higher than those in the extracellular fluid.

2 The iodide ions diffuse to the apical surface of each follicle cell, where they are converted to an activated form of iodide (I^+) by the enzyme *thyroid peroxidase*. This reaction sequence, which occurs at the apical membrane surface, also attaches one or two iodide ions to the tyrosine portions of a thyroglobulin molecule within the follicle cavity.

3 Tyrosine molecules with attached iodide ions become linked by covalent bonds, forming molecules of thyroid hormones that remain incorporated into thyroglobulin. Thyroid peroxidase probably carries out the pairing process. The hormone **thyroxine** (thī-ROKS-ēn), also known as *tetraiodothyronine* or **T_4,** contains four iodide ions. A related molecule called **triiodothyronine,** or **T_3,** contains three iodide ions. Eventually, each molecule of thyroglobulin contains four to eight molecules of T_3 or T_4 hormones or both.

The major factor controlling the rate of thyroid hormone release is the concentration of TSH in the circulating blood (**Figure 18–11b**). TSH stimulates iodide transport into the follicle cells and stimulates the production of thyroglobulin and thyroid peroxidase. TSH also stimulates the release of thyroid

Figure 18–10 The Thyroid Gland.



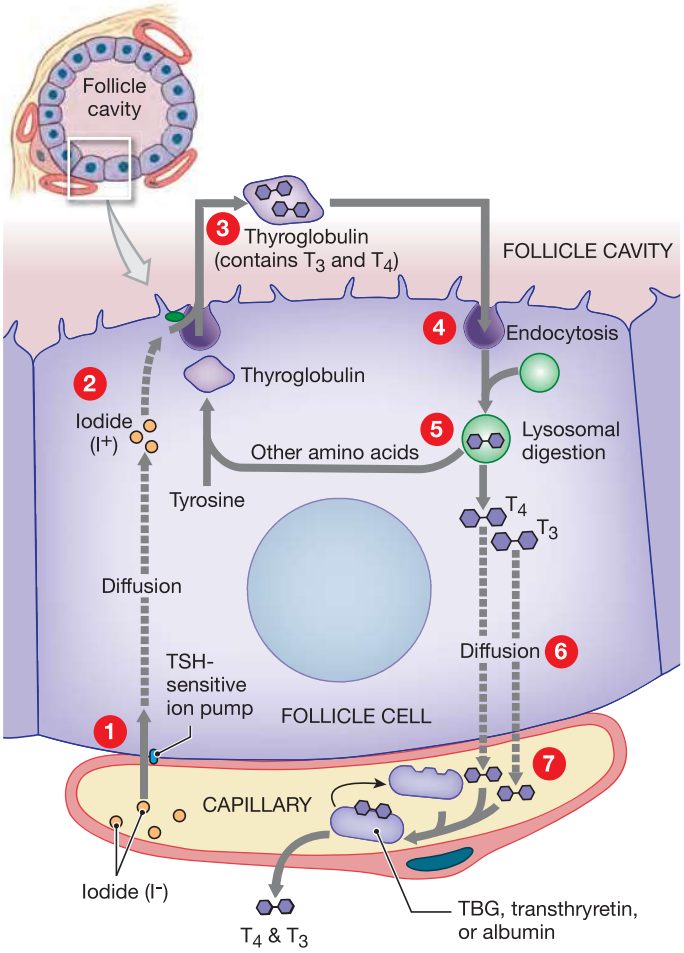
a Location and anatomy of the thyroid gland

b Histological organization of the thyroid

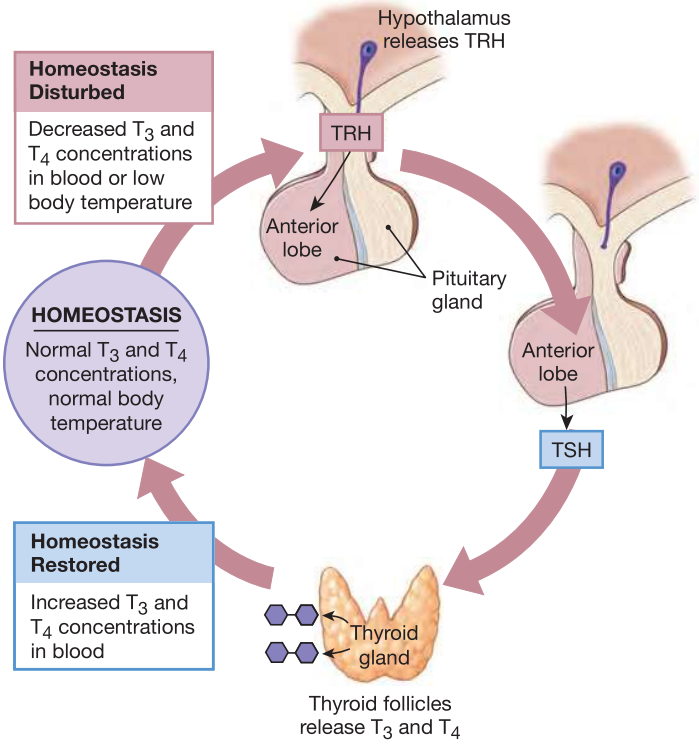
c Histological details of the thyroid gland showing thyroid follicles and both of the cell types in the follicular epithelium ATLAS: Plate 18c

18

Figure 18–11 The Thyroid Follicles.



a The synthesis, storage, and secretion of thyroid hormones. For a detailed explanation of the numbered events, see the text.



b The regulation of thyroid secretion

hormones. Under the influence of TSH, the following steps occur (**Figure 18–11a**):

4 Follicle cells remove thyroglobulin from the follicles by endocytosis.

5 Lysosomal enzymes break down the thyroglobulin, and the amino acids and thyroid hormones enter the cytoplasm. The amino acids are then recycled and used to synthesize more thyroglobulin.

6 The released molecules of T_3 and T_4 diffuse across the basement membrane and enter the bloodstream. About 90 percent of all thyroid secretions is T_4, and T_3 is secreted in comparatively small amounts.

7 About 75 percent of the T_4 molecules and 70 percent of the T_3 molecules entering the bloodstream become attached to transport proteins called **thyroid-binding globulins (TBGs).** Most of the rest of the T_4 and T_3 in the circulation is attached to **transthyretin,** also known as *thyroid-binding prealbumin (TBPA)*, or to *albumin*, one of the plasma proteins. Only the relatively small quantities of thyroid hormones that remain unbound—roughly 0.3 percent of the circulating T_3 and 0.03 percent of the circulating T_4—are free to diffuse into peripheral tissues.

An equilibrium exists between the amount of bound and unbound thyroid hormones. At any moment, free thyroid hormones are being bound to carriers at the same rate at which bound hormones are being released. When unbound thyroid hormones diffuse out of the bloodstream and into other tissues, the equilibrium is disturbed. The carrier proteins then release additional thyroid hormones until a new equilibrium is reached. The bound thyroid hormones make up a substantial reserve: The bloodstream normally has more than a week's supply of thyroid hormones.

TSH plays a key role in both the synthesis and the release of thyroid hormones. In the absence of TSH, the thyroid follicles become inactive, and neither synthesis nor secretion occurs. TSH binds to plasma membrane receptors and, by stimulating adenylate cyclase, it activates key enzymes involved in thyroid hormone production (**Figure 18–3**).

Functions of Thyroid Hormones

Thyroid hormones affect almost every cell in the body. They enter target cells by means of an energy-dependent transport system. Inside a target cell, they bind to receptors (1) in the cytoplasm, (2) on the surfaces of mitochondria, and (3) in the nucleus.

- Thyroid hormones bound to cytoplasmic receptors are essentially held in storage. If intracellular levels of thyroid hormones decline, the bound thyroid hormones are released into the cytoplasm.
- The thyroid hormones binding to mitochondria increase the rates of mitochondrial ATP production.
- The binding to receptors in the nucleus activates genes that control the synthesis of enzymes involved in energy transformation and utilization. One specific effect is the accelerated production of sodium–potassium ATPase. Recall that this membrane protein ejects intracellular sodium and recovers extracellular potassium. As noted in Chapter 3, this exchange pump uses large amounts of ATP. ↩ p. 92

Thyroid hormones also activate genes that code for enzymes involved in glycolysis and ATP production. Coupled with the direct effect of thyroid hormones on mitochondria, this effect increases the metabolic rate of the cell. The effect is called the **calorigenic effect** (*calor*, heat) of thyroid hormones because the cell consumes more energy and generates more heat. In young children, TSH production increases in cold weather, and the calorigenic effect may help them adapt to cold climates. (This response does not occur in adults.) In growing children, thyroid hormones are also essential to normal development of the skeletal, muscular, and nervous systems.

The thyroid gland produces large amounts of T_4, but T_3 is primarily responsible for the observed effects of thyroid hormones: a strong, immediate, and short-lived increase in the rate of cellular metabolism. At any moment, T_3 released from the thyroid gland accounts for only 10–15 percent of the T_3 in peripheral tissues. However, enzymes in the liver, kidneys, and other tissues convert T_4 to T_3. Roughly 85–90 percent of the T_3 that reaches the target cells comes from the conversion of T_4 within peripheral tissues. **Table 18–3** summarizes the effects of thyroid hormones on major organs and systems.

Iodine and Thyroid Hormones

Iodine in the diet is absorbed at the digestive tract as iodide (I^-). Each day the follicle cells in the thyroid gland absorb 120–150 μg of I^-, the minimum dietary amount needed to maintain normal thyroid function. The iodine ions are actively transported into the thyroid follicle cells. As a result, the concentration of I^- inside thyroid follicle cells is generally about 30 times higher than that in the blood plasma. If plasma I^- levels rise, so do levels inside the follicle cells.

Table 18–3 Effects of Thyroid Hormones on Peripheral Tissues

1. Elevates rates of oxygen consumption and energy consumption; in children, may cause a rise in body temperature
2. Increases heart rate and force of contraction; generally results in a rise in blood pressure
3. Increases sensitivity to sympathetic stimulation
4. Maintains normal sensitivity of respiratory centers to changes in oxygen and carbon dioxide concentrations
5. Stimulates red blood cell formation and thus enhances oxygen delivery
6. Stimulates activity in other endocrine tissues
7. Accelerates turnover of minerals in bone

The thyroid follicles contain most of the iodide reserves in the body. TSH stimulates the active transport of iodide. The resulting increase in the rate of iodide movement into the cytoplasm accelerates the formation of thyroid hormones.

The typical diet in the United States provides approximately 500 μg of iodide per day, roughly three times the minimum daily requirement. Much of the excess is due to the I^- added to table salt sold as "iodized salt." For this reason, iodide deficiency is seldom responsible for limiting the rate of thyroid hormone production. (This is not necessarily the case in other countries.) The kidneys remove excess I^- from the blood, and each day the liver excretes a small amount of I^- (about 20 μg) into the *bile*, an exocrine product stored in the gallbladder. Iodide excreted by the kidneys is eliminated in urine. The I^- excreted in bile is eliminated in feces. The losses in the bile continue even if the diet contains less than the minimum iodide requirement and can gradually deplete the iodide reserves in the thyroid. Thyroid hormone production then declines, regardless of the circulating levels of TSH.

The C Cells of the Thyroid Gland and Calcitonin

The thyroid also contains a second population of endocrine cells. These cells are the **C (clear) cells,** or *parafollicular cells* (**Figure 18–10c**). They lie sandwiched between the cuboidal follicle cells and their basement membrane. They are larger than the cells of the follicular epithelium and do not stain as clearly.

C cells produce the hormone **calcitonin (CT),** which helps to regulate Ca^{2+} concentrations in body fluids. We introduced the functions of this hormone in Chapter 6. ↩ p. 187 The net effect of calcitonin release is a drop in the Ca^{2+} concentration in body fluids. Calcitonin (1) inhibits osteoclasts, which slows the rate of Ca^{2+} release from bone, and (2) stimulates Ca^{2+} excretion by the kidneys.

The control of calcitonin secretion is an example of direct endocrine regulation: Neither the hypothalamus nor the pituitary gland is involved. The C cells respond directly to an elevation in the Ca^{2+} concentration of blood. When the concentration rises, calcitonin secretion increases. The Ca^{2+} concentration then drops, eliminating the stimulus and "turning off" the C cells.

Calcitonin is probably most important during childhood, when it stimulates bone growth and mineral deposition in the skeleton. It also appears to be important in reducing the loss of bone mass (1) during prolonged starvation and (2) in the late stages of pregnancy. At that time the maternal skeleton competes with the developing fetus for calcium ions from the diet. The role of calcitonin in the healthy nonpregnant adult is unclear.

In several chapters, you have seen the importance of Ca^{2+} in controlling muscle cell and neuron activities. Calcium ion concentrations also affect the sodium permeabilities of excitable membranes. At high Ca^{2+} concentrations, sodium permeability decreases and membranes become less responsive. Such problems are relatively rare.

Problems caused by lower-than-normal Ca^{2+} concentrations are equally dangerous and much more common. When calcium ion concentrations decline, sodium permeabilities increase. As a result, cells become extremely excitable. If calcium levels fall too far, convulsions or muscular spasms can result. The *parathyroid glands* and *parathyroid hormone* are largely responsible for maintaining adequate calcium levels.

Checkpoint

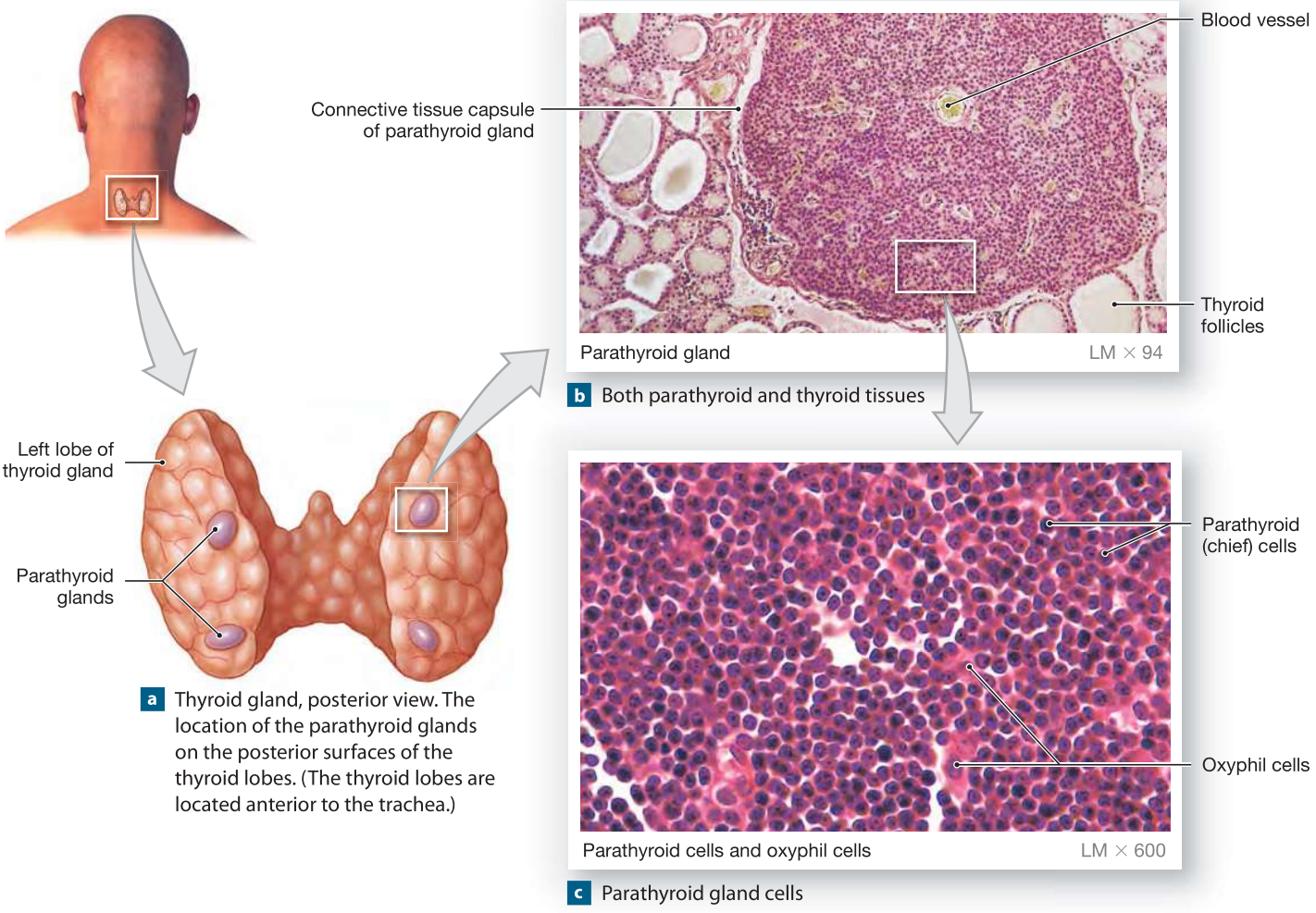
11. Identify the hormones of the thyroid gland.
12. What signs and symptoms would you expect to see in an individual whose diet lacks iodine?
13. When a person's thyroid gland is removed, signs of decreased thyroid hormone concentration do not appear until about one week later. Why?

See the blue Answers tab at the back of the book.

18-5 The four parathyroid glands, embedded in the posterior surface of the thyroid gland, secrete parathyroid hormone to elevate plasma Ca^{2+}

There are normally two pairs of **parathyroid glands** embedded in the posterior surfaces of the thyroid gland (**Figure 18–12a**). A dense capsule surrounding each parathyroid gland separates it from the cells of the thyroid gland. Altogether, the four parathy-

Figure 18–12 The Parathyroid Glands.



a Thyroid gland, posterior view. The location of the parathyroid glands on the posterior surfaces of the thyroid lobes. (The thyroid lobes are located anterior to the trachea.)

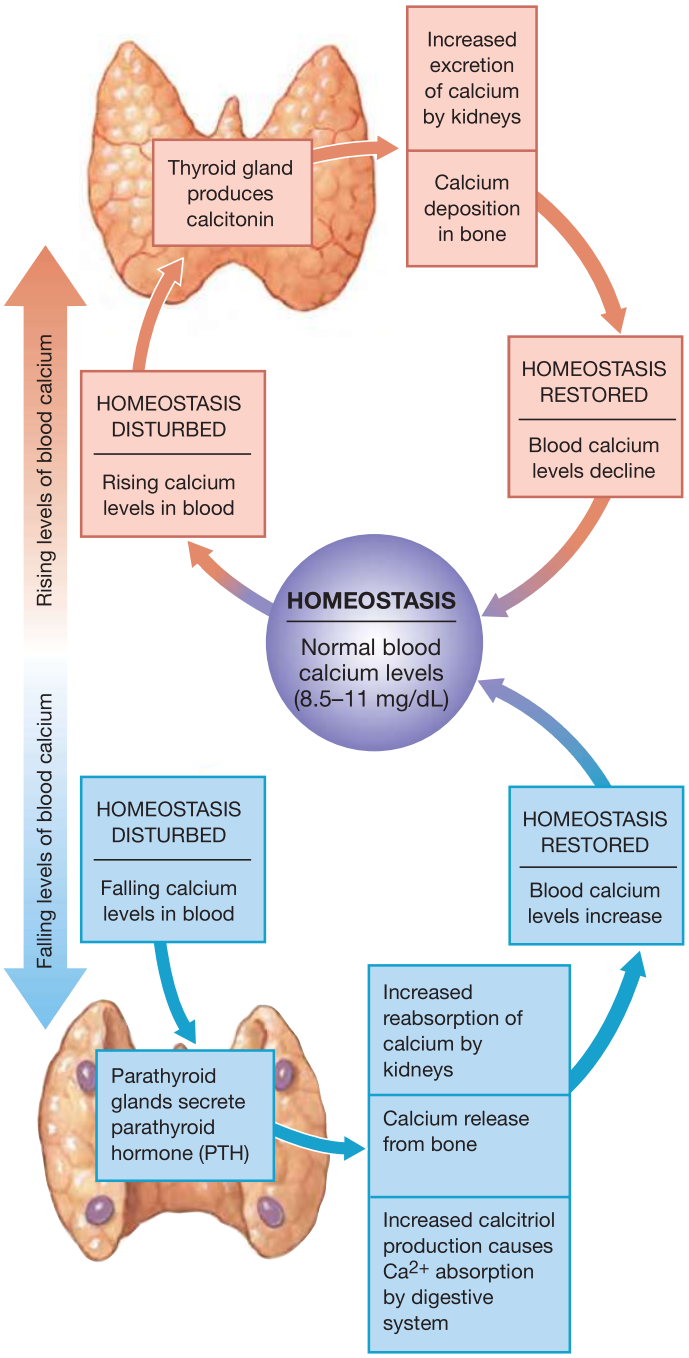
roid glands weigh a mere 1.6 g (0.06 oz). The histological appearance of a single parathyroid gland is shown in **Figure 18–12b,c**. The parathyroid glands have at least two cell populations. The **parathyroid (chief) cells** produce parathyroid hormone. The functions of the other cells, called *oxyphils*, are unknown.

Like the C cells of the thyroid gland, the parathyroid cells monitor the circulating concentration of calcium ions. When the Ca^{2+} concentration of the blood falls below normal, the parathyroid cells secrete **parathyroid hormone (PTH),** or *parathormone*. The net result of PTH secretion is an increase in Ca^{2+} concentration in body fluids. Parathyroid hormone has three major effects:

1. It mobilizes calcium from bone by affecting osteoblast and osteoclast activity. PTH probably inhibits osteoblasts, thereby reducing the rate of calcium deposition in bone, but it has other, more significant effects. Osteoclasts have no PTH receptors, but PTH triggers the release of a growth factor known as RANKL, which increases osteoclast numbers. With more osteoclasts, the rates of mineral turnover and Ca^{2+} release accelerate. As bone matrix erodes, plasma Ca^{2+} rises.
2. It enhances the reabsorption of Ca^{2+} by the kidneys, reducing urinary losses.
3. It stimulates the formation and secretion of *calcitriol* by the kidneys. In general, the effects of calcitriol complement or enhance those of PTH, but calcitriol also enhances Ca^{2+} and PO_4^{3-} absorption by the digestive tract. ↩ p. 185

Figure 18–13 illustrates the roles of calcitonin and PTH in regulating Ca^{2+} concentrations. It is likely that PTH, aided by calcitriol, is the primary regulator of circulating calcium ion concentrations in healthy adults. Information about the hormones of the thyroid gland and parathyroid glands is summarized in **Table 18–4**.

Figure 18–13 The Homeostatic Regulation of Calcium Ion Concentrations.



Checkpoint

14. Describe the location of the parathyroid glands.
15. Identify the hormone secreted by the parathyroid glands.
16. The removal of the parathyroid glands would result in a decrease in the blood concentration of which important mineral?

See the blue Answers tab at the back of the book.

18-6 The adrenal glands, consisting of a cortex and medulla, cap the kidneys and secrete several hormones

A yellow, pyramid-shaped **adrenal** (ad-RĒ-nal) **gland** (*ad-, near* + *renes*, kidneys), or *suprarenal gland*, sits on the superior border of each kidney (**Figure 18–14**). Each adrenal gland lies about at the level of the 12th rib. A dense fibrous capsule firmly attaches each adrenal gland to the superior portion of each kidney. The adrenal gland on each side nestles among the kidney, the diaphragm, and the major arteries and veins that run along the posterior wall of the abdominopelvic cavity. The adrenal glands project into the peritoneal cavity, and their anterior surfaces are covered by a layer of parietal peritoneum. Like other endocrine glands, the adrenal glands are highly vascularized.

Table 18–4 Hormones of the Thyroid Gland and Parathyroid Glands

Gland/Cells	Hormone	Target	Hormonal Effect	Regulatory Control
THYROID GLAND				
Follicular epithelium	Thyroxine (T_4) Triiodothyronine (T_3)	Most cells	Increases energy utilization, oxygen consumption, growth, and development	Stimulated by TSH from the anterior lobe of the pituitary gland
C cells	Calcitonin (CT)	Bone, kidneys	Decreases Ca^{2+} concentrations in body fluids	Stimulated by elevated blood Ca^{2+} levels; actions opposed by PTH
PARATHYROID GLANDS				
Parathyroid (chief) cells	Parathyroid hormone (PTH)	Bone, kidneys	Increases Ca^{2+} concentrations in body fluids	Stimulated by low blood Ca^{2+} levels; PTH effects enhanced by calcitriol and opposed by calcitonin

A typical adrenal gland weighs about 5.0 g (0.18 oz), but its size can vary greatly as secretory demands change. The adrenal gland has two parts with separate endocrine functions: a superficial **adrenal cortex** and an inner **adrenal medulla** (Figure 18–14b).

The Adrenal Cortex

The yellowish color of the adrenal cortex is due to stored lipids, especially cholesterol and various fatty acids. The adrenal cortex produces more than two dozen steroid hormones. They are collectively called **corticosteroids.** In the bloodstream, these hormones are bound to transport proteins called *transcortins*.

Corticosteroids are vital. If the adrenal glands are destroyed or removed, the individual will die unless corticosteroids are administered. Like other steroid hormones, corticosteroids exert their effects by turning on transcription of certain genes in the nuclei of their target cells and determining their transcription rates. The resulting changes in the nature and concentration of enzymes in the cytoplasm affect cellular metabolism.

Deep to the adrenal capsule are three distinct regions, or zones, in the adrenal cortex (Figure 18–14c): (1) an outer *zona glomerulosa*; (2) a middle *zona fasciculata*; and (3) an inner *zona reticularis*. Each zone synthesizes specific steroid hormones (Table 18–5).

The Zona Glomerulosa

The **zona glomerulosa** (glō-mer-ū-LŌ-suh) is the outer region of the adrenal cortex. It produces **mineralocorticoids,** steroid hormones that affect the electrolyte composition of body fluids. **Aldosterone** is the principal mineralocorticoid of the zona glomerulosa.

The zona glomerulosa accounts for about 15 percent of the volume of the adrenal cortex (Figure 18–14c). A *glomerulus* is a little ball, and as the term *zona glomerulosa* implies, the endocrine cells in this region form small, dense knots or clusters. This zone extends from the capsule to the radiating cords of the deeper zona fasciculata.

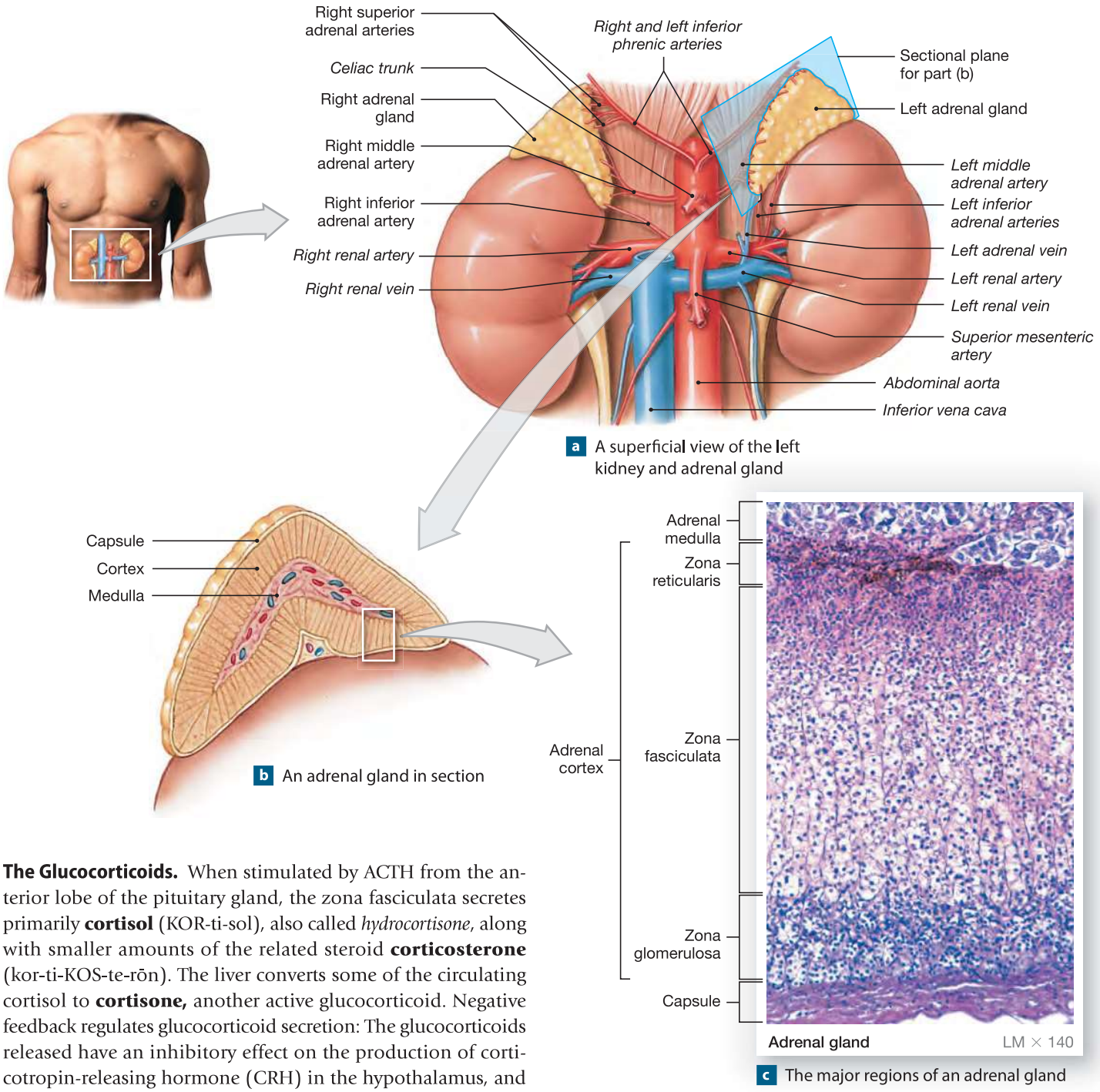
Aldosterone. Aldosterone stimulates the conservation of sodium ions and the elimination of potassium ions. This hormone targets cells that regulate the ionic composition of excreted fluids. It causes the retention of sodium ions by the kidneys, sweat glands, salivary glands, and pancreas, preventing Na^+ loss in urine, sweat, saliva, and digestive secretions. A loss of K^+ accompanies this retention of Na^+. As a secondary effect, the retention of Na^+ enhances the osmotic reabsorption of water by the kidneys, sweat glands, salivary glands, and pancreas. The effect at the kidneys is most dramatic when normal levels of ADH are present. In addition, aldosterone increases the sensitivity of salt receptors in the taste buds of the tongue. As a result, a person's interest in (and consumption of) salty food increases.

Aldosterone secretion occurs in response to a drop in blood Na^+ content, blood volume, or blood pressure, or to a rise in blood K^+ concentration. Changes in either Na^+ or K^+ concentration have a direct effect on the zona glomerulosa, but the secretory cells are most sensitive to changes in potassium levels. A rise in potassium levels is very effective in stimulating the release of aldosterone. Aldosterone release also occurs in response to *angiotensin II*. We discuss this hormone, part of the *renin–angiotensin system*, later in this chapter.

The Zona Fasciculata

The **zona fasciculata** (fa-sik-ū-LA-tuh; *fasciculus*, little bundle) produces steroid hormones collectively known as **glucocorticoids,** due to their effects on glucose metabolism. This zone begins at the inner border of the zona glomerulosa and extends toward the adrenal medulla (Figure 18–14c). It contributes about 78 percent of the cortical volume. The endocrine cells are larger and contain more lipids than those of the zona glomerulosa, and the lipid droplets give the cytoplasm a pale, foamy appearance. The cells of the zona fasciculata form individual cords composed of stacks of cells. Adjacent cords are separated by flattened blood vessels (sinusoids) with fenestrated walls.

Figure 18–14 The Adrenal Gland. ATLAS: Plates 61a,b; 62b



The Glucocorticoids. When stimulated by ACTH from the anterior lobe of the pituitary gland, the zona fasciculata secretes primarily **cortisol** (KOR-ti-sol), also called *hydrocortisone*, along with smaller amounts of the related steroid **corticosterone** (kor-ti-KOS-te-rōn). The liver converts some of the circulating cortisol to **cortisone,** another active glucocorticoid. Negative feedback regulates glucocorticoid secretion: The glucocorticoids released have an inhibitory effect on the production of corticotropin-releasing hormone (CRH) in the hypothalamus, and on ACTH in the anterior lobe (**Figure 18–8a**).

Effects of Glucocorticoids. Glucocorticoids speed up the rates of glucose synthesis and glycogen formation, especially in the liver. Adipose tissue responds by releasing fatty acids into the blood, and other tissues begin to break down fatty acids and proteins instead of glucose. This process is another example of a glucose-sparing effect (p. 607).

Glucocorticoids also show **anti-inflammatory** effects. That is, they inhibit the activities of white blood cells and other components of the immune system. "Steroid creams" are commonly used to control irritating allergic rashes, such as poison ivy rash, and injections of glucocorticoids may be used to control more

severe allergic reactions. How do these treatments work? Glucocorticoids slow the migration of phagocytic cells into an injury site and cause phagocytic cells already in the area to become less active. In addition, mast cells exposed to these steroids are less likely to release histamine and other chemicals that promote inflammation. pp. 138–139 As a result, swelling and further irritation are dramatically reduced. On the negative side, the rate of wound healing decreases, and the weakening of the region's defenses makes it more susceptible to infectious organisms. For that reason, the topical steroids used to treat superficial rashes should never be applied to open wounds.

The Zona Reticularis

The **zona reticularis** (re-tik-ū-LAR-is; *reticulum*, network) forms a narrow band bordering each adrenal medulla (**Figure 18–14c**). This zone accounts for only about 7 percent of the total volume of the adrenal cortex. The endocrine cells of the zona reticularis form a folded, branching network, and fenestrated blood vessels wind among the cells.

Under stimulation by ACTH, the zona reticularis normally produces small quantities of androgens, the sex hormones produced in large quantities by the testes in males. Once in the bloodstream, some of the androgens from the zona reticularis are converted to estrogens, the dominant sex hormones in females. Adrenal androgens stimulate the development of pubic hair in boys and girls before puberty. Adrenal androgens are not important in adult men, but in adult women they promote muscle mass and blood cell formation, and support the sex drive.

The Adrenal Medulla

The boundary between the adrenal cortex and the adrenal medulla is irregular, and the supporting connective tissues and blood vessels are extensively interconnected. The adrenal medulla is pale gray or pink, due in part to the many blood vessels in the area. It contains large, rounded cells— similar to cells in sympathetic ganglia that are innervated by preganglionic sympathetic fibers. The sympathetic division of the autonomic nervous system controls secretory activities of the adrenal medullae. p. 520

The adrenal medulla contains two populations of secretory cells: One produces epinephrine (adrenaline), the other norepinephrine (noradrenaline). Evidence suggests that the two types of cells are distributed in different areas and that their secretory activities can be independently controlled. The secretions are packaged in vesicles that form dense clusters just inside plasma membranes. The hormones in these vesicles are continuously released at low levels by exocytosis. Sympathetic stimulation dramatically accelerates the rate of exocytosis and hormone release.

Epinephrine and Norepinephrine

Epinephrine makes up 75–80 percent of the secretions from the adrenal medullae. The rest is norepinephrine. These hormones interact with alpha and beta receptors on plasma membranes, as we described in Chapter 16. p. 525 Stimulation of α_1 and β_1 receptors, the most common types, speeds up the use of cellular energy and the mobilization of energy reserves.

Activation of the adrenal medullae has the following effects:

- In skeletal muscles, epinephrine and norepinephrine trigger mobilization of glycogen reserves and accelerate the breakdown of glucose to provide ATP. This combination increases both muscular strength and endurance.
- In adipose tissue, stored fats are broken down into fatty acids, which are released into the bloodstream for other tissues to use for ATP production.

Table 18–5 The Adrenal Hormones

Region/Zone	Hormone	Primary Target	Hormonal Effect	Regulatory Control
CORTEX				
Zona glomerulosa	Mineralocorticoids (primarily aldosterone)	Kidneys	Increase renal reabsorption of Na^+ and water (especially in the presence of ADH) and accelerate urinary loss of K^+	Stimulated by angiotensin II, elevated plasma K^+ or a fall in plasma Na^+; inhibited by ANP and BNP
Zona fasciculata	Glucocorticoids (cortisol [hydrocortisone], corticosterone)	Most cells	Release of amino acids from skeletal muscles and lipids from adipose tissues; promote liver formation of glucose and glycogen; promote peripheral utilization of lipids; anti-inflammatory effects	Stimulated by ACTH from the anterior lobe of the pituitary gland
Zona reticularis	Androgens	Most cells	Not important in adult men; encourages bone growth, muscle growth, and blood formation in children and women	Stimulated by ACTH from the anterior lobe of the pituitary gland
MEDULLA				
	Epinephrine, norepinephrine	Most cells	Increases cardiac activity, blood pressure, glycogen breakdown, blood glucose levels; releases lipids by adipose tissue	Stimulated during sympathetic activation by sympathetic preganglionic fiber

- In the liver, glycogen molecules are broken down. The resulting glucose molecules are released into the bloodstream, primarily for use by neural tissue, which cannot shift to fatty acid metabolism.
- In the heart, the stimulation of β_1 receptors triggers an increase in the rate and force of cardiac muscle contraction.

The metabolic changes that follow the release of catecholamines such as E and NE reach their peak 30 seconds after adrenal stimulation, and they persist for several minutes. As a result, the effects of stimulating the adrenal medullae outlast the other signs of sympathetic activation.

Checkpoint

17. **Identify the two regions of the adrenal gland, and cite the hormones secreted by each.**
18. **List the three zones of the adrenal cortex.**
19. **What effect would elevated cortisol levels have on blood glucose levels?**

See the blue Answers tab at the back of the book.

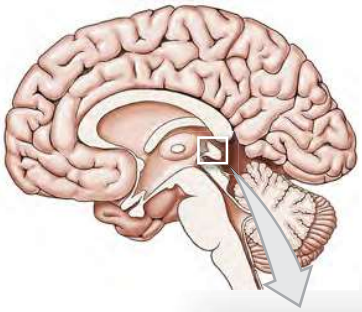
18-7 The pineal gland, attached to the roof of the third ventricle, secretes melatonin

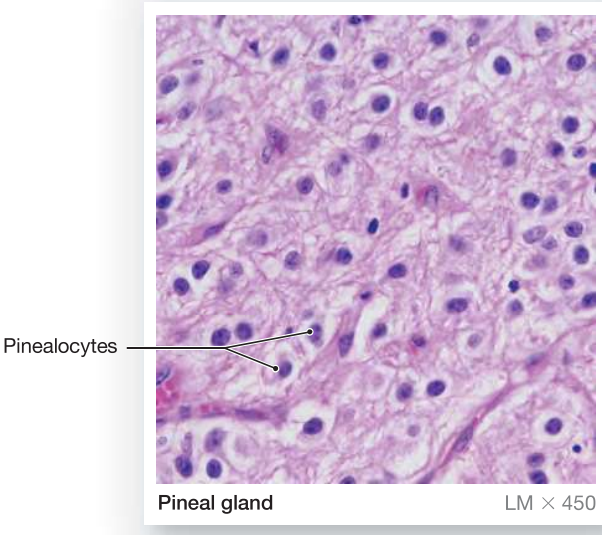
The **pineal gland,** part of the epithalamus, lies in the posterior portion of the roof of the third ventricle. The pineal gland contains neurons, neuroglia, and special secretory cells called **pinealocytes** (pin-Ē-al-ō-sīts). These cells synthesize the hormone **melatonin** from molecules of the neurotransmitter *serotonin* (**Figure 18–15**). Collaterals from the visual pathways enter the pineal gland and affect the rate of melatonin production. This rate is lowest during daylight hours and highest at night.

Among the functions suggested for melatonin in humans are the following:

- *Inhibiting Reproductive Functions.* In some mammals, melatonin slows the maturation of sperm, oocytes, and reproductive organs by reducing the rate of GnRH secretion. The significance of this effect in humans remains unclear. Circumstantial evidence suggests that melatonin may play a role in the timing of human sexual maturation. Melatonin levels in the blood decline at puberty, and pineal tumors that eliminate melatonin production cause premature puberty in young children.
- *Protecting against Damage by Free Radicals.* Melatonin is a very effective *antioxidant*. It may protect CNS neurons from free radicals, such as nitric oxide (NO) or hydrogen peroxide (H_2O_2), that may form in active neural tissue.

Figure 18–15 The Pineal Gland.





- *Influencing Circadian Rhythms.* Because its activity is cyclical, the pineal gland may also be involved in maintaining basic *circadian rhythms*—daily changes in physiological processes that follow a regular day–night pattern. ↩ p. 466 Increased melatonin secretion in darkness has been suggested as a primary cause of *seasonal affective disorder (SAD)*. This condition can develop during the winter in people who live at high latitudes, where sunlight is scarce or lacking. It is characterized by changes in mood, eating habits, and sleeping patterns.

Checkpoint

20. **Identify the hormone-secreting cells of the pineal gland.**
21. **Increased amounts of light would inhibit the production of which hormone?**
22. **List three possible functions of melatonin.**

See the blue Answers tab at the back of the book.

18-8 The pancreas, located in the abdominopelvic cavity, is both an exocrine organ and endocrine gland

The **pancreas** lies within the abdominopelvic cavity in the loop between the inferior border of the stomach and the proximal portion of the small intestine (**Figure 18–1**). It is a slender, pale organ with a nodular (lumpy) consistency (**Figure 18–16a**). The pancreas is 20–25 cm (8–10 in.) long and weighs about 80 g (2.8 oz) in adults. We will consider its anatomy further in Chapter 24, because it is primarily an exocrine organ that makes digestive enzymes.

The **exocrine pancreas** consists of clusters of gland cells, called *pancreatic acini*, and their attached ducts. The exocrine pancreas takes up roughly 99 percent of the pancreatic volume. Together the gland and duct cells secrete large quantities of an alkaline, enzyme-rich fluid that reaches the lumen of the digestive tract through a network of secretory ducts.

The **endocrine pancreas** consists of small groups of cells scattered among the exocrine cells. The endocrine clusters are known as **pancreatic islets,** or the *islets of Langerhans* (LAN-ger-hanz) (**Figure 18–16b**). Pancreatic islets account for only about 1 percent of all cells in the pancreas. Nevertheless, a typical pancreas contains roughly 2 million pancreatic islets and their secretions are vital to our survival.

18

The Pancreatic Islets

The pancreatic islets are surrounded by an extensive, fenestrated capillary network that carries pancreatic hormones into the bloodstream. Each islet contains four types of cells:

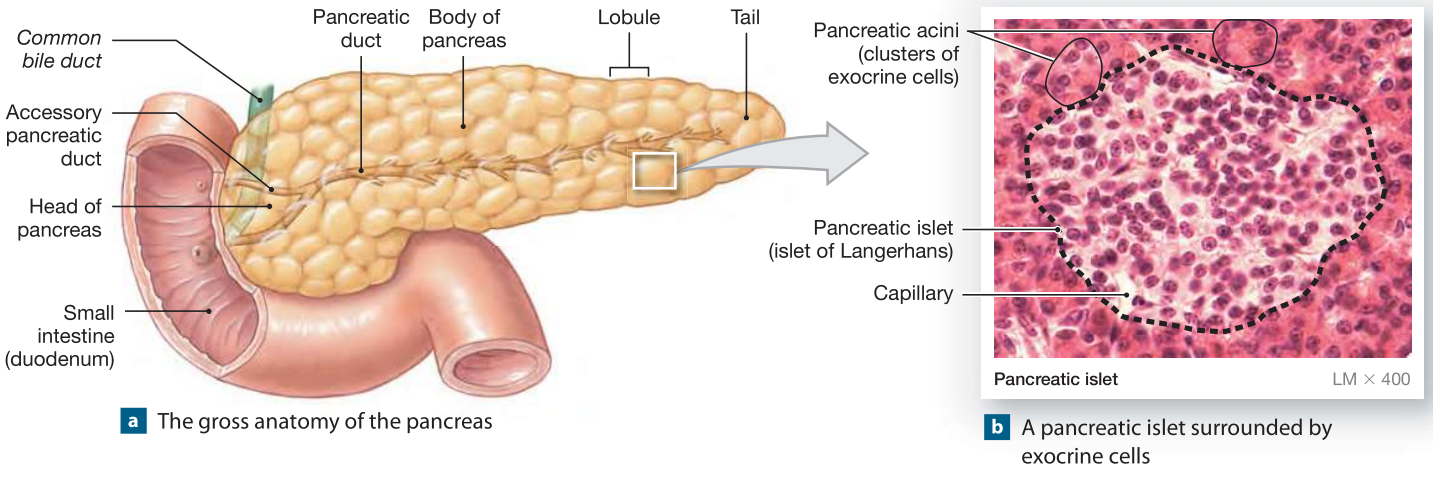
1. **Alpha cells** produce the hormone glucagon (GLOO-ka-gon). Glucagon raises blood glucose levels by increasing the rates of glycogen breakdown and glucose release by the liver.
2. **Beta cells** produce the hormone insulin (IN-suh-lin). Insulin lowers blood glucose levels by increasing the rate of glucose uptake and utilization by most body cells, and by increasing glycogen synthesis in skeletal muscles and the liver. Beta cells also secrete *amylin*, a recently discovered peptide hormone whose role is unclear.
3. **Delta cells** produce a peptide hormone identical to growth hormone–inhibiting hormone (GH–IH), a hypothalamic regulatory hormone. GH–IH suppresses the release of glucagon and insulin by other islet cells and slows the rates of food absorption and enzyme secretion along the digestive tract.
4. **F cells** produce the hormone **pancreatic polypeptide (PP).** PP inhibits gallbladder contractions and regulates the production of some pancreatic enzymes. It may also help control the rate of nutrient absorption by the digestive tract.

We will focus on insulin and glucagon, the hormones that regulate blood glucose levels (**Figure 18–17**). When blood glucose levels rise, beta cells secrete insulin, which then stimulates the transport of glucose across plasma membranes and into target cells. When blood glucose levels decline, alpha cells secrete glucagon, which stimulates glycogen breakdown and glucose release by the liver.

Tips & Tricks

To help in differentiating between the polysaccharide storage molecule "glycogen" and the pancreatic hormone "glucagon," remember that glyco***gen*** literally means ***gen***erates sugar; and associate gluca***gon*** with the Penta***gon***, both of which "issue orders."

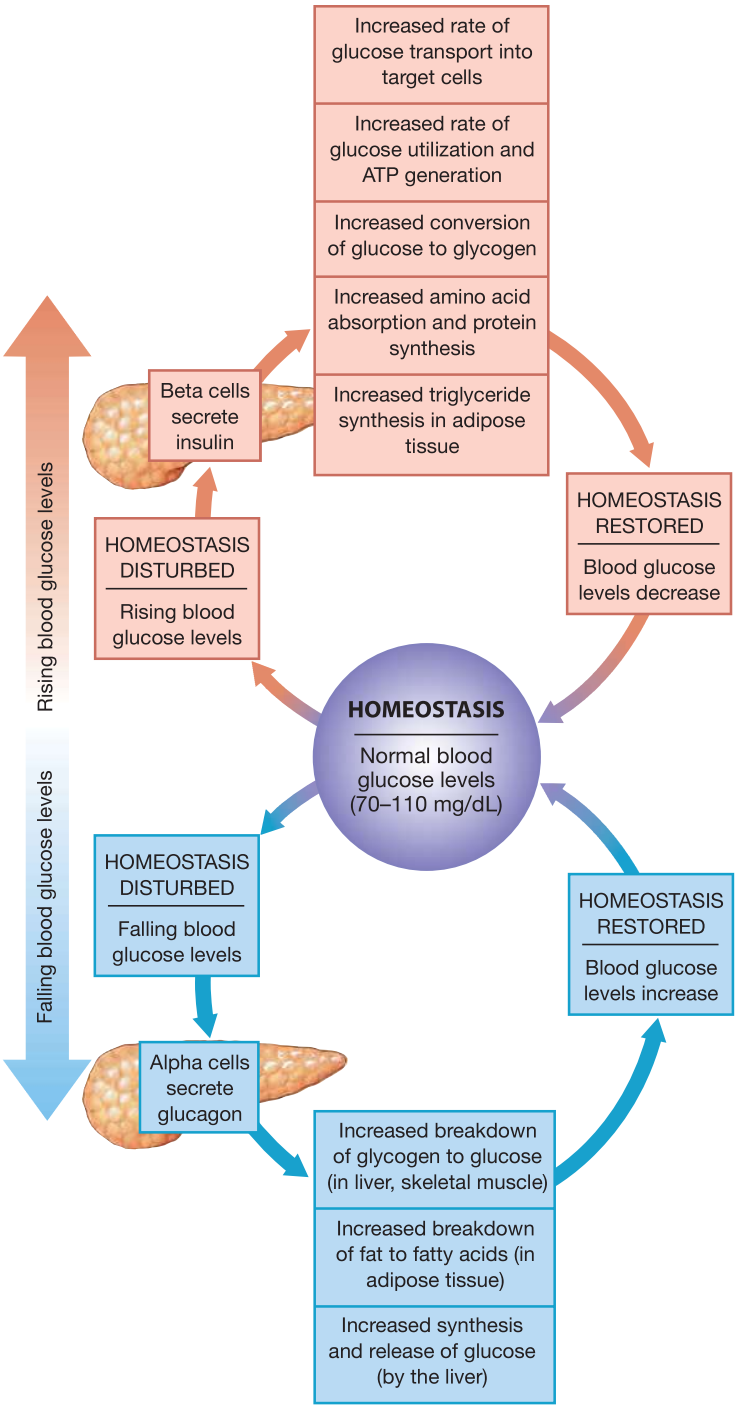
Figure 18–16 The Endocrine Pancreas. ATLAS: Plate 49e



a The gross anatomy of the pancreas

b A pancreatic islet surrounded by exocrine cells

Figure 18–17 The Regulation of Blood Glucose Concentrations.



Insulin

Insulin is a peptide hormone released by beta cells when glucose concentrations exceed normal levels (70–110 mg/dL). Elevated levels of some amino acids, including arginine and leucine, also stimulate secretion of insulin. This hormone affects cellular metabolism in a series of steps that begins when insulin binds to receptor proteins on the plasma membrane of a target cell. Binding activates the receptor, which functions as a kinase, attaching phosphate groups to intracellular enzymes. These enzymes then produce primary and secondary effects in the cell. The biochemical details of these effects remain unresolved.

One of the most important effects is the enhancement of glucose absorption and utilization. Insulin receptors are present in most plasma membranes, and cells that have them are called *insulin dependent*. However, cells in the brain and kidneys, cells in the lining of the digestive tract, and red blood cells lack insulin receptors. These cells are called *insulin independent*, because they can absorb and utilize glucose without insulin stimulation.

The effects of insulin on its target cells include the following:

- *Accelerating Glucose Uptake (All Target Cells).* This effect results from an increase in the number of glucose transport proteins in the plasma membrane. These proteins move glucose into the cell by facilitated diffusion, which follows the concentration gradient for glucose and does not require ATP.
- *Accelerating Glucose Utilization (All Target Cells) and Enhanced ATP Production.* This effect occurs for two reasons: (1) The rate of glucose use is proportional to its availability, so when more glucose enters the cell, more is used. (2) Second messengers activate a key enzyme involved in the initial steps of glycolysis.
- *Stimulating Glycogen Formation (Skeletal Muscles and Liver Cells).* When excess glucose enters these cells, it is stored as glycogen.
- *Stimulating Amino Acid Absorption and Protein Synthesis.*
- *Stimulating Triglyceride Formation in Adipose Tissue.* Insulin stimulates the absorption of fatty acids and glycerol by adipocytes, which store these components as triglycerides. Adipocytes also increase their absorption of glucose, and excess glucose is used in the synthesis of additional triglycerides.

To summarize, the pancreas secretes insulin when glucose is abundant. The hormone stimulates glucose utilization to support growth and to build carbohydrate (glycogen) and lipid (triglyceride) reserves. The accelerated use of glucose soon brings circulating glucose levels within normal limits.

Tips & Tricks

The function of ***in***sulin is to get glucose ***in***to cells.

Glucagon

When glucose concentrations fall below normal, alpha cells release glucagon to mobilize energy reserves. When glucagon binds to a receptor in the target cell's plasma membrane, the

hormone activates adenylate cyclase. As we have seen, cAMP acts as a second messenger that activates cytoplasmic enzymes (p. 599). The primary effects of glucagon are as follows:

- *Stimulating the Breakdown of Glycogen in Skeletal Muscle and Liver Cells.* The glucose molecules released are either metabolized for energy (in skeletal muscle fibers) or released into the bloodstream (by liver cells).
- *Stimulating the Breakdown of Triglycerides in Adipose Tissue.* The adipocytes then release the fatty acids into the bloodstream for use by other tissues.
- *Stimulating the Production and Release of Glucose by the Liver.* Liver cells absorb amino acids from the bloodstream, convert them to glucose, and release the glucose into the circulation. This process of glucose synthesis in the liver is called *gluconeogenesis* (gloo-kō-nē-ō-JEN-e-sis).

The results are a reduction in glucose use and the release of more glucose into the bloodstream. Blood glucose concentrations soon rise toward normal levels.

Pancreatic alpha cells and beta cells monitor blood glucose concentrations, and they secrete glucagon and insulin without endocrine or nervous instructions. Yet because the alpha cells and beta cells are highly sensitive to changes in blood glucose levels, any hormone that affects blood glucose concentrations indirectly affects the production of both insulin and glucagon. Autonomic activity also influences insulin production: Parasympathetic stimulation enhances insulin release, and sympathetic stimulation inhibits it. Information about insulin, glucagon, and other pancreatic hormones is summarized in **Table 18–6**.

Diabetes Mellitus

Whether glucose is absorbed at the digestive tract or manufactured and released by the liver, very little glucose leaves the body intact once it has entered the bloodstream. The kidneys reabsorb virtually all glucose, so glucose does not appear in the urine. However, in diabetes mellitus, sugars accumulate in the blood and urine as a result of faulty glucose metabolism.

Diabetes mellitus can be caused by genetic abnormalities, and some of the genes responsible have been identified. Mutations that result in inadequate insulin production, the synthesis of abnormal insulin molecules, or the production of defective receptor proteins produce comparable symptoms. Under these conditions, obesity accelerates the onset and severity of the disease. Diabetes mellitus can also result from other pathological conditions, injuries, immune disorders, or hormonal imbalances.

The two major types of diabetes mellitus are insulin-dependent (type 1) diabetes and non-insulin-dependent (type 2) diabetes. Persons with type 1 diabetes require insulin to live and usually require multiple injections daily, or continuous infusion. Most diabetes patients have type 2 diabetes. Initially they produce sufficient insulin, but their bodies don't use it well. Weight loss through diet and exercise can be an effective treatment, but most patients require oral medicines, and some progress to needing insulin. This disorder is described in **Spotlight Figure 18–18.**

Checkpoint

23. **Identify the types of cells in the pancreatic islets and the hormones produced by each.**
24. **Why does a person with type 1 or type 2 diabetes urinate frequently and have increased thirst?**
25. **What effect would increased levels of glucagon have on the amount of glycogen stored in the liver?**

See the blue Answers tab at the back of the book.

Table 18–6 Hormones Produced by the Pancreatic Islets

Structure/Cells	Hormone	Primary Targets	Hormonal Effect	Regulatory Control
PANCREATIC ISLETS				
Alpha cells	Glucagon	Liver, adipose tissue	Mobilizes lipid reserves; promotes glucose synthesis and glycogen breakdown in liver; elevates blood glucose concentrations	Stimulated by low blood glucose concentrations; inhibited by GH–IH from delta cells
Beta cells	Insulin	Most cells	Facilitates uptake of glucose by target cells; stimulates formation and storage of lipids and glycogen	Stimulated by high blood glucose concentrations, parasympathetic stimulation, and high levels of some amino acids; inhibited by GH–IH from delta cells and by sympathetic activation
Delta cells	GH–IH (somatostatin)	Other islet cells, digestive epithelium	Inhibits insulin and glucagon secretion; slows rates of nutrient absorption and enzyme secretion along digestive tract	Stimulated by protein-rich meal; mechanism unclear
F cells	Pancreatic polypeptide (PP)	Digestive organs	Inhibits gallbladder contraction; regulates production of pancreatic enzymes; influences rate of nutrient absorption by digestive tract	Stimulated by protein-rich meal and by parasympathetic stimulation

Spotlight

Figure 18–18
Diabetes Mellitus

Untreated diabetes mellitus disrupts metabolic activities throughout the body. Clinical problems arise because the tissues involved are experiencing an energy crisis—in essence, most of the tissues are responding as they would during chronic starvation, breaking down lipids and even proteins because they are unable to absorb glucose from their surroundings. Problems involving abnormal changes in blood vessel structure are particularly dangerous. An estimated 23.6 million people in the United States have some form of diabetes.

Retinal Damage

The proliferation of capillaries and hemorrhaging at the retina may cause partial or complete blindness. This condition is called **diabetic retinopathy.**

Early Heart Attacks

Degenerative blockages in cardiac circulation can lead to early heart attacks. For a given age group, heart attacks are three to five times more likely in diabetic individuals than in nondiabetic people.

Kidney Degeneration

Degenerative changes in the kidneys, a condition called **diabetic nephropathy**, can lead to kidney failure.

Peripheral Nerve Problems

Abnormal blood flow to neural tissues is probably responsible for a variety of neural problems with peripheral nerves, including abnormal autonomic function. These disorders are collectively termed **diabetic neuropathy.**

Diabetes Mellitus

Diabetes mellitus (mel-Ī-tus; *mellitum*, honey) is characterized by glucose concentrations that are high enough to overwhelm the reabsorption capabilities of the kidneys. (The presence of abnormally high glucose levels in the blood in general is called **hyperglycemia** [hī-per-glī-SĒ-mē-ah].) Glucose appears in the urine (**glycosuria**; glī-kō-SOO-rē-a), and urine volume generally becomes excessive (**polyuria**).

subdivided into

Type 1 Diabetes

Type 1 (insulin dependent) diabetes is characterized by inadequate insulin production by the pancreatic beta cells. Persons with type 1 diabetes require insulin to live and usually require multiple injections daily, or continuous infusion through an insulin pump or other device. This form of diabetes accounts for only around 5% –10% of cases; it often develops in childhood.

Type 2 Diabetes

Type 2 (non-insulin dependent) diabetes is the most common form of diabetes mellitus. Most people with this form of diabetes produce normal amounts of insulin, at least initially, but their tissues do not respond properly, a condition known as insulin resistance. Type 2 diabetes is associated with obesity, and weight loss through diet and exercise can be an effective treatment.

Peripheral Tissue Damage

Blood flow to the distal portions of the limbs is reduced, and peripheral tissues may suffer as a result. For example, a reduction in blood flow to the feet can lead to tissue death, ulceration, infection, and loss of toes or a major portion of one or both feet.

18-9 Many organs have secondary endocrine functions

As we noted earlier, many organs of other body systems have secondary endocrine functions. Examples are the intestines (digestive system), the kidneys (urinary system), the heart (cardiovascular system), the thymus (lymphatic system), and the *gonads*—the testes in males and the ovaries in females (reproductive system).

Several new hormones from these endocrine tissues have been identified. In many cases, their structures and modes of action remain uncertain, and we have not described them in this chapter. However, in one instance, researchers traced a significant new hormone to an unexpected site of origin, leading to the realization that the body's adipose tissue has important endocrine functions. We include the endocrine functions of adipose tissue in this section, although all of the details have yet to be worked out. **Table 18–7** provides an overview of some of the hormones those organs of other systems produce.

The Intestines

The intestines process and absorb nutrients. They release a variety of hormones that coordinate the activities of the digestive system. Most digestive processes are hormonally controlled locally, although the autonomic nervous system can affect the pace of digestive activities. We describe these hormones in Chapter 24.

The Kidneys

The kidneys release the steroid hormone *calcitriol*, the peptide hormone *erythropoietin*, and the enzyme *renin*. Calcitriol is important for calcium ion homeostasis. Erythropoietin and renin are involved in the regulation of blood volume and blood pressure.

Calcitriol

Calcitriol is a steroid hormone secreted by the kidneys in response to parathyroid hormone (PTH) (**Figure 18–19a**). *Cholecalciferol* (vitamin D_3) is a related steroid that is synthesized in the skin or absorbed from the diet. Cholecalciferol is converted to calcitriol, although not directly. The term *vitamin D* applies to the entire group of related steroids, including calcitriol, cholecalciferol, and various intermediate products.

The best-known function of calcitriol is to stimulate calcium and phosphate ion absorption along the digestive tract. The effects of PTH on Ca^{2+} absorption result primarily from stimulation of calcitriol release. Calcitriol's other effects on calcium metabolism include (1) stimulating the formation and differentiation of osteoprogenitor cells and osteoclasts, (2) stimulating bone resorption by osteoclasts, (3) stimulating Ca^{2+} reabsorption by the kidneys, and (4) suppressing PTH production. Evidence indicates that calcitriol also affects lymphocytes and keratinocytes in the skin, but these effects have nothing to do with regulating calcium levels.

Erythropoietin

Erythropoietin (e-rith-rō-POY-e-tin; *erythros*, red + *poiesis*, making), or **EPO,** is a peptide hormone released by the kidneys in response to low oxygen levels in kidney tissues. EPO stimulates the bone marrow to produce red blood cells. The increase in the number of red blood cells elevates blood volume. Because these cells transport oxygen, this increase also improves oxygen delivery to peripheral tissues. We will consider EPO again in Chapter 19.

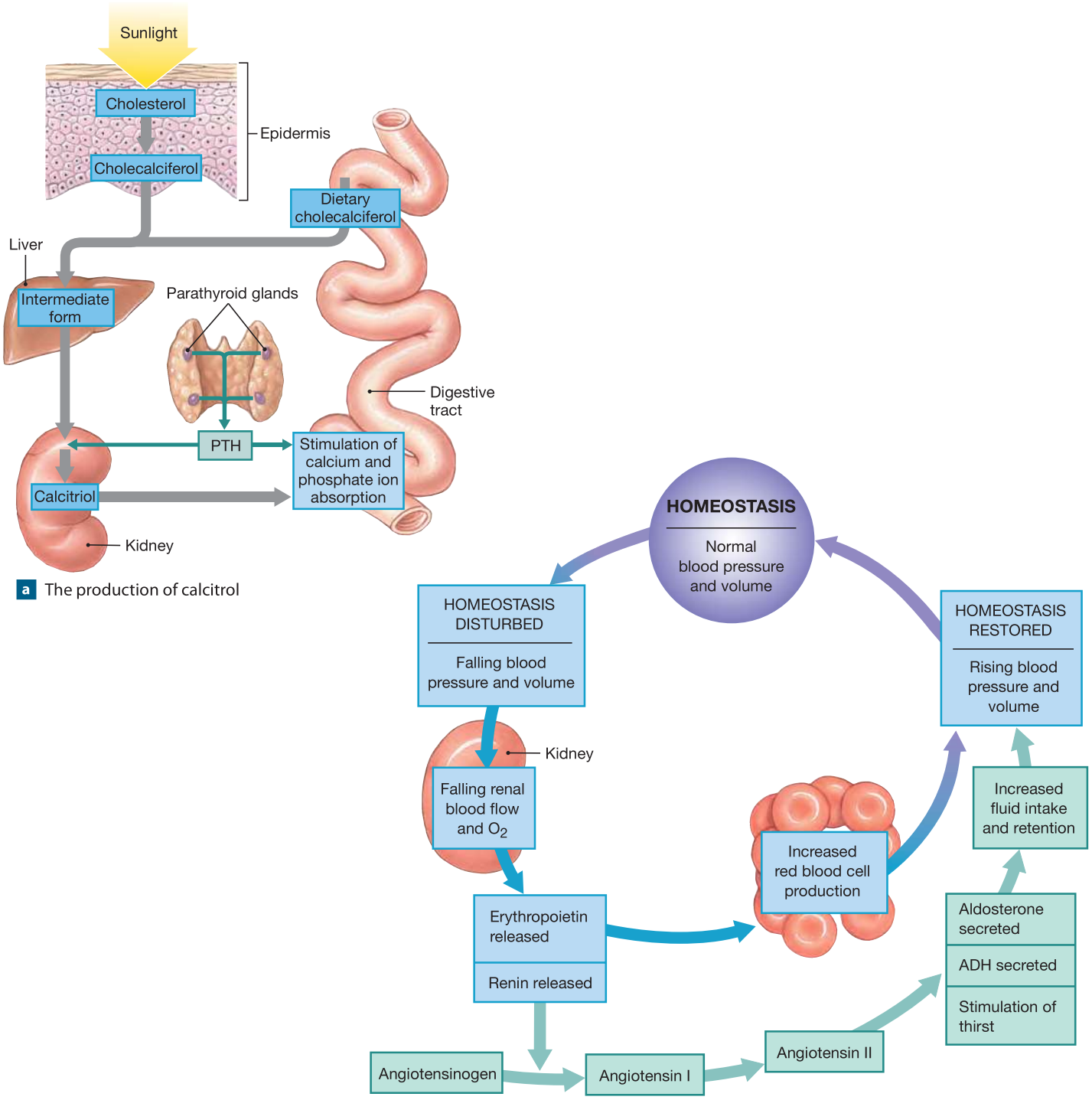
Renin

Specialized kidney cells release **renin** in response to (1) sympathetic stimulation or (2) a decline in renal blood flow. Once in the bloodstream, renin functions as an enzyme that starts an enzymatic cascade known as the *renin–angiotensin system* (**Figure 18–19b**). First, renin converts **angiotensinogen,** a plasma protein produced by the liver, to angiotensin I. In the capillaries of the lungs, **angiotensin I** is then modified to the

Table 18–7 Representative Hormones Produced by Organs of Other Systems

Organ	Hormone	Primary Target	Hormonal Effect
Intestines	Many (secretin, gastrin, cholecystokinin, etc.)	Other regions and organs of the digestive system	Coordinate digestive activities
Kidneys	Erythropoietin (EPO) Calcitriol	Red bone marrow Intestinal lining, bone, kidneys	Stimulates red blood cell production Stimulates calcium and phosphate absorption; stimulates Ca^{+} release from bone; inhibits PTH secretion
Heart	Natriuretic peptides (ANP and BNP)	Kidneys, hypothalamus, adrenal gland	Increase water and salt loss at kidneys; decrease thirst; suppress secretion of ADH and aldosterone
Thymus	Thymosins (many)	Lymphocytes and other cells of the immune response	Coordinate and regulate immune response
Gonads	*See Table 18–8*		
Adipose tissues	Leptin	Hypothalamus	Suppression of appetite; permissive effects on GnRH and gonadotropin synthesis

Figure 18–19 Endocrine Functions of the Kidneys.



hormone **angiotensin II.** This hormone, in turn, stimulates the secretion of aldosterone by the adrenal cortex, and of ADH at the posterior lobe of the pituitary gland. The combination of aldosterone and ADH restricts salt and water losses by the kidneys. Angiotensin II also stimulates thirst and elevates blood pressure.

Because renin plays such a key role in the renin–angiotensin system, many physiological and endocrinological

references consider renin to be a hormone. We will take a closer look at the renin–angiotensin system when we examine the control of blood pressure and blood volume in Chapter 21.

The Heart

The endocrine cells in the heart are cardiac muscle cells in the walls of the *atria* (chambers that receive blood from the veins) and the *ventricles* (chambers that pump blood to the rest of the body). If blood volume becomes too great, these cells are stretched excessively, to the point at which they begin to secrete **natriuretic peptides** (nā-trē-ū-RET-ik; *natrium*, sodium + *ouresis*, making water). In general, the effects of natriuretic peptides oppose those of angiotensin II: Natriuretic peptides promote the loss of Na^+ and water by the kidneys, and inhibit renin release and the secretion of ADH and aldosterone. They also suppress thirst and prevent angiotensin II and norepinephrine from elevating blood pressure. The net result is a reduction in both blood volume and blood pressure, thereby reducing the stretching of the cardiac muscle cells in the heart walls. We discuss two natriuretic peptides—*ANP* (atrial natriuretic peptide) and *BNP* (brain natriuretic peptide)—when we consider the control of blood pressure and volume in Chapters 21 and 26.

The Thymus

The **thymus** is located in the mediastinum, generally just deep to the sternum. This gland produces several hormones that are important in developing and maintaining immune defenses. **Thymosin** (THĪ-mō-sin) is the name originally given to an extract from the thymus that promotes the development and maturation of *lymphocytes*, the white blood cells responsible for immunity. The extract actually contains a blend of several complementary hormones. The term *thymosins* is now sometimes used to refer to all thymic hormones. We consider the histological organization of the thymus and the functions of the thymosins in Chapter 22.

The Gonads

Information about the reproductive hormones of the testes and ovaries is presented in Table 18–8. In males, the **interstitial cells** of the testes produce the male hormones known as androgens. **Testosterone** (tes-TOS-ter-ōn) is the most important androgen. During embryonic development, the production of testosterone affects the development of CNS structures, including hypothalamic nuclei, which will later influence sexual behaviors. **Nurse cells** in the testes support the differentiation and physical maturation of sperm. Under FSH stimulation, these cells secrete the hormone **inhibin.** It inhibits the secretion of FSH at the anterior lobe of the pituitary gland and perhaps suppresses GnRH release at the hypothalamus.

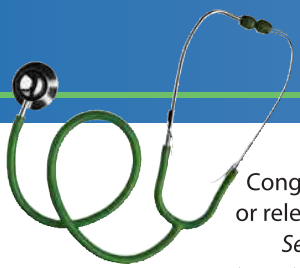
In females, steroid hormones called **estrogens** are produced in the ovaries under FSH and LH stimulation. **Estradiol** is the principal estrogen. Circulating FSH stimulates the secretion of inhibin by ovarian cells, and inhibin suppresses FSH release through a feedback mechanism comparable to that in males.

At ovulation, follicles in the ovary release an immature gamete, or oocyte. The remaining follicle cells then reorganize into a *corpus luteum* (LOO-tē-um; "yellow body") that releases a mixture of estrogens and **progestins. Progesterone** (prō-JES-ter-ōn) is the principal progestin. During pregnancy, the placenta and uterus produce additional hormones that interact with those produced by the ovaries and the pituitary gland to promote normal fetal development and delivery. We consider the hormonal aspects of pregnancy in Chapter 29.

Table 18–8 Hormones of the Reproductive System

Structure/Cells	Hormone	Primary Target	Hormonal Effect	Regulatory Control
TESTES				
Interstitial cells	Androgens	Most cells	Support functional maturation of sperm, protein synthesis in skeletal muscles, male secondary sex characteristics, and associated behaviors	Stimulated by LH from the anterior lobe of the pituitary gland
Nurse cells	Inhibin	Pituitary gland	Inhibits secretion of FSH	Stimulated by FSH from the anterior lobe
OVARIES				
Follicular cells	Estrogens	Most cells	Support follicle maturation, female secondary sex characteristics, and associated behaviors	Stimulated by FSH and LH from the anterior lobe of the pituitary gland
	Inhibin	Pituitary gland	Inhibits secretion of FSH	Stimulated by FSH from anterior lobe
Corpus luteum	Progestins	Uterus, mammary glands	Prepare uterus for implantation; prepare mammary glands for secretory activity	Stimulated by LH from the anterior lobe of the pituitary gland

Profound implications for a little hormone



Regulation of hormone levels often involves negative feedback control mechanisms involving the endocrine organ, neural regulatory factors, and the target tissues. Abnormalities may result from hormone overproduction (hypersecretion), or underproduction (hyposecretion), or from abnormal cellular sensitivity to the hormone.

Primary disorders result from problems within the endocrine organ. The underlying cause may be a metabolic factor. Hypothyroidism due to a lack of dietary iodine is an example. An endocrine organ may also malfunction due to physical damage that destroys cells or disrupts the normal blood supply. Congenital problems may also affect the regulation, production, or release of hormones by endocrine cells.

Secondary disorders result from problems in other organs or target tissues. Such disorders often involve the hypothalamus or pituitary gland. For example, if the hypothalamus or pituitary gland doesn't produce enough TRH and/or TSH, then secondary hypothyroidism occurs.

Abnormalities in target cells can affect their sensitivity or responsiveness to a particular hormone. For example, type 2 diabetes results from the target cell's decreased sensitivity to insulin.

Endocrine disorders often reflect either abnormal hormone production or abnormal cellular sensitivity to hormones. The signs and symptoms highlight the significance of normally "silent" hormonal contributions. The characteristics of these disorders are summarized in **Table 18–9**.

Table 18–9 Clinical Implications of Endocrine Malfunctions

Hormone	Underproduction or Tissue Insensitivity	Principal Signs and Symptoms	Overproduction or Tissue Hypersensitivity	Principal Signs and Symptoms
Growth hormone (GH)	Pituitary growth failure	Retarded growth, abnormal fat distribution, low blood glucose hours after a meal	Gigantism, acromegaly	Excessive growth
Antidiuretic hormone (ADH) or vasopressin (VP)	Diabetes insipidus	Polyuria, dehydration, thirst	SIADH (syndrome of inappropriate ADH secretion)	Increased body weight and water content
Thyroxine (T_4), triiodothyronine (T_3)	Myxedema, cretinism	Low metabolic rate; low body temperature; impaired physical and mental development	Hyperthyroidism, Graves disease	High metabolic rate and body temperature
Parathyroid hormone (PTH)	Hypoparathyroidism	Muscular weakness, neurological problems, formation of dense bones, tetany due to low blood Ca^{2+} concentrations	Hyperparathyroidism	Neurological, mental, muscular problems due to high blood Ca^{2+} concentrations; weak and brittle bones
Insulin	Diabetes mellitus (type 1)	High blood glucose, impaired glucose utilization, dependence on lipids for energy; glycosuria	Excess insulin production or administration	Low blood glucose levels, possibly causing coma
Mineralocorticoids (MCs)	Hypoaldosteronism	Polyuria, low blood volume, high blood K^+, low blood Na^+ concentrations	Aldosteronism	Increased body weight due to Na^+ and water retention; low blood K^+ concentration
Glucocorticoids (GCs)	Addison's disease	Inability to tolerate stress, mobilize energy reserves, or maintain normal blood glucose concentrations	Cushing's disease	Excessive breakdown of tissue proteins and lipid reserves; impaired glucose metabolism
Epinephrine (E), norepinephrine (NE)	None identified		Pheochromocytoma	High metabolic rate, body temperature, and heart rate; elevated blood glucose levels
Estrogens (females)	Hypogonadism	Sterility, lack of secondary sex characteristics	Adrenogenital syndrome	Overproduction of androgens by zona reticularis of adrenal cortex leads to masculinization
			Precocious puberty	Premature sexual maturation and related behavioral changes
Androgens (males)	Hypogonadism	Sterility, lack of secondary sex characteristics	Adrenogenital syndrome (gynecomastia)	Abnormal production of estrogen, sometimes due to adrenal or interstitial cell tumors; leads to breast enlargement
			Precocious puberty	Premature sexual maturation and related behavioral changes

Adipose Tissue

Recall from Chapter 4 that adipose tissue is a type of loose connective tissue. p. 124 Adipose tissue produces a peptide hormone called **leptin,** which has several functions. Its best known function is feedback control of appetite. When we eat, adipose tissue absorbs glucose and lipids and synthesizes triglycerides for storage. At the same time, it releases leptin into the bloodstream. Leptin binds to hypothalamic neurons involved with emotion and appetite control. The result is a sense of fullness (satiation) and the suppression of appetite.

Leptin was first discovered in a strain of obese mice that had a defective leptin gene. When treated with leptin, these overweight mice quickly turned into slim, athletic animals. The initial hope that leptin could be used to treat human obesity was soon dashed, however. Most obese people appear to have defective leptin receptors (or leptin pathways) in the appetite centers of the CNS. Their circulating leptin levels are already several times higher than those in individuals of normal body weight. Additional leptin would have no effect. Researchers are now investigating the structure of the receptor protein and the biochemistry of the pathway triggered by leptin binding.

Leptin must be present for normal levels of GnRH and gonadotropin synthesis to take place. This explains why (1) thin girls commonly enter puberty relatively late, (2) an increase in body fat can improve fertility, and (3) women stop menstruating when their body fat content becomes very low.

18

Checkpoint

26. **Identify two hormones secreted by the kidneys.**
27. **Identify a hormone released by adipose tissue.**
28. **Describe the action of renin in the bloodstream.**

See the blue Answers tab at the back of the book.

18-10 Hormones interact to produce coordinated physiological responses

We usually study hormones individually, but the extracellular fluids contain a mixture of hormones whose concentrations change daily or even hourly. As a result, cells never respond to only one hormone. Instead, they respond to multiple hormones. When a cell receives instructions from two hormones at the same time, four outcomes are possible:

1. The two hormones may have opposing or **antagonistic effects,** as in the case of PTH and calcitonin, or insulin and glucagon. The net result depends on the balance between the two hormones. In general, when two antagonistic hormones are present, the observed effects are weaker than those produced by either hormone acting unopposed.
2. The two hormones may have additive effects, so that the net result is greater than the effect that each would produce acting alone. In some cases, the net result is greater than the *sum* of the hormones' individual effects. This interaction is a **synergistic effect** (sin-er-JIS-tik; *synairesis*, a drawing together). An example is the glucose-sparing action of GH and glucocorticoids.
3. One hormone can have a **permissive effect** on another. In such cases, the first hormone is needed for the second to produce its effect. For example, epinephrine does not change energy consumption unless thyroid hormones are also present in normal concentrations.
4. Finally, hormones may produce different, but complementary, results in specific tissues and organs. These **integrative effects** are important in coordinating the activities of diverse physiological systems. The differing effects of calcitriol and parathyroid hormone on tissues involved in calcium metabolism are an example.

When multiple hormones regulate a complex process, it is very difficult to determine whether a hormone has synergistic, permissive, or integrative effects. Next we consider three examples of processes regulated by complex hormonal interactions: growth, the response to stress, and behavior.

Role of Hormones in Growth

Several endocrine organs work together to bring about normal growth. Several hormones—GH, thyroid hormones, insulin, PTH, calcitriol, and reproductive hormones—are especially important. Many others have secondary effects on growth. The circulating concentrations of these hormones are regulated independently. Every time the hormonal mixture changes, metabolic operations are modified to some degree. The modifications vary in duration and intensity, producing unique individual growth patterns.

- *Growth Hormone (GH).* The effects of GH on protein synthesis and cellular growth are most apparent in children. GH supports their muscular and skeletal development. In adults, growth hormone helps to maintain normal blood glucose concentrations and to mobilize lipid reserves in adipose tissue. GH is not the primary hormone involved, however. An adult with a GH deficiency but normal levels of thyroxine (T_4), insulin, and glucocorticoids will have no physiological problems.
- *Thyroid Hormones.* Normal growth also requires appropriate levels of thyroid hormones. If these hormones are absent during fetal development or for the first year after birth, the

Just say NO

The use of hormones to improve athletic performance is banned by the International Olympic Committee, the U.S. Olympic Committee, the National Collegiate Athletic Association, Major League Baseball, and the National Football League. The American Medical Association and the American College of Sports Medicine condemn the practice. Yet a significant number of amateur and professional athletes persist in this dangerous practice. Athletes most often use synthetic forms of testosterone, but they might use any combination of testosterone, GH, EPO, and a variety of synthetic hormones.

Androgen Abuse

The use of *anabolic steroids,* or androgens, has become popular with many amateur and professional athletes. The goal of steroid use is to increase muscle mass, endurance, and "competitive spirit." The use of steroids such as *androstenedione*, which the body can convert to testosterone, was highlighted in 2004. Several prominent sports trainers, including the trainer of baseball slugger Barry Bonds, were arrested for providing synthetic steroids to their clients. (Performance-enhancing drugs were banned by Major League Baseball in 1999.)

One supposed justification for this steroid use has been the unfounded opinion that compounds manufactured in the body are not only safe, but good for you. In reality, the administration of natural or synthetic androgens in abnormal amounts carries unacceptable health risks. Androgens are known to produce several complications, including (1) premature closure of epiphyseal cartilages, (2) various liver dysfunctions (including jaundice and liver tumors), (3) prostate gland enlargement and urinary tract obstruction, and (4) testicular atrophy and infertility. Links to heart attacks, impaired cardiac function, and strokes have also been suggested.

Moreover, the normal regulation of androgen production involves a feedback mechanism comparable to that described for adrenal steroids earlier in this chapter. GnRH stimulates the production of LH, and LH stimulates the secretion of testosterone and other androgens by the interstitial cells of the testes. Circulating androgens, in turn, inhibit the production of both GnRH and LH. Thus, when synthetic androgens are administered in high doses, they can suppress the normal production of testosterone and depress the manufacture of GnRH by the hypothalamus. *This suppression of GnRH release can be permanent*.

The use of androgenic "bulking agents" by female bodybuilders not only may add muscle mass, but can also alter muscular proportions and secondary sex characteristics. For example, women taking steroids can develop irregular menstrual periods and changes in body hair distribution (including baldness). Finally, androgen abuse can depress the immune system.

EPO Abuse

EPO is readily available because it is now synthesized by recombinant DNA techniques. Endurance athletes, such as cyclists and marathon runners, sometimes use it to boost the number of oxygen-carrying red blood cells in the bloodstream. This effect increases the oxygen content of blood, but it also makes blood more viscous. For this reason, the heart must work harder to push the blood through the blood vessels. This effort can result in death due to heart failure or stroke in young and otherwise healthy individuals. The 2007 Tour de France bicycle race was tainted by competitors testing positive for banned substances, including testosterone, erythropoietin, and an illegal blood transfusion.

Androgens and EPO are hormones with reasonably well-understood effects. Because drug testing is now widespread in amateur and professional sports, athletes interested in "getting an edge" are experimenting with drugs not easily detected by standard tests. The long-term and short-term effects of these drugs are difficult to predict.

GHB Use

One drug recently used by amateur athletes is **gamma-hydroxybutyrate (GHB).** It was tested for use as an anesthetic in the 1960s but rejected, in part because it was linked to seizures. In 1990, the drug appeared in health-food stores, where it was sold as an anabolic agent and diet aid. It has also been used as a "date rape" drug. According to the FDA, GHB and related compounds—sold or distributed under the names Renewtrient, Revivarant, Blue Nitro, Firewater, and Serenity—have recently been responsible for 145 serious illnesses and at least eight deaths. Signs and symptoms include reduced heart rate, lowered body temperature, confusion, hallucinations, seizures, and coma at doses from 0.25 teaspoon to 4 tablespoons.

nervous system fails to develop normally, and mental retardation results. If T_4 concentrations decline later in life but before puberty, normal skeletal development does not continue.

- *Insulin.* Growing cells need adequate supplies of energy and nutrients. Without insulin, the passage of glucose and amino acids across plasma membranes stops or is drastically reduced.
- *Parathyroid Hormone (PTH) and Calcitriol.* Parathyroid hormone and calcitriol promote the absorption of calcium salts from the bloodstream for deposition in bone. Without adequate levels of both hormones, bones can still enlarge, but are poorly mineralized, weak, and flexible. For example, *rickets* is a condition typically caused by inadequate calcitriol production due to vitamin D deficiency in growing children. As a result, the lower limb bones are so weak that they bend under the body's weight. ↩ p. 152
- *Reproductive Hormones.* The presence or absence of reproductive hormones (androgens in males, estrogens in females) affects the activity of osteoblasts in key locations and the growth of specific cell populations. Androgens and estrogens stimulate cell growth and differentiation in their target tissues, but their targets differ. The differential growth induced by each accounts for gender-related differences in skeletal proportions and secondary sex characteristics.

The Hormonal Responses to Stress

Any condition—physical or emotional—that threatens homeostasis is a form of **stress.** Specific homeostatic adjustments oppose many stresses. For example, a decrease in body temperature leads to shivering or changes in the pattern of blood flow, which can restore normal body temperature.

In addition, the body has a *general* response to stress that can occur while other, more specific responses are under way. A wide variety of stress-causing factors produce the same general pattern of hormonal and physiological adjustments. These responses are part of the **general adaptation syndrome (GAS),** also known as the **stress response.** Hans Selye first described the GAS in 1936. It has three phases: the *alarm phase*, the *resistance phase*, and the *exhaustion phase* (**Spotlight Figure 18–20**).

The Effects of Hormones on Behavior

As we have seen, the hypothalamus regulates many endocrine functions, and hypothalamic neurons monitor the levels of many circulating hormones. Other portions of the CNS are also quite sensitive to hormonal stimulation.

We can see the behavioral effects of specific hormones most clearly in individuals whose endocrine glands are oversecreting or undersecreting. But even normal changes in circulating hormone levels can cause behavioral changes. For example, in *precocious* (premature) *puberty*, sex hormones are produced at an inappropriate time, perhaps as early as age 5 or 6. Not only does an affected child begin to develop adult secondary sex characteristics, but the child's behavior also changes. The "nice little kid" disappears, and the child becomes aggressive and assertive due to the effects of sex hormones on CNS function. In normal teenagers, these behaviors are usually attributed to environmental stimuli, such as peer pressure, but here we can see that they have a physiological basis as well. In adults, changes in the mixture of hormones reaching the CNS can affect intellectual capabilities, memory, learning, and emotional states.

We now briefly turn to the effects of aging on hormone production.

Aging and Hormone Production

The endocrine system undergoes relatively few functional changes with age. The most dramatic exception is the decline in the concentrations of reproductive hormones. We noted the effects of these hormonal changes on the skeletal system in Chapter 6 (p. 192), and we will continue the discussion in Chapter 29.

Blood and tissue concentrations of many other hormones, including TSH, thyroid hormones, ADH, PTH, prolactin, and glucocorticoids, do not change with advancing age. Circulating hormone levels may remain within normal limits, but some endocrine tissues become less responsive to stimulation. For example, in elderly individuals, smaller amounts of GH and insulin are secreted after a carbohydrate-rich meal. The reduced levels of GH and other tropic hormones affect tissues throughout the body. These hormonal effects involve the reductions in bone density and muscle mass noted in earlier chapters.

Finally, age-related changes in peripheral tissues may make them less responsive to some hormones. This loss of sensitivity has been documented in the case of glucocorticoids and ADH.

Extensive integration occurs between the endocrine system and other body systems. For all systems, the endocrine system adjusts metabolic rates and substrate utilization. It also regulates growth and development. **Figure 18–21** shows the functional relationships between the endocrine system and other systems studied so far.

Checkpoint

29. **Insulin lowers blood glucose levels, and glucagon causes glucose levels to rise. What is this type of hormonal interaction called?**
30. **The lack of which hormones would inhibit skeletal formation?**
31. **Why do levels of GH–RH and CRH rise during the resistance phase of the general adaptation syndrome?**
32. **Discuss the general role of the endocrine system in the functioning of other body systems.**
33. **Discuss the functional relationship between the endocrine system and the muscular system.**

See the blue Answers tab at the back of the book.

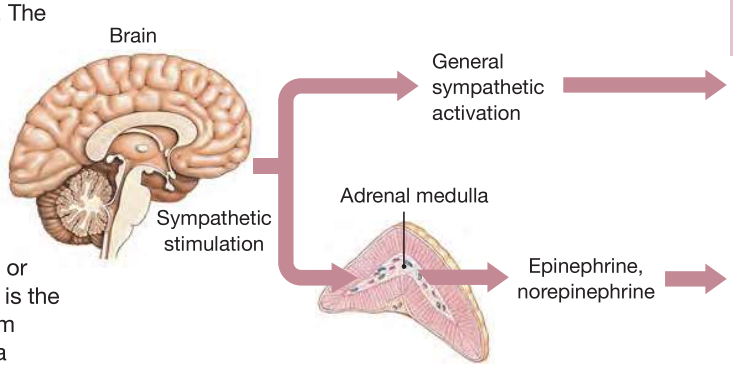
Spotlight

Figure 18–20
The General Adaptation Syndrome

Alarm Phase ("Fight or Flight")

ALARM

During the **alarm phase**, an immediate response to the stress occurs. The sympathetic division of the autonomic nervous system directs this response. In the alarm phase, (1) energy reserves are mobilized, mainly in the form of glucose, and (2) the body prepares to deal with the stress-causing factor by "fight or flight" responses. Epinephrine is the dominant hormone of the alarm phase. Its secretion is part of a generalized sympathetic activation.



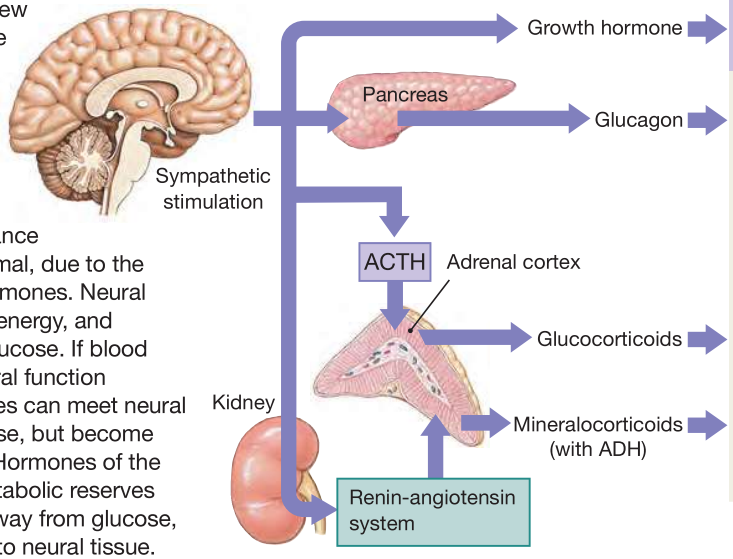
Immediate Short-Term Responses to Crises

- Increased mental alertness
- Increased energy use by all cells
- Mobilization of glycogen and lipid reserves
- Changes in circulation
- Reduction in digestive activity and urine production
- Increased sweat gland secretion
- Increased heart rate and respiratory rate

Resistance Phase

RESISTANCE

If a stress lasts longer than a few hours, the individual enters the **resistance phase** of the GAS. Glucocorticoids are the dominant hormones of the resistance phase. Epinephrine, GH, and thyroid hormones are also involved. Energy demands in the resistance phase remain higher than normal, due to the combined effects of these hormones. Neural tissue has a high demand for energy, and requires a reliable supply of glucose. If blood glucose levels fall too far, neural function deteriorates. Glycogen reserves can meet neural demand during the alarm phase, but become depleted after several hours. Hormones of the resistance phase mobilize metabolic reserves and shift tissue metabolism away from glucose, thus increasing its availability to neural tissue.



Long-Term Metabolic Adjustments

- Mobilization of remaining energy reserves: Lipids are released by adipose tissue; amino acids are released by skeletal muscle
- Conservation of glucose: Peripheral tissues (except neural) break down lipids to obtain energy
- Elevation of blood glucose concentrations: Liver synthesizes glucose from other carbohydrates, amino acids, and lipids
- Conservation of salts and water, loss of K^+ and H^+

Exhaustion Phase

EXHAUSTION

The body's lipid reserves are sufficient to maintain the resistance phase for weeks or even months. But when the resistance phase ends, homeostatic regulation breaks down and the **exhaustion phase** begins. Unless corrective actions are taken almost immediately, the failure of one or more organ systems will prove fatal. The production of aldosterone throughout the resistance phase results in a conservation of Na^+ at the expense of K^+. As the body's K^+ content declines, a variety of cells begin to malfunction. The underlying problem of the exhaustion phase is the body's inability to sustain the endocrine and metabolic adjustments of the resistance phase.

Collapse of Vital Systems

- Exhaustion of lipid reserves
- Cumulative structural or functional damage to vital organs
- Inability to produce glucocorticoids
- Failure of electrolyte balance

SYSTEM INTEGRATOR

Body System → Endocrine System

Endocrine System → Body System

Integumentary

Protects superficial endocrine organs; epidermis synthesizes vitamin D_3

Sex hormones stimulate sebaceous gland activity, influence hair growth, fat distribution, and apocrine sweat gland activity; PRL stimulates development of mammary glands; adrenal hormones alter dermal blood flow; MSH stimulates melanocyte activity

Integumentary Page 165

Skeletal

Protects endocrine organs, especially in brain, chest, and pelvic cavity

Skeletal growth regulated by several hormones; calcium mobilization regulated by parathyroid hormone and calcitonin; sex hormones speed growth and closure of epiphyseal cartilages at puberty and help maintain bone mass in adults

Skeletal Page 275

Muscular

Skeletal muscles provide protection for some endocrine organs

Hormones adjust muscle metabolism, energy production, and growth; regulate calcium and phosphate levels in body fluids; speed skeletal muscle growth

Muscular Page 369

Nervous

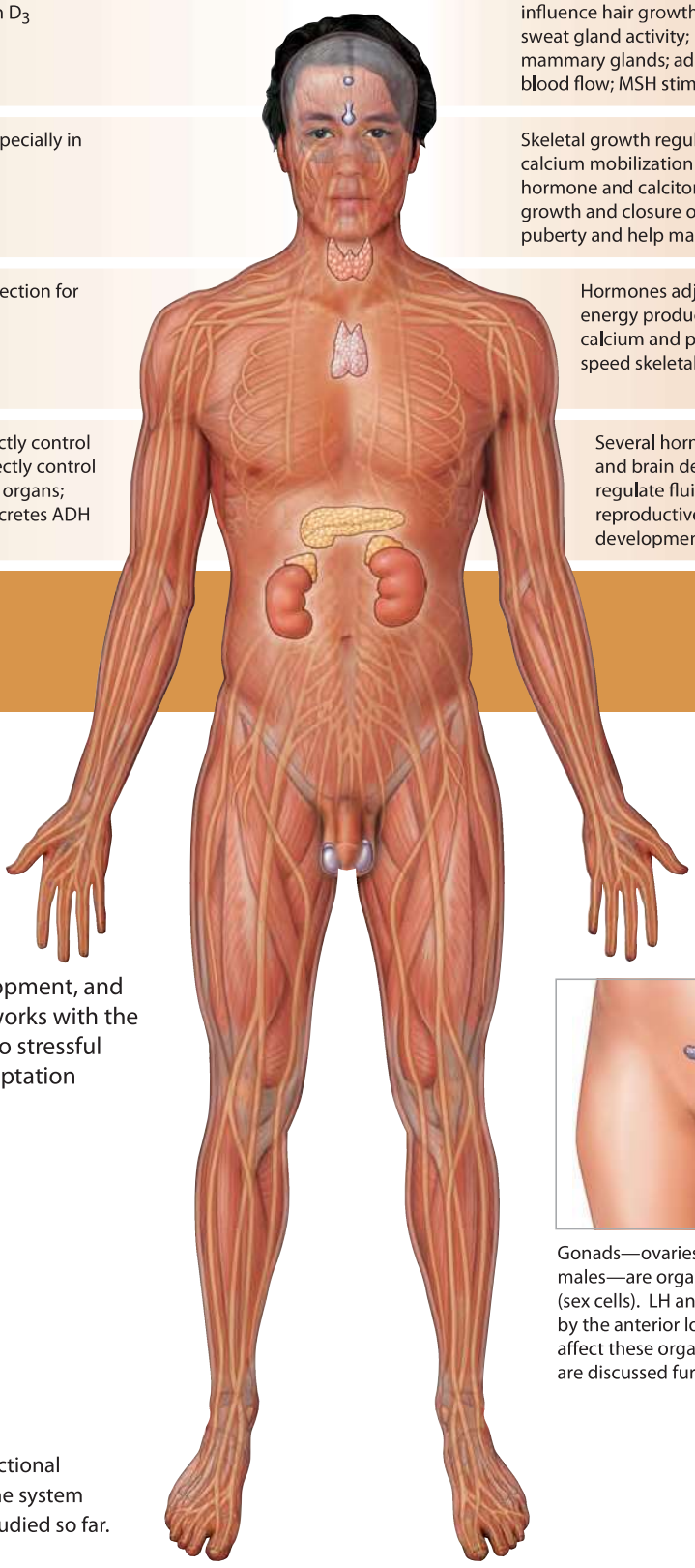
Hypothalamic hormones directly control pituitary secretions and indirectly control secretions of other endocrine organs; controls adrenal medullae; secretes ADH and oxytocin

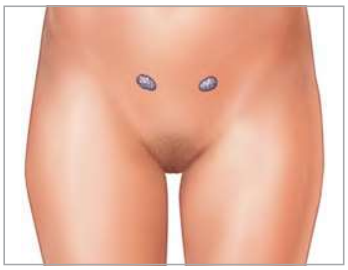
Several hormones affect neural metabolism and brain development; hormones help regulate fluid and electrolyte balance; reproductive hormones influence CNS development and behaviors

Nervous Page 543

The ENDOCRINE System

The endocrine system provides long-term regulation and adjustments of homeostatic mechanisms that affect many body functions. For example, the endocrine system regulates fluid and electrolyte balance, cell and tissue metabolism, growth and development, and reproductive functions. It also works with the nervous system in responding to stressful stimuli through the general adaptation syndrome.





Gonads—ovaries in females and testes in males—are organs that produce gametes (sex cells). LH and FSH, hormones secreted by the anterior lobe of the pituitary gland, affect these organs. The ovaries and testes are discussed further in Chapter 28.

Figure 18–21 diagrams the functional relationships between the endocrine system and other body systems we have studied so far.

Cardiovascular Page 759
Lymphatic Page 807
Respiratory Page 857
Digestive Page 910
Urinary Page 992
Reproductive Page 1072

Related Clinical Terms

adrenalectomy: Surgical removal of an adrenal gland.
empty sella syndrome: Condition in which the pituitary gland becomes shrunken or flattened.
exophthalmos: Abnormal protrusion of the eyeballs.
galactorrhea: A milky discharge from the nipple unrelated to normal breast feeding.
Hashimoto's disease: Disorder that affects the thyroid gland, also known as chronic lymphocytic thyroiditis, causing the immune system to attack the thyroid gland. It is the most common cause of hypothyroidism in the United States.
hirsutism: Excessive growth of facial or body hair in a woman. Hirsutism is a sign of hyperandrogenism, or the presence of abnormally high levels of androgens. It may be a sign of polycystic ovarian syndrome, congenital adrenal hyperplasia (CAH), or androgen-secreting tumors, all of which may cause infertility in women.
hypocalcemic tetany: Muscle spasms affecting the face and upper extremities; caused by low Ca^{2+} concentrations in body fluids.
hypophysectomy: Surgical removal of the pituitary gland.
multiple endocrine neoplasia: A group of rare diseases caused by genetic defects that lead to hyperplasia and hyperfunction in two or more components of the endocrine system; *type I* is characterized by tumors of the pituitary, parathyroid glands, and pancreatic islet cells, with peptic ulcers and sometimes Zollinger-Ellison syndrome; *type II* is characterized by thyroid medullary carcinoma, pheochromocytoma, and parathyroid hyperplasia; *type III* is similar to type II but includes neuromas of the oral region, neurofibromas, ganglioneuromas of the gastrointestinal tract, and café-au-lait spots.
polyglandular deficiency syndrome: Disorders characterized by the failure of two or more endocrine glands to make hormones in sufficient quantities for the body to function normally.
posttraumatic stress disorder (PTSD): A common anxiety disorder that develops after being exposed to a life-threatening situation or terrifying event.
prolactinoma: Noncancerous pituitary tumor that produces prolactin, resulting in too much prolactin in the blood.
psychosocial dwarfism: Growth disorder occurring between the ages of 2 and 15, caused by extreme emotional deprivation or stress.
thyroidectomy: Surgical removal of all or part of the thyroid gland.
thyroid function tests: Blood and radionuclide tests to determine thyroid gland activity.
thyrotoxicosis: A condition caused by the oversecretion of thyroid hormones (hyperthyroidism). Signs and symptoms include increases in metabolic rate, blood pressure, and heart rate; excitability and emotional instability; and lowered energy reserves.
virilism: A disorder of females in which there is development of secondary male sexual characteristics such as hirsutism and lowered voice caused by a number of conditions that affect hormone regulation.

Chapter Review

Study Outline

18-1 Homeostasis is preserved through intercellular communication p. 594

1. In general, the nervous system performs short-term "crisis management," whereas the endocrine system regulates longer-term, ongoing metabolic processes.
2. **Paracrine communication** involves the use of chemical signals to transfer information from cell to cell within a single tissue.
3. **Endocrine communication** results when chemicals, called hormones, are released into the circulation by *endocrine cells*. The hormones alter the metabolic activities of many tissues and organs simultaneously by modifying the activities of **target cells**. *(Table 18–1)*

18-2 The endocrine system regulates physiological processes through the binding of hormones to receptors p. 596

4. The endocrine system includes all the cells and endocrine tissues of the body that produce hormones or paracrine factors. (*Figure 18–1*)
5. Hormones can be divided into three groups according to their chemical structure: *amino acid derivatives*; *peptide hormones*; and *lipid derivatives*, including **steroid hormones** and **eicosanoids.** *(Spotlight Figure 18–2)*
6. Hormones may circulate freely or bound to transport proteins. Free hormones are rapidly removed from the bloodstream.
7. Receptors for *catecholamines*, peptide hormones, and eicosanoids are in the plasma membranes of target cells. Thyroid and steroid hormones cross the plasma membrane and bind to receptors in the cytoplasm or nucleus, activating or inactivating specific genes. *(Figures 18–3, 18–4)*
8. **Endocrine reflexes** are the functional counterparts of neural reflexes.
9. The hypothalamus regulates the activities of the nervous and endocrine systems by (1) secreting **regulatory hormones,** which control the activities of endocrine cells in the anterior lobe of the pituitary gland; (2) acting as an endocrine organ by releasing hormones into the bloodstream at the posterior lobe of the pituitary gland; and (3) exerting direct neural control over the endocrine cells of the adrenal medullae. *(Figure 18–5)*

18-3 The bilobed pituitary gland is an endocrine organ that releases nine peptide hormones p. 603

10. The **pituitary gland**, or **hypophysis**, releases nine important peptide hormones. All bind to membrane receptors and use cyclic-AMP as a second messenger. *(Figures 18–6 through 18–9; Table 18–2)*
11. The **anterior lobe** of the pituitary gland, or **adenohypophysis**, can be subdivided into the **pars distalis**, the **pars intermedia**, and the **pars tuberalis**. *(Figure 18–6)*
12. At the median eminence of the hypothalamus, neurons release regulatory factors (either **releasing hormones**, **RH**, or **inhibiting hormones**, **IH**) into the surrounding interstitial fluids through **fenestrated capillaries**. *(Figure 18–7)*
13. The **hypophyseal portal system** ensures that these regulatory factors reach the intended target cells in the pituitary before they enter the general circulation. *(Figure 18–7)*
14. **Thyroid-stimulating hormone (TSH)** triggers the release of thyroid hormones. *Thyrotropin-releasing hormone (TRH)* from the hypothalamus promotes the pituitary's secretion of TSH. *(Figure 18–8)*
15. **Adrenocorticotropic hormone (ACTH)** stimulates the release of *glucocorticoids* by the adrenal cortex. Corticotropin-releasing hormone (CRH) from the hypothalamus causes the pituitary to secrete ACTH. *(Figure 18–8)*
16. **Follicle-stimulating hormone (FSH)** stimulates follicle development and estrogen secretion in females and sperm production in males. **Luteinizing hormone (LH)** causes *ovulation* and *progestin* production in females, and androgen production in males. Gonadotropin-releasing hormone (GnRH) from the hypothalamus promotes the pituitary's secretion of both FSH and LH. *(Figure 18–8)*
17. **Prolactin (PRL)** from the pituitary, together with other hormones, stimulates both the development of the mammary glands and milk production. *(Figure 18–8)*
18. **Growth hormone (GH,** or **somatotropin)** from the pituitary stimulates cell growth and replication through the release of **somatomedins** or **IGF**s from liver cells. The production of GH is regulated by **growth hormone–releasing hormone (GH–RH)** and **growth hormone–inhibiting hormone (GH–IH)** from the hypothalamus. *(Figure 18–8)*
19. **Melanocyte-stimulating hormone (MSH)** may be secreted by the pars intermedia of the pituitary during fetal development, early childhood, pregnancy, or certain diseases. This hormone stimulates melanocytes to produce melanin.
20. The **posterior lobe** of the pituitary gland, or **neurohypophysis**, contains the unmyelinated axons of hypothalamic neurons. Neurons of the **supraoptic** and **paraventricular nuclei** manufacture **antidiuretic hormone (ADH)** and **oxytocin**, respectively. ADH decreases the amount of water lost at the kidneys and, in higher concentrations, elevates blood pressure. In women, oxytocin stimulates contractile cells in the mammary glands and has a stimulatory effect on smooth muscles in the uterus. *(Figure 18–9; Table 18–2)*

18-4 The thyroid gland lies inferior to the larynx and requires iodine for hormone synthesis p. 609

21. The thyroid gland lies anterior to the *thyroid cartilage* of the larynx and consists of two **lobes** connected by a narrow **isthmus**. *(Figure 18–10)*
22. The thyroid gland contains numerous **thyroid follicles**. Thyroid follicles release several hormones, including **thyroxine** and **triiodothyronine** *(Figures 18–10, 18–11; Table 18–4)*
23. Most of the thyroid hormones entering the bloodstream are attached to special **thyroid-binding globulins (TBGs)**; the rest are attached to either **transthyretin** or albumin. *(Figure 18–11)*
24. In target cells, thyroid hormones are held in storage in the cytoplasm, bound to mitochondria (where they increase ATP production), or bound to receptors activating genes that control energy utilization. They also exert a **calorigenic effect**. *(Table 18–3)*
25. The **C cells** of the thyroid follicles produce **calcitonin (CT)**, which helps regulate Ca^{2+} concentrations in body fluids, especially during childhood and pregnancy. *(Figure 18–10; Table 18–4)*

18-5 The four parathyroid glands, embedded in the posterior surface of the thyroid, secrete parathyroid hormone to elevate plasma Ca^{2+} p. 614

26. Four **parathyroid glands** are embedded in the posterior surface of the thyroid gland. **Parathyroid chief cells** produce **parathyroid hormone (PTH)** in response to lower-than-normal concentrations of Ca^{2+}. The parathyroid glands, aided by *calcitriol*, are the primary regulators of blood calcium levels in healthy adults. *(Figures 18–12, 18–13; Table 18–4)*

18-6 The adrenal glands, consisting of a cortex and medulla, cap the kidneys and secrete several hormones p. 615

27. One **adrenal** *(suprarenal)* **gland** lies along the superior border of each kidney. The gland is subdivided into the superficial **adrenal cortex** and the inner **adrenal medulla**. *(Figure 18–14)*
28. The adrenal cortex manufactures steroid hormones called **corticosteroids**. The cortex can be subdivided into three areas: (1) the **zona glomerulosa**, which releases **mineralocorticoids**, principally **aldosterone**; (2) the **zona fasciculata**, which produces **glucocorticoids**, notably **cortisol** and **corticosterone**; and (3) the **zona reticularis**, which produces androgens under ACTH stimulation. *(Figure 18–14; Table 18–5)*
29. The adrenal medulla produces epinephrine (75–80 percent of medullary secretion) and norepinephrine (20–25 percent). *(Figure 18–14; Table 18–5)*

18-7 The pineal gland, attached to the roof of the third ventricle, secretes melatonin p. 619

30. The **pineal gland** contains **pinealocytes**, which synthesize **melatonin**. Suggested functions include inhibiting reproductive functions, protecting against damage by free radicals, and setting circadian rhythms. *(Figure 18–15)*

18-8 The pancreas, located in the abdominopelvic cavity, is both an exocrine organ and endocrine gland p. 620

31. The pancreas contains both exocrine and endocrine cells. Cells of the endocrine pancreas form clusters called **pancreatic islets** *(islets of Langerhans)*. These islets contain **alpha cells**, which secrete the hormone glucagon; **beta cells**, which secrete **insulin**; **delta cells**, which secrete **somatostatin (GH–IH)**; and **F cells**, which secrete **pancreatic polypeptide**. *(Figure 18–16; Table 18–6)*
32. Insulin lowers blood glucose by increasing the rate of glucose uptake and utilization by most body cells; glucagon raises blood glucose by increasing the rates of glycogen breakdown and glucose manufacture in the liver. *(Figure 18–17; Table 18–6)*

33. Diabetes mellitus is an endocrine disorder characterized by insulin deficiency and faulty glucose metabolism. *(Spotlight Figure 18–18)*

18-9 Many organs have secondary endocrine functions p. 624

34. The intestines produce hormones important in coordinating digestive activities. *(Table 18–7)*
35. Endocrine cells in the kidneys produce the hormones *calcitriol* and *erythropoietin* and the enzyme *renin*. *(Table 18–7)*
36. **Calcitriol** stimulates calcium and phosphate ion absorption along the digestive tract. *(Figure 18–19)*
37. **Erythropoietin (EPO)** stimulates red blood cell production by the bone marrow. *(Figure 18–19)*
38. **Renin** converts **angiotensinogen** to **angiotensin I.** In the capillaries of the lungs, angiotensin I is converted to **angiotensin II,** a hormone that (1) stimulates the adrenal production of aldosterone, (2) stimulates the pituitary release of ADH, (3) promotes thirst, and (4) elevates blood pressure. *(Figure 18–19)*
39. Specialized muscle cells in the heart produce **natriuretic peptides** (*ANP* and *BNP*) when blood volume becomes excessive. In general, their actions oppose those of angiotensin II. *(Table 18–7)*
40. The thymus produces several hormones, collectively known as **thymosins,** which play a role in developing and maintaining normal immune defenses. *(Table 18–7)*
41. The **interstitial cells** of the testes produce androgens. **Testosterone** is the most important sex hormone in males. *(Table 18–8)*
42. In females, *oocytes* develop in follicles, and follicle cells produce **estrogens,** especially **estradiol.** After ovulation, the remaining follicle cells reorganize into a *corpus luteum*. Those cells release a mixture of estrogens and **progestins,** especially **progesterone.** *(Table 18–8)*
43. Adipose tissue secretes **leptin** (a feedback control for appetite).

18-10 Hormones interact to produce coordinated physiological responses p. 628

44. Endocrine system hormones often interact, producing (1) **antagonistic** (opposing) **effects;** (2) **synergistic** (additive) **effects;** (3) **permissive effects,** in which one hormone is necessary for another to produce its effect; or (4) **integrative effects,** in which hormones produce different, but complementary, results.
45. Normal growth requires the cooperation of several endocrine organs. Several hormones are especially important: GH, thyroid hormones, insulin, PTH, calcitriol, and reproductive hormones.
46. Any condition that threatens homeostasis is a **stress.** Our bodies respond to a variety of stress-causing factors through the **general adaptation syndrome (GAS),** or **stress response.**
47. The GAS can be divided into three phases: (1) the **alarm phase** (an immediate, "fight or flight" response, under the direction of the sympathetic division of the ANS); (2) the **resistance phase,** dominated by glucocorticoids; and (3) the **exhaustion phase,** the eventual breakdown of homeostatic regulation and failure of one or more organ systems. *(Spotlight Figure 18–20)*
48. Many hormones affect the CNS. Changes in the normal mixture of hormones can significantly alter intellectual capabilities, memory, learning, and emotional states.
49. The endocrine system undergoes few functional changes with advanced age. The major changes include a decline in the concentration of growth hormone and reproductive hormones.
50. The endocrine system provides long-term regulation and homeostatic adjustments that affect many body systems. *(Figure 18–21)*

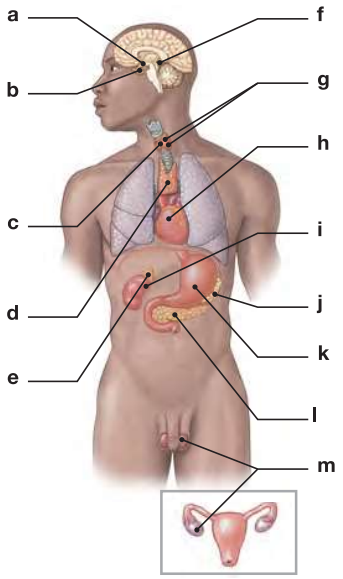
Review Questions

See the blue Answers tab at the back of the book.

LEVEL 1 Reviewing Facts and Terms

1. Identify the endocrine glands and tissues in the following diagram.

(a) _____
(b) _____
(c) _____
(d) _____
(e) _____
(f) _____
(g) _____
(h) _____
(i) _____
(j) _____
(k) _____
(l) _____
(m) _____



2. The use of a chemical messenger to transfer information from cell to cell within a single tissue is referred to as _____ communication.
   (a) direct
   (b) paracrine
   (c) hormonal
   (d) endocrine
3. Cyclic-AMP functions as a second messenger to
   (a) build proteins and catalyze specific reactions.
   (b) activate adenylate cyclase.
   (c) open ion channels and activate key enzymes in the cytoplasm.
   (d) bind the hormone–receptor complex to DNA segments.
4. Adrenocorticotropic hormone (ACTH) stimulates the release of
   (a) thyroid hormones by the hypothalamus.
   (b) gonadotropins by the adrenal glands.
   (c) growth hormones by the hypothalamus.
   (d) steroid hormones by the adrenal glands.
5. FSH production in males supports
   (a) the maturation of sperm by stimulating nurse cells.
   (b) the development of muscles and strength.
   (c) the production of male sex hormones.
   (d) an increased desire for sexual activity.
6. The two hormones released by the posterior lobe of the pituitary gland are
   (a) GH and gonadotropin.
   (b) estrogen and progesterone.
   (c) GH and prolactin.
   (d) ADH and oxytocin.
7. All of the following are true of the endocrine system, *except* that it
   (a) releases chemicals into the bloodstream for distribution throughout the body.
   (b) releases hormones that simultaneously alter the metabolic activities of many different tissues and organs.
   (c) produces effects that can last for hours, days, and even longer.
   (d) produces rapid, local, brief-duration responses to specific stimuli.
   (e) functions to control ongoing metabolic processes.
8. A cell's hormonal sensitivities are determined by the
   (a) chemical nature of the hormone.
   (b) quantity of circulating hormone.
   (c) shape of the hormone molecules.
   (d) presence or absence of appropriate receptors.
   (e) thickness of its plasma membrane.
9. Endocrine organs can be regulated by all of the following, *except*
   (a) hormones from other endocrine glands.
   (b) changes in the genetic makeup of certain hypothalamic cells.
   (c) direct neural stimulation.
   (d) changes in the composition of extracellular fluid.
   (e) releasing hormones from the hypothalamus.
10. What three higher-level mechanisms are involved in integrating the activities of the nervous and endocrine systems?
11. Which seven hormones are released by the anterior lobe of the pituitary gland?
12. What six hormones primarily affect growth?
13. What five primary effects result from the action of thyroid hormones?
14. What effects do calcitonin and parathyroid hormone have on blood calcium levels?
15. What three zones make up the adrenal cortex, and what kind of hormones does each zone produce?
16. Which two hormones are released by the kidneys, and what is the importance of each hormone?
17. What are the four opposing effects of atrial natriuretic peptide and angiotensin II?
18. What four cell populations make up the endocrine pancreas? Which hormone does each type of cell produce?

LEVEL 2 Reviewing Concepts

19. What is the primary difference in the way the nervous and endocrine systems communicate with their target cells?
20. In what ways can a hormone modify the activities of its target cells?
21. What is an endocrine reflex? Compare endocrine reflexes and neural reflexes.
22. How would blocking the activity of phosphodiesterase affect a cell that responds to hormonal stimulation by the cAMP second-messenger system?
23. How does control of the adrenal medulla differ from control of the adrenal cortex?
24. A researcher observes that stimulation by a particular hormone induces a marked increase in the activity of G proteins in the target plasma membrane. The hormone being studied is probably
   (a) a steroid.
   (b) a peptide.
   (c) testosterone.
   (d) estrogen.
   (e) aldosterone.
25. Increased blood calcium levels would result in *increased*
   (a) secretion of calcitonin.
   (b) secretion of PTH.
   (c) retention of calcium by the kidneys.
   (d) osteoclast activity.
   (e) excitability of neural membranes.
26. In type 2 diabetes mellitus, insulin levels are frequently normal, yet the target cells are less sensitive to the effects of insulin. This suggests that the target cells
   (a) are impermeable to insulin.
   (b) may lack enough insulin receptors.
   (c) cannot convert insulin to an active form.
   (d) have adequate internal supplies of glucose.
   (e) both b and c.

LEVEL 3 Critical Thinking and Clinical Applications

27. Roger has been extremely thirsty. He drinks numerous glasses of water every day and urinates a great deal. Name two disorders that could produce these signs and symptoms. What test could a clinician perform to determine which disorder Roger has?
28. Julie is pregnant but is not receiving prenatal care. She has a poor diet consisting mostly of fast food. She drinks no milk, preferring colas instead. How would this situation affect Julie's level of parathyroid hormone?

29. Sherry tells her physician that she has been restless and irritable lately. She has a hard time sleeping and complains of diarrhea and weight loss. During the examination, her physician notices a higher-than-normal heart rate and a fine tremor in her outstretched fingers. What tests could the physician perform to make a positive diagnosis of Sherry's condition?
30. What are two benefits of having a portal system connect the median eminence of the hypothalamus with the anterior lobe of the pituitary gland?
31. Pamela and her teammates are considering taking testosterone supplements (anabolic steroids) to enhance their competitive skills. What natural effects of this hormone are they hoping to gain? What additional side effects might these women expect should they begin an anabolic steroid regime?

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- Biochemistry, Secretion, and Transport of Hormones
- The Actions of Hormones on Target Cells
- The Hypothalamic-Pituitary Axis
- Response to Stress