

56

The Endocrine System

Concept Outline

56.1 Regulation is often accomplished by chemical messengers.

Types of Regulatory Molecules. Regulatory molecules may function as neurotransmitters, hormones, or as organ-specific regulators.

Endocrine Glands and Hormones. Endocrine glands secrete molecules called hormones into the blood.

Paracrine Regulation. Paracrine regulators act within organs that produce them.

56.2 Lipophilic and polar hormones regulate their target cells by different means.

Hormones That Enter Cells. Steroid and thyroid hormones act by entering target cells and stimulating specific genes.

Hormones That Do Not Enter Cells. All other hormones bind to receptors on the cell surface and activate second-messenger molecules within the target cells.

56.3 The hypothalamus controls the secretions of the pituitary gland.

The Posterior Pituitary Gland. The posterior pituitary receives and releases hormones from the hypothalamus.

The Anterior Pituitary Gland. The anterior pituitary produces a variety of hormones under stimulation from hypothalamic releasing hormones.

56.4 Endocrine glands secrete hormones that regulate many body functions.

The Thyroid and Parathyroid Glands. The thyroid hormones regulate metabolism; the parathyroid glands regulate calcium balance.

The Adrenal Glands. The adrenal medulla secretes epinephrine during the fight-or-flight reaction, while the adrenal cortex secretes steroid hormones that regulate glucose and mineral balance.

The Pancreas. The islets of Langerhans in the pancreas secrete insulin, which acts to lower blood glucose, and glucagon, which acts to raise blood glucose.

Other Endocrine Glands. The gonads, pineal gland, thymus, kidneys, and other organs secrete important hormones that have a variety of functions.



FIGURE 56.1

The endocrine system controls when animals breed. These Japanese macaques live in a close-knit community whose members cooperate to ensure successful breeding and raising of offspring. Not everybody breeds at the same time because hormone levels vary among individuals.

The tissues and organs of the vertebrate body cooperate to maintain homeostasis of the body's internal environment and control other body functions such as reproduction. Homeostasis is achieved through the actions of many regulatory mechanisms that involve all the organs of the body. Two systems, however, are devoted exclusively to the regulation of the body organs: the nervous system and the endocrine system (figure 56.1). Both release regulatory molecules that control the body organs by first binding to receptor proteins in the cells of those organs. In this chapter we will examine these regulatory molecules, the cells and glands that produce them, and how they function to regulate the body's activities.

56.1 Regulation is often accomplished by chemical messengers.

Types of Regulatory Molecules

As we discussed in chapter 54, the axons of neurons secrete chemical messengers called *neurotransmitters* into the synaptic cleft. These chemicals diffuse only a short distance to the postsynaptic membrane, where they bind to their receptor proteins and stimulate the postsynaptic cell (another neuron, or a muscle or gland cell). Synaptic transmission generally affects only the one postsynaptic cell that receives the neurotransmitter.

A **hormone** is a regulatory chemical that is secreted into the blood by an **endocrine gland** or an organ of the body exhibiting an endocrine function. The blood carries the hormone to every cell in the body, but only the **target cells** for a given hormone can respond to it. Thus, the difference between a neurotransmitter and a hormone is not in the chemical nature of the regulatory molecule, but rather in the way it is transported to its target cells, and its distance from these target cells. A chemical regulator called norepinephrine, for example, is released as a neurotransmitter by sympathetic nerve endings and is also secreted by the adrenal gland as a hormone.

Some specialized neurons secrete chemical messengers into the blood rather than into a narrow synaptic cleft. In these cases, the chemical that the neurons secrete is some-

times called a **neurohormone**. The distinction between the nervous system and endocrine system blurs when it comes to such molecules. Indeed, because some neurons in the brain secrete hormones, the brain can be considered an endocrine gland!

In addition to the chemical messengers released as neurotransmitters and as hormones, other chemical regulatory molecules are released and act *within* an organ. In this way, the cells of an organ regulate one another. This type of regulation is not endocrine, because the regulatory molecules work without being transported by the blood, but is otherwise similar to the way that hormones regulate their target cells. Such regulation is called **paracrine**. Another type of chemical messenger that is released into the environment is called a *pheromone*. These messengers aid in the communication between animals, not in the regulation within an animal. A comparison of the different types of chemical messengers used for regulation is given in figure 56.2.

Regulatory molecules released by axons at a synapse are neurotransmitters, those released by endocrine glands into the blood are hormones, and those that act within the organ in which they are produced are paracrine regulators.

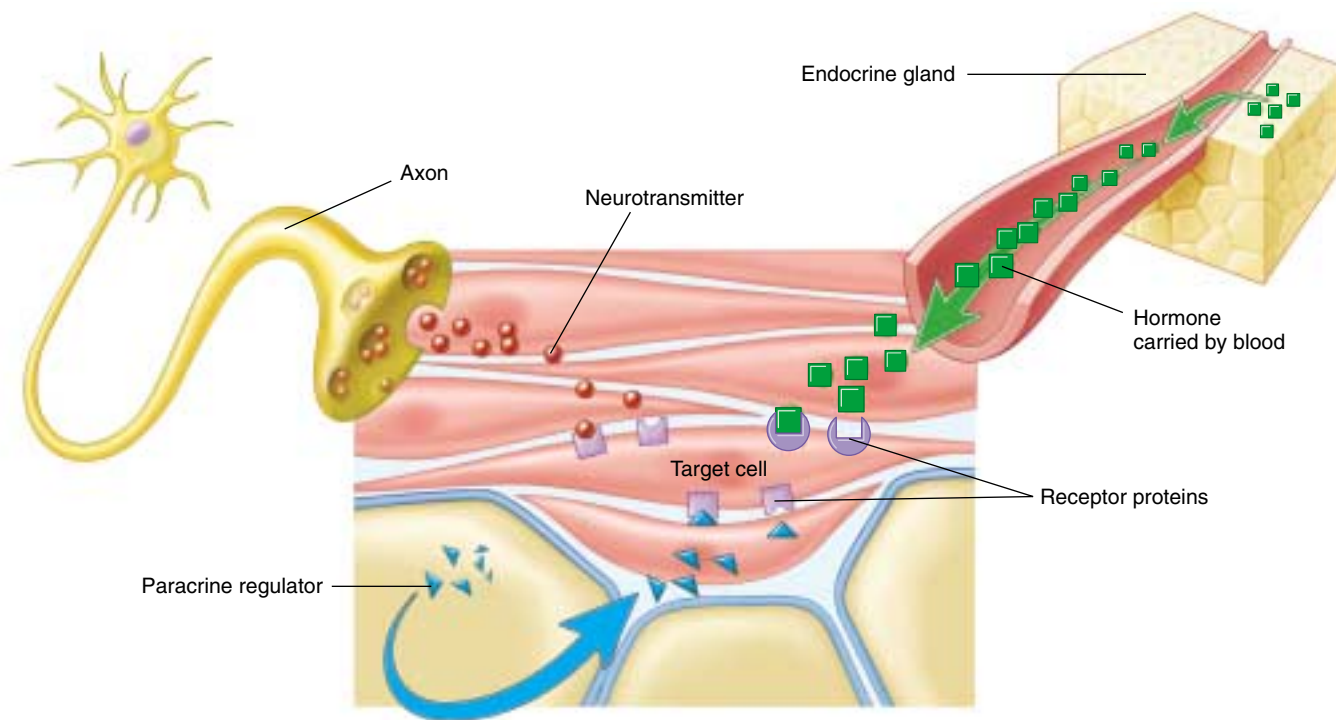


FIGURE 56.2

The functions of organs are influenced by neural, paracrine, and endocrine regulators. Each type of chemical regulator binds in a specific fashion to receptor proteins on the surface of or within the cells of target organs.

Endocrine Glands and Hormones

The endocrine system (figure 56.3) includes all of the organs that function exclusively as endocrine glands—such as the thyroid gland, pituitary gland, adrenal glands, and so on (table 56.1)—as well as organs that secrete hormones in addition to other functions. Endocrine glands lack ducts and thus must secrete into surrounding blood capillaries, unlike exocrine glands, which secrete their products into a duct.

Hormones secreted by endocrine glands belong to four different chemical categories:

1. **Polypeptides.** These hormones are composed of chains of amino acids that are shorter than about 100 amino acids. Some important examples include insulin and antidiuretic hormone (ADH).
2. **Glycoproteins.** These are composed of a polypeptide significantly longer than 100 amino acids to which is attached a carbohydrate. Examples include follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
3. **Amines.** Derived from the amino acids tyrosine and tryptophan, they include hormones secreted by the adrenal medulla, thyroid, and pineal glands.
4. **Steroids.** These hormones are lipids derived from cholesterol, and include the hormones testosterone, estradiol, progesterone, and cortisol.

Steroid hormones can be subdivided into **sex steroids**, secreted by the testes, ovaries, placenta, and adrenal cortex, and **corticosteroids**, secreted only by the adrenal cortex (the outer portion of the adrenal gland). The corticosteroids include cortisol, which regulates glucose balance, and aldosterone, which regulates salt balance.

The amine hormones secreted by the adrenal medulla (the inner portion of the adrenal gland), known as **catecholamines**, include epinephrine (adrenaline) and norepinephrine (noradrenaline). These are derived from the amino acid tyrosine. Another hormone derived from tyrosine is thyroxine, secreted by the thyroid gland. The pineal gland secretes a different amine hormone, melatonin, derived from tryptophan.

All hormones may be categorized as lipophilic (fat-soluble) or hydrophilic (water-soluble). The **lipophilic hormones** include the steroid hormones and thyroxine; all other hormones are water-soluble. This distinction is important in understanding how these hormones regulate their target cells.

Neural and Endocrine Interactions

The endocrine system is an extremely important regulatory system in its own right, but it also interacts and cooperates with the nervous system to regulate the activities of the other organ systems of the body. The secretory activity of many endocrine glands is controlled by the nervous system. Among such glands are the adrenal medulla, posterior pitu-

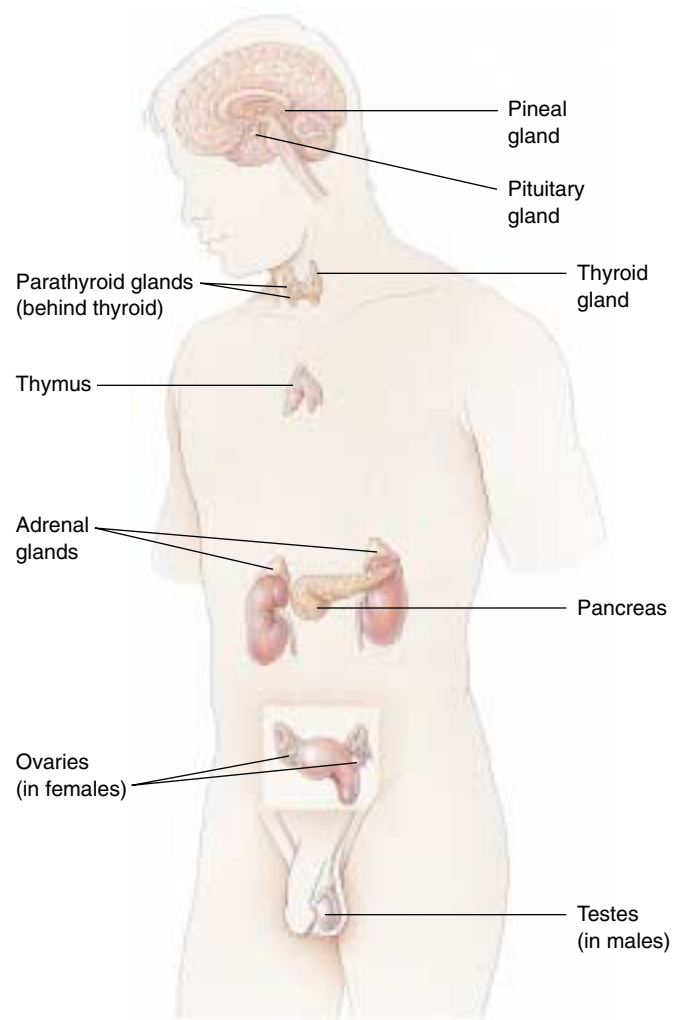


FIGURE 56.3

The human endocrine system. The major endocrine glands are shown, but many other organs secrete hormones in addition to their primary functions.

itary, and pineal gland. These three glands are derived from the neural ectoderm (to be discussed in chapter 60), the same embryonic tissue layer that forms the nervous system. The major site for neural regulation of the endocrine system, however, is the brain's regulation of the anterior pituitary gland. As we'll see, the hypothalamus controls the hormonal secretions of the anterior pituitary, which in turn regulates other endocrine glands. On the other hand, the secretion of a number of hormones is largely independent of neural control. The release of insulin by the pancreas and aldosterone by the adrenal cortex, for example, are stimulated primarily by increases in the blood concentrations of glucose and potassium (K^+), respectively.

Any organ that secretes a hormone from a ductless gland is part of the endocrine system. Hormones may be any of a variety of different chemicals.

Table 56.1 Principal Endocrine Glands and Their Hormones*

Endocrine Gland and Hormone	Target Tissue	Principal Actions	Chemical Nature
POSTERIOR LOBE OF PITUITARY			
Antidiuretic hormone (ADH)	Kidneys	Stimulates reabsorption of water; conserves water	Peptide (9 amino acids)
Oxytocin	Uterus Mammary glands	Stimulates contraction Stimulates milk ejection	Peptide (9 amino acids)
ANTERIOR LOBE OF PITUITARY			
Growth hormone (GH)	Many organs	Stimulates growth by promoting protein synthesis and fat breakdown	Protein
Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates secretion of adrenal cortical hormones such as cortisol	Peptide (39 amino acids)
Thyroid-stimulating hormone (TSH)	Thyroid gland	Stimulates thyroxine secretion	Glycoprotein
Luteinizing hormone (LH)	Gonads	Stimulates ovulation and corpus luteum formation in females; stimulates secretion of testosterone in males	Glycoprotein
Follicle-stimulating hormone (FSH)	Gonads	Stimulates spermatogenesis in males; stimulates development of ovarian follicles in females	Glycoprotein
Prolactin (PRL)	Mammary glands	Stimulates milk production	Protein
Melanocyte-stimulating hormone (MSH)	Skin	Stimulates color change in reptiles and amphibians; unknown function in mammals	Peptide (two forms; 13 and 22 amino acids)
THYROID GLAND			
Thyroxine (thyroid hormone)	Most cells	Stimulates metabolic rate; essential to normal growth and development	Iodinated amino acid
Calcitonin	Bone	Lowers blood calcium level by inhibiting loss of calcium from bone	Peptide (32 amino acids)
PARATHYROID GLANDS			
Parathyroid hormone	Bone, kidneys, digestive tract	Raises blood calcium level by stimulating bone breakdown; stimulates calcium reabsorption in kidneys; activates vitamin D	Peptide (34 amino acids)

*These are hormones released from endocrine glands. As discussed previously, many hormones are released from other body organs.

Paracrine Regulation

Paracrine regulation occurs in many organs and among the cells of the immune system. Some of these regulatory molecules are known as **cytokines**, particularly if they regulate different cells of the immune system. Other paracrine regulators are called **growth factors**, because they promote growth and cell division in specific organs. Examples include *platelet-derived growth factor*, *epidermal growth factor*, and the *insulin-like growth factors* that stimulate cell division and proliferation of their target cells. *Nerve growth factor* is a regulatory molecule that belongs to a family of paracrine regulators of the nervous system called **neurotrophins**.

Nitric oxide, which can function as a neurotransmitter (see chapter 54), is also produced by the endothelium of blood vessels. In this context, it is a paracrine regulator because it diffuses to the smooth muscle layer of the blood vessel and promotes vasodilation. The endothelium of blood vessels also

produces other paracrine regulators, including *endothelin*, which stimulates vasoconstriction, and *bradykinin*, which promotes vasodilation. This paracrine regulation supplements the regulation of blood vessels by autonomic nerves.

The most diverse group of paracrine regulators are the **prostaglandins**. A prostaglandin is a 20-carbon-long fatty acid that contains a five-member carbon ring. This molecule is derived from the precursor molecule *arachidonic acid*, released from phospholipids in the cell membrane under hormonal or other stimulation. Prostaglandins are produced in almost every organ and participate in a variety of regulatory functions, including:

- 1. Immune system.** Prostaglandins promote many aspects of inflammation, including pain and fever. Drugs that inhibit prostaglandin synthesis help to alleviate these symptoms.
- 2. Reproductive system.** Prostaglandins may play a

Table 56.1 Principal Endocrine Glands and Their Hormones

Endocrine Gland and Hormone	Target Tissue	Principal Actions	Chemical Nature
ADRENAL MEDULLA			
Epinephrine (adrenaline) and norepinephrine (noradrenaline)	Smooth muscle, cardiac muscle, blood vessels	Initiate stress responses; raise heart rate, blood pressure, metabolic rate; dilate blood vessels; mobilize fat; raise blood glucose level	Amino acid derivatives
ADRENAL CORTEX			
Aldosterone	Kidney tubules	Maintains proper balance of Na ⁺ and K ⁺ ions	Steroid
Cortisol	Many organs	Adaptation to long-term stress; raises blood glucose level; mobilizes fat	Steroid
PANCREAS			
Insulin	Liver, skeletal muscles, adipose tissue	Lowers blood glucose level; stimulates storage of glycogen in liver	Peptide (51 amino acids)
Glucagon	Liver, adipose tissue	Raises blood glucose level; stimulates breakdown of glycogen in liver	Peptide (29 amino acids)
OVARY			
Estradiol	General	Stimulates development of secondary sex characteristics in females	Steroid
Progesterone	Female reproductive structures	Stimulates growth of sex organs at puberty and monthly preparation of uterus for pregnancy	Steroid
	Uterus	Completes preparation for pregnancy	
	Mammary glands	Stimulates development	
TESTIS			
Testosterone	Many organs	Stimulates development of secondary sex characteristics in males and growth spurt at puberty	Steroid
	Male reproductive structures	Stimulates development of sex organs; stimulates spermatogenesis	
PINEAL GLAND			
Melatonin	Gonads, pigment cells	Function not well understood; influences pigmentation in some vertebrates; may control biorhythms in some animals; may influence onset of puberty in humans	Amino acid derivative

role in ovulation. Excessive prostaglandin production may be involved in premature labor, endometriosis, or dysmenorrhea (painful menstrual cramps).

- 3. Digestive system.** Prostaglandins produced by the stomach and intestines may inhibit gastric secretions and influence intestinal motility and fluid absorption.
- 4. Respiratory system.** Some prostaglandins cause constriction, whereas others cause dilation of blood vessels in the lungs and of bronchiolar smooth muscle.
- 5. Circulatory system.** Prostaglandins are needed for proper function of blood platelets in the process of blood clotting.
- 6. Urinary system.** Prostaglandins produced in the renal medulla cause vasodilation, resulting in increased renal blood flow and increased excretion of urine.

The synthesis of prostaglandins are inhibited by aspirin. Aspirin is the most widely used of the **nonsteroidal anti-**

inflammatory drugs (NSAIDs), a class of drugs that also includes indomethacin and ibuprofen. These drugs produce their effects because they specifically inhibit the enzyme cyclooxygenase-2 (cox-2), needed to produce prostaglandins from arachidonic acid. Through this action, the NSAIDs inhibit inflammation and associated pain. Unfortunately, NSAIDs also inhibit another similar enzyme, cox-1, which helps maintain the wall of the digestive tract, and in so doing can produce severe unwanted side effects, including gastric bleeding and prolonged clotting time. A new kind of pain reliever, celecoxib (Celebrex), inhibits cox-2 but not cox-1, a potentially great benefit to arthritis sufferers and others who must use pain relievers regularly.

The neural and endocrine control systems are supplemented by paracrine regulators, including the prostaglandins, which perform many diverse functions.

56.2 Lipophilic and polar hormones regulate their target cells by different means.

Hormones That Enter Cells

As we mentioned previously, hormones can be divided into those that are lipophilic (lipid-soluble) and those that are hydrophilic (water-soluble). The lipophilic hormones—all of the steroid hormones (figure 56.4) and thyroxine—as well as other lipophilic regulatory molecules (including the retinoids, or vitamin A) can easily enter cells. This is because the lipid portion of the cell membrane does not present a barrier to the entry of lipophilic regulators. Therefore, all lipophilic regulatory molecules have a similar mechanism of action. Water-soluble hormones, in contrast, cannot pass through cell membranes. They must regulate their target cells through different mechanisms.

Steroid hormones are lipids themselves and thus lipophilic; thyroxine is lipophilic because it is derived from a nonpolar amino acid. Because these hormones are not water-soluble, they don't dissolve in plasma but rather travel in the blood attached to protein carriers. When the hormones arrive at their target cells, they dissociate from their carriers and pass through the plasma membrane of

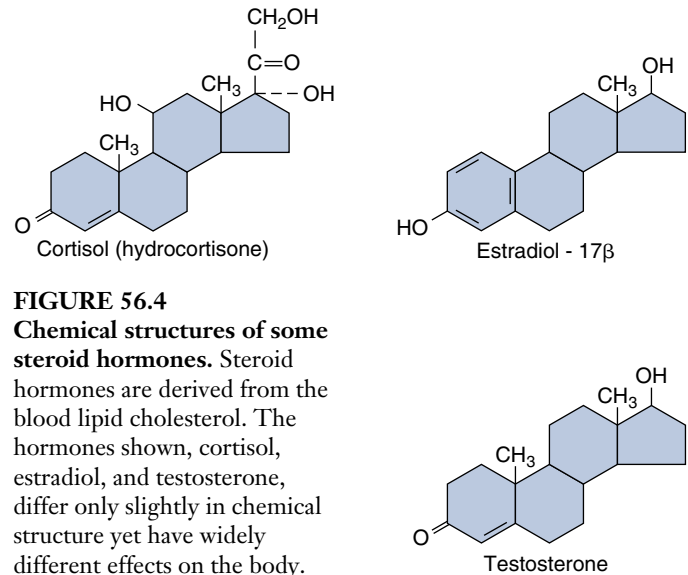


FIGURE 56.4
Chemical structures of some steroid hormones. Steroid hormones are derived from the blood lipid cholesterol. The hormones shown, cortisol, estradiol, and testosterone, differ only slightly in chemical structure yet have widely different effects on the body. Steroid hormones are secreted by the adrenal cortex, testes, ovaries, and placenta.

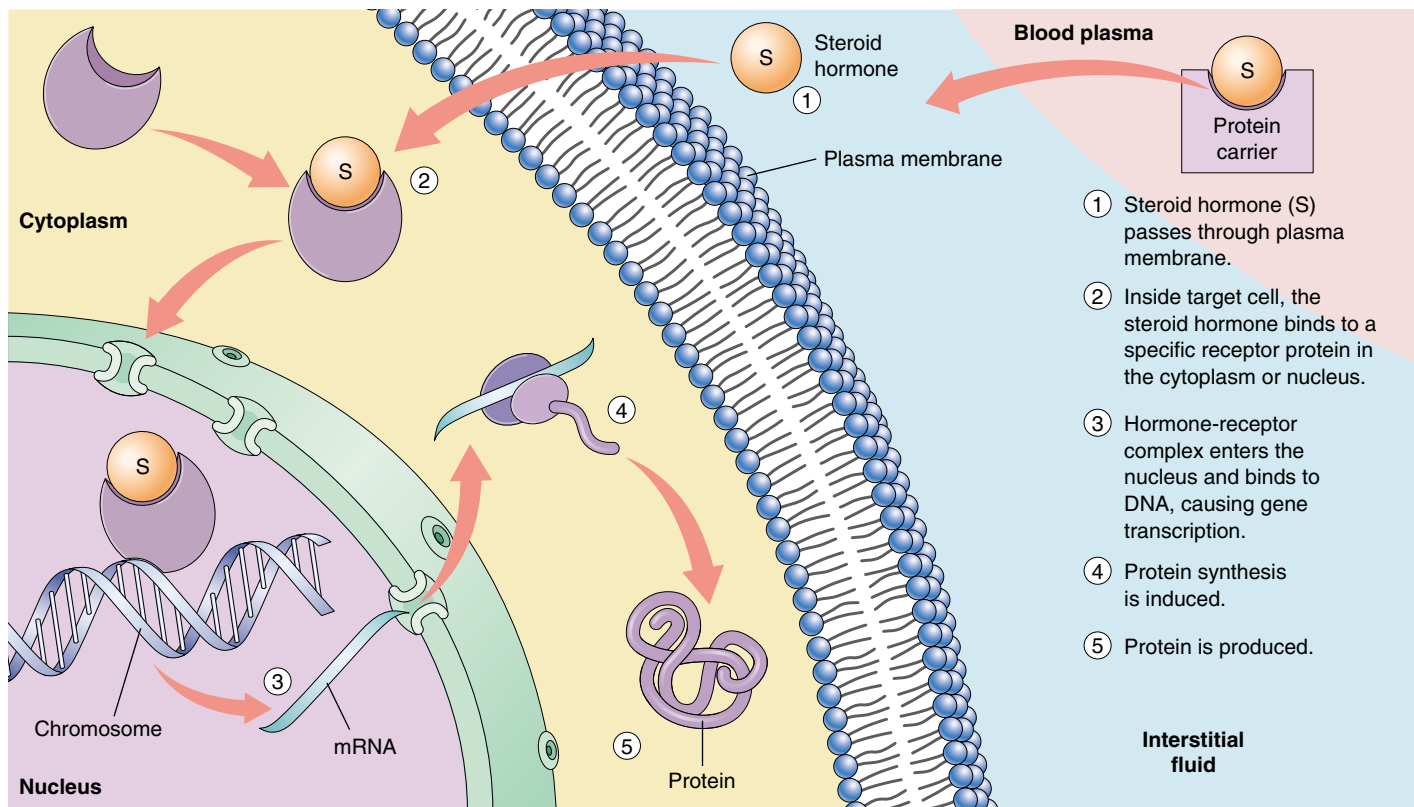


FIGURE 56.5
The mechanism of steroid hormone action. Steroid hormones are lipid-soluble and thus readily diffuse through the plasma membrane of cells. They bind to receptor proteins in either the cytoplasm or nucleus (not shown). If the steroid binds to a receptor in the cytoplasm, the hormone-receptor complex moves into the nucleus. The hormone-receptor complex then binds to specific regions of the DNA, stimulating the production of messenger RNA (mRNA).

the cell (figure 56.5). Some steroid hormones then bind to very specific receptor proteins in the cytoplasm, and then move as a hormone-receptor complex into the nucleus. Other steroids travel directly into the nucleus before encountering their receptor proteins. Whether the steroid finds its receptor in the nucleus or translocates with its receptor to the nucleus from the cytoplasm, the rest of the story is the same.

The hormone receptor, activated by binding to the lipophilic hormone, is now also able to bind to specific regions of the DNA. These DNA regions are known as the hormone response elements. The binding of the hormone-receptor complex has a direct effect on the level of transcription at that site by activating genetic transcription. This produces messenger RNA (mRNA), which then codes for the production of specific proteins. These proteins often have enzymatic activity that changes the metabolism of the target cell in a specific fashion.

The thyroid hormone's mechanism of action resembles that of the steroid hormones. Thyroxine contains four iodines and so is often abbreviated T_4 (for *tetraiodothyronine*). The thyroid gland also secretes smaller amounts of a similar molecule that has only three iodines, called *triiodothyronine* (and abbreviated T_3). Both hormones enter target cells, but all of the T_4 that enters is changed into T_3 (figure 56.6). Thus, only the T_3 form of the hormone enters the nucleus and binds to nuclear receptor proteins. The hormone-receptor complex, in turn, binds to the appropriate hormone response elements on DNA.

The lipophilic hormones pass through the target cell's plasma membrane and bind to intracellular receptor proteins. The hormone-receptor complex then binds to specific regions of DNA, thereby activating genes and regulating the target cells.

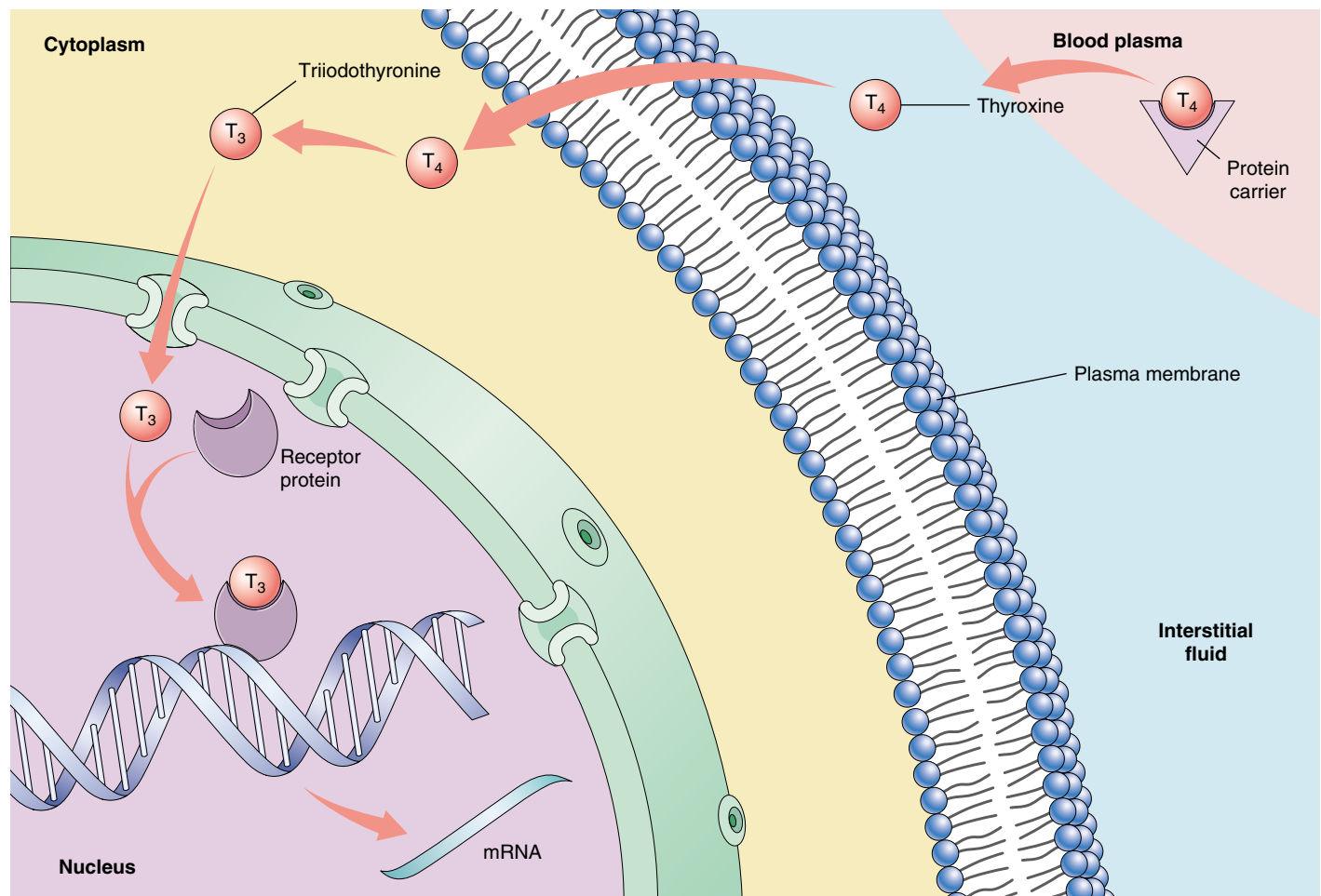


FIGURE 56.6

The mechanism of thyroxine action. Thyroxine contains four iodines. When it enters the target cell, thyroxine is changed into triiodothyronine, with three iodines. This hormone moves into the nucleus and binds to nuclear receptors. The hormone-receptor complex then binds to regions of the DNA and stimulates gene transcription.

Hormones That Do Not Enter Cells

Hormones that are too large or too polar to cross the plasma membranes of their target cells include all of the peptide and glycoprotein hormones, as well as the catecholamine hormones epinephrine and norepinephrine. These hormones bind to receptor proteins located on the outer surface of the plasma membrane—the hormones do *not* enter the cell. If you think of the hormone as a messenger sent from an endocrine gland to the target cell, it is evident that a second messenger is needed within the target cell to produce the effects of the hormone. A number of different molecules in the cell can serve as second messengers, as we saw in chapter 7. The interaction between the hormone and its receptor activates mechanisms in the plasma membrane that increase the concentration of the second messengers within the target cell cytoplasm.

The binding of a water-soluble hormone to its receptor is reversible and usually very brief. After the hormone binds to its receptor and activates a second-messenger system, it dissociates from the receptor and may travel in the blood to another target cell somewhere else in the body. Eventually, enzymes (primarily in the liver) degrade the hormone by converting it into inactive derivatives.

The Cyclic AMP Second-Messenger System

The action of the hormone epinephrine can serve as an example of a second-messenger system. Epinephrine can bind to two categories of receptors, called *alpha* (α)- and *beta* (β)-*adrenergic receptors*. The interaction of epinephrine with each type of receptor activates a different second-messenger system in the target cell.

In the early 1960s, Earl Sutherland showed that cyclic adenosine monophosphate, or **cyclic AMP (cAMP)**, serves as a second messenger when epinephrine binds to β -adrenergic receptors on the plasma membranes of liver cells (figure 56.7). The cAMP second-messenger system was the first such system to be described.

The β -adrenergic receptors are associated with membrane proteins called *G proteins* (see chapters 7 and 54). Each G protein is composed of three subunits, and the binding of epinephrine to its receptor causes one of the G protein subunits to dissociate from the other two. This subunit then diffuses within the plasma membrane until it encounters **adenylyl cyclase**, a membrane enzyme that is inactive until it binds to the G protein subunit. When activated by the G protein subunit, adenylyl cyclase catalyzes the formation of cAMP from ATP. The cAMP formed at the inner surface of the plasma membrane diffuses within the cytoplasm, where it binds to and activates **protein kinase-A**, an enzyme that adds phosphate groups to specific cellular proteins.

The identities of the proteins that are phosphorylated by protein kinase-A varies from one cell type to the next, and this variation is one of the reasons epinephrine has such di-

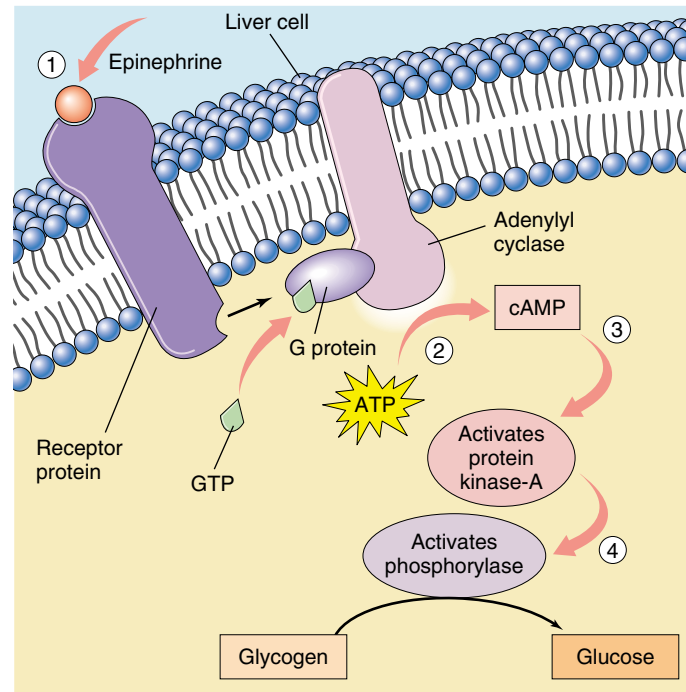


FIGURE 56.7

The action of epinephrine on a liver cell. (1) Epinephrine binds to specific receptor proteins on the cell surface. (2) Acting through intermediary G proteins, the hormone-bound receptor activates the enzyme adenylyl cyclase, which converts ATP into cyclic AMP (cAMP). (3) Cyclic AMP performs as a second messenger and activates protein kinase-A, an enzyme that was previously present in an inactive form. (4) Protein kinase-A phosphorylates and thereby activates the enzyme phosphorylase, which catalyzes the hydrolysis of glycogen into glucose.

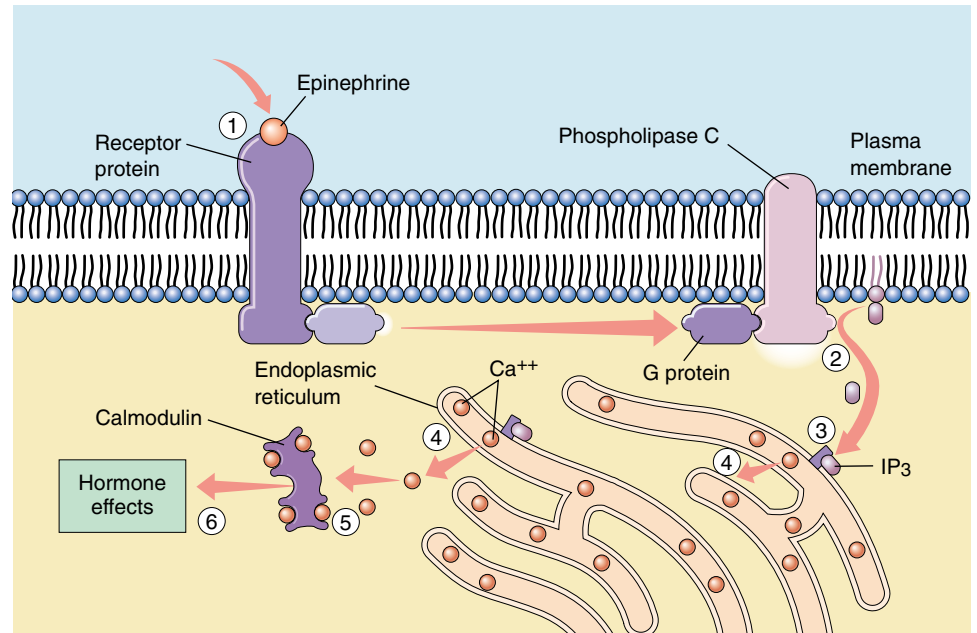
verse effects on different tissues. In liver cells, protein kinase-A phosphorylates and thereby activates another enzyme, phosphorylase, which converts glycogen into glucose. Through this multistep mechanism, epinephrine causes the liver to secrete glucose into the blood during the fight-or-flight reaction, when the adrenal medulla is stimulated by the sympathetic division of the autonomic nervous system (see chapter 54). In cardiac muscle cells, protein kinase-A phosphorylates a different set of cellular proteins, which cause the heart to beat faster and more forcefully.

The IP_3/Ca^{++} Second-Messenger System

When epinephrine binds to α -adrenergic receptors, it doesn't activate adenylyl cyclase and cause the production of cAMP. Instead, through a different type of G protein, it activates another membrane-bound enzyme, phospholipase C (figure 56.8). This enzyme cleaves certain membrane phospholipids to produce the second messenger, inositol

FIGURE 56.8

The IP_3/Ca^{++} second-messenger system. (1) The hormone epinephrine binds to specific receptor proteins on the cell surface. (2) Acting through G proteins, the hormone-bound receptor activates the enzyme phospholipase C, which converts membrane phospholipids into inositol trisphosphate (IP_3). (3) IP_3 diffuses through the cytoplasm and binds to receptors on the endoplasmic reticulum. (4) The binding of IP_3 to its receptors stimulates the endoplasmic reticulum to release Ca^{++} into the cytoplasm. (5) Some of the released Ca^{++} binds to a regulatory protein called calmodulin. (6) The $Ca^{++}/calmodulin$ complex activates other intracellular proteins, ultimately producing the effects of the hormone.



trisphosphate (IP_3). IP_3 diffuses into the cytoplasm from the plasma membrane and binds to receptors located on the surface of the endoplasmic reticulum.

Recall from chapter 5 that the endoplasmic reticulum is a system of membranous sacs and tubes that serves a variety of functions in different cells. One of its functions is to accumulate Ca^{++} by actively transporting Ca^{++} out of the cytoplasm. Other pumps transport Ca^{++} from the cytoplasm through the plasma membrane to the extracellular fluid. These two mechanisms keep the concentration of Ca^{++} in the cytoplasm very low. Consequently, there is an extremely steep concentration gradient for Ca^{++} between the cytoplasm and the inside of the endoplasmic reticulum, and between the cytoplasm and the extracellular fluid.

When IP_3 binds to its receptors on the endoplasmic reticulum, it stimulates the endoplasmic reticulum to release its stored Ca^{++} . Calcium channels in the plasma membrane may also open, allowing Ca^{++} to diffuse into the cell from the extracellular fluid. Some of the Ca^{++} that has suddenly entered the cytoplasm then binds to a protein called calmodulin, which has regulatory functions analogous to those of cyclic AMP. One of the actions of calmodulin is to activate another type of protein kinase, resulting in the phosphorylation of a different set of cellular proteins.

What is the advantage of having multiple second-messenger systems? Consider the antagonistic actions of epinephrine and insulin on liver cells. Epinephrine uses cAMP as a second messenger to promote the hydrolysis of glycogen to glucose, while insulin stimulates the synthesis of glycogen from glucose. Clearly, insulin cannot use cAMP as a second messenger. Although the exact mechanism of in-

ulin's action is still not well understood, insulin may act in part through the IP_3/Ca^{++} second-messenger system.

Not all large polar hormones act by increasing the concentration of a second messenger in the cytoplasm of the target cell. Others cause a change in the shape of a membrane protein called an ion channel (see chapters 6 and 54). If these channels are normally "closed," then a change in shape will open them allowing a particular ion to enter or leave the cell depending on its concentration gradient. If an ion channel is normally open, a chemical messenger can cause it to close. For example, some hormones open Ca^{++} channels on smooth muscle cell membranes; other hormones close them. This will increase or decrease, respectively, the amount of muscle contraction.

The molecular mechanism for changing the shape of an ion channel is similar to that for activating a second messenger. The hormone first binds to a receptor protein on the outer surface of the target cell. This receptor protein may then use a G protein to signal the ion channel to change shape.

Although G proteins play a major role in many hormone functions they don't seem to be necessary for all identified actions of hormones on target cells. In the cases where G proteins are not involved, the receptor protein is connected directly to the enzyme or ion channel.

The water-soluble hormones cannot pass through the plasma membrane; they must rely on second messengers within the target cells to mediate their actions. Such second messengers include cyclic AMP (cAMP), inositol trisphosphate (IP_3), and Ca^{++} . In many cases, the second messengers activate previously inactive enzymes.

56.3 The hypothalamus controls the secretions of the pituitary gland.

The Posterior Pituitary Gland

The **pituitary gland** hangs by a stalk from the hypothalamus of the brain (figure 56.9) posterior to the optic chiasm (see chapter 54). A microscopic view reveals that the gland consists of two parts. The anterior portion appears glandular and is called the **anterior pituitary**; the posterior portion appears fibrous and is the **posterior pituitary**. These two portions of the pituitary gland have different embryonic origins, secrete different hormones, and are regulated by different control systems.

The Posterior Pituitary Gland

The posterior pituitary appears fibrous because it contains axons that originate in cell bodies within the hypothalamus and extend along the stalk of the pituitary as a tract of

fibers. This anatomical relationship results from the way that the posterior pituitary is formed in embryonic development. As the floor of the third ventricle of the brain forms the hypothalamus, part of this neural tissue grows downward to produce the posterior pituitary. The hypothalamus and posterior pituitary thus remain interconnected by a tract of axons.

The endocrine role of the posterior pituitary gland first became evident in 1912, when a remarkable medical case was reported: a man who had been shot in the head developed the need to urinate every 30 minutes or so, 24 hours a day. The bullet had lodged in his pituitary gland. Subsequent research demonstrated that removal of this gland produces the same symptoms. Pituitary extracts were found to contain a substance that makes the kidneys conserve water, and in the early 1950s investigators isolated a peptide from the posterior pituitary, **antidiuretic hormone**

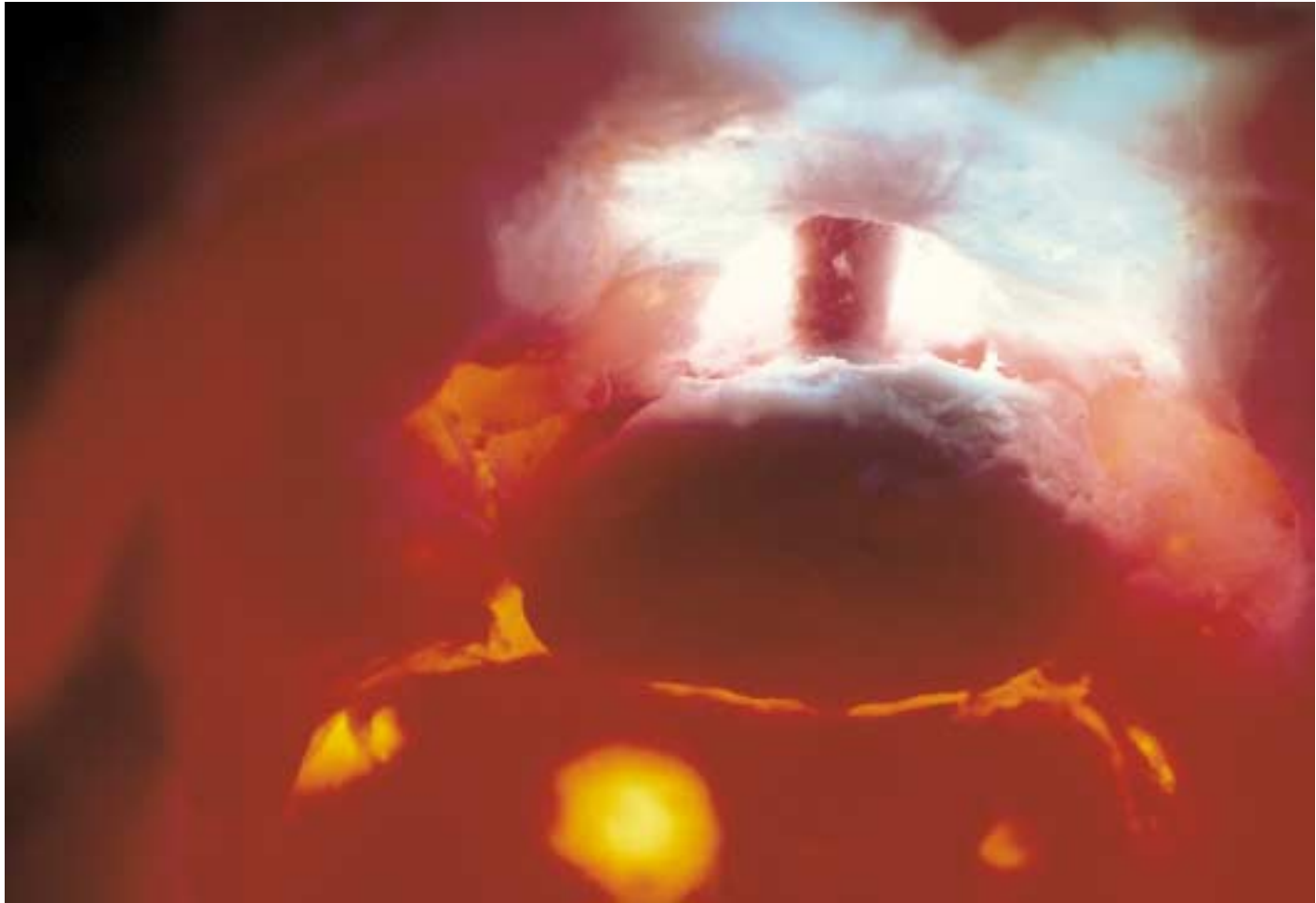
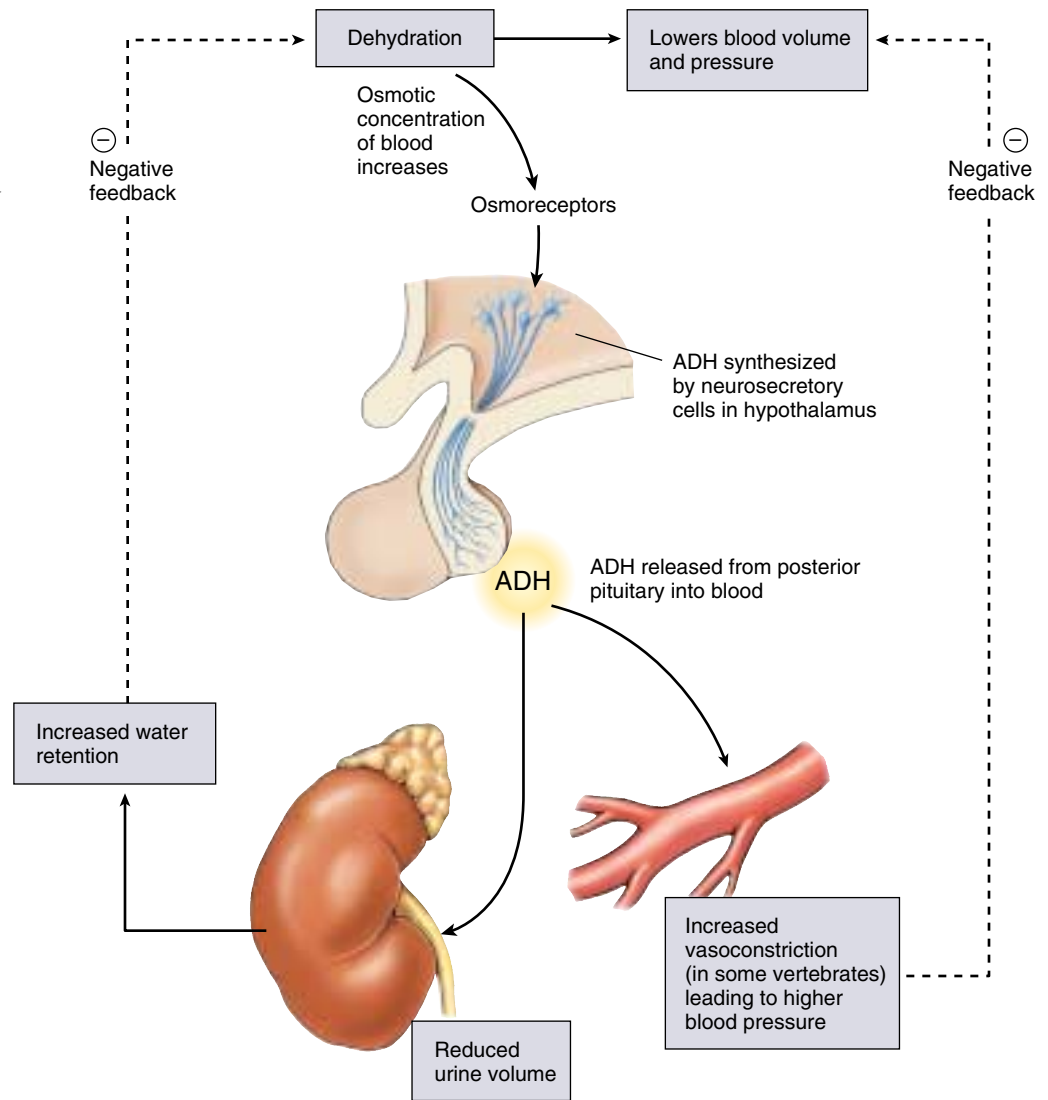


FIGURE 56.9

The pituitary gland hangs by a short stalk from the hypothalamus. The pituitary gland (the oval structure hanging from the stalk), shown here enlarged 15 times, regulates hormone production in many of the body's endocrine glands.

FIGURE 56.10

The effects of antidiuretic hormone (ADH). An increase in the osmotic concentration of the blood stimulates the posterior pituitary gland to secrete ADH, which promotes water retention by the kidneys. This works as a negative feedback loop to correct the initial disturbance of homeostasis.



(ADH, also known as **vasopressin**), that stimulates water retention by the kidneys (figure 56.10). When ADH is missing, the kidneys do not retain water and excessive quantities of urine are produced. This is why the consumption of alcohol, which inhibits ADH secretion, leads to frequent urination.

The posterior pituitary also secretes **oxytocin**, a second peptide hormone which, like ADH, is composed of nine amino acids. Oxytocin stimulates the milk-ejection reflex, so that contraction of the smooth muscles around the mammary glands and ducts causes milk to be ejected from the ducts through the nipple. During suckling, sensory receptors in the nipples send impulses to the hypothalamus, which triggers the release of oxytocin. Oxytocin is also needed to stimulate uterine contractions in women during childbirth. Oxytocin secretion continues after childbirth in a woman who is breast-feeding, which is why the uterus of a nursing mother returns to its normal size after pregnancy more quickly than does the uterus of a mother who does not breast-feed.

ADH and oxytocin are actually *produced* by neuron cell bodies located in the hypothalamus. These two hormones are transported along the axon tract that runs from the hypothalamus to the posterior pituitary and are stored in the posterior pituitary. In response to the appropriate stimulation—increased blood plasma osmolarity in the case of ADH, the suckling of a baby in the case of oxytocin—the hormones are released by the posterior pituitary into the blood. Because this reflex control involves both the nervous and endocrine systems, the secretion of ADH and oxytocin are **neuroendocrine reflexes**.

The posterior pituitary gland contains axons originating from neurons in the hypothalamus. These neurons produce ADH and oxytocin, which are stored in and released from the posterior pituitary gland in response to neural stimulation from the hypothalamus.

The Anterior Pituitary Gland

The anterior pituitary, unlike the posterior pituitary, does not develop from a downgrowth of the brain; instead, it develops from a pouch of epithelial tissue that pinches off from the roof of the embryo's mouth. Because it is epithelial tissue, the anterior pituitary is a complete gland—it produces the hormones it secretes. Many, but not all, of these hormones stimulate growth in their target organs, including other endocrine glands. Therefore, the hormones of the anterior pituitary gland are collectively termed *tropic hormones* (Greek *trophe*, “nourishment”), or *tropins*. When the target organ of a tropic hormone is another endocrine gland, that gland is stimulated by the tropic hormone to secrete its own hormones.

The hormones produced and secreted by different cell types in the anterior pituitary gland (figure 56.11) include the following:

1. **Growth hormone (GH, or *somatotropin*)** stimulates the growth of muscle, bone (indirectly), and other tissues and is also essential for proper metabolic regulation.
2. **Adrenocorticotrophic hormone (ACTH, or *corticotropin*)** stimulates the adrenal cortex to produce corticosteroid hormones, including cortisol (in humans) and corticosterone (in many other vertebrates), which regulate glucose homeostasis.
3. **Thyroid-stimulating hormone (TSH, or *thyrotropin*)** stimulates the thyroid gland to produce thyroxine, which in turn stimulates oxidative respiration.
4. **Luteinizing hormone (LH)** is needed for ovulation and the formation of a corpus luteum in the female menstrual cycle (see chapter 59). It also stimulates the testes to produce testosterone, which is needed for sperm production and for the development of male secondary sexual characteristics.

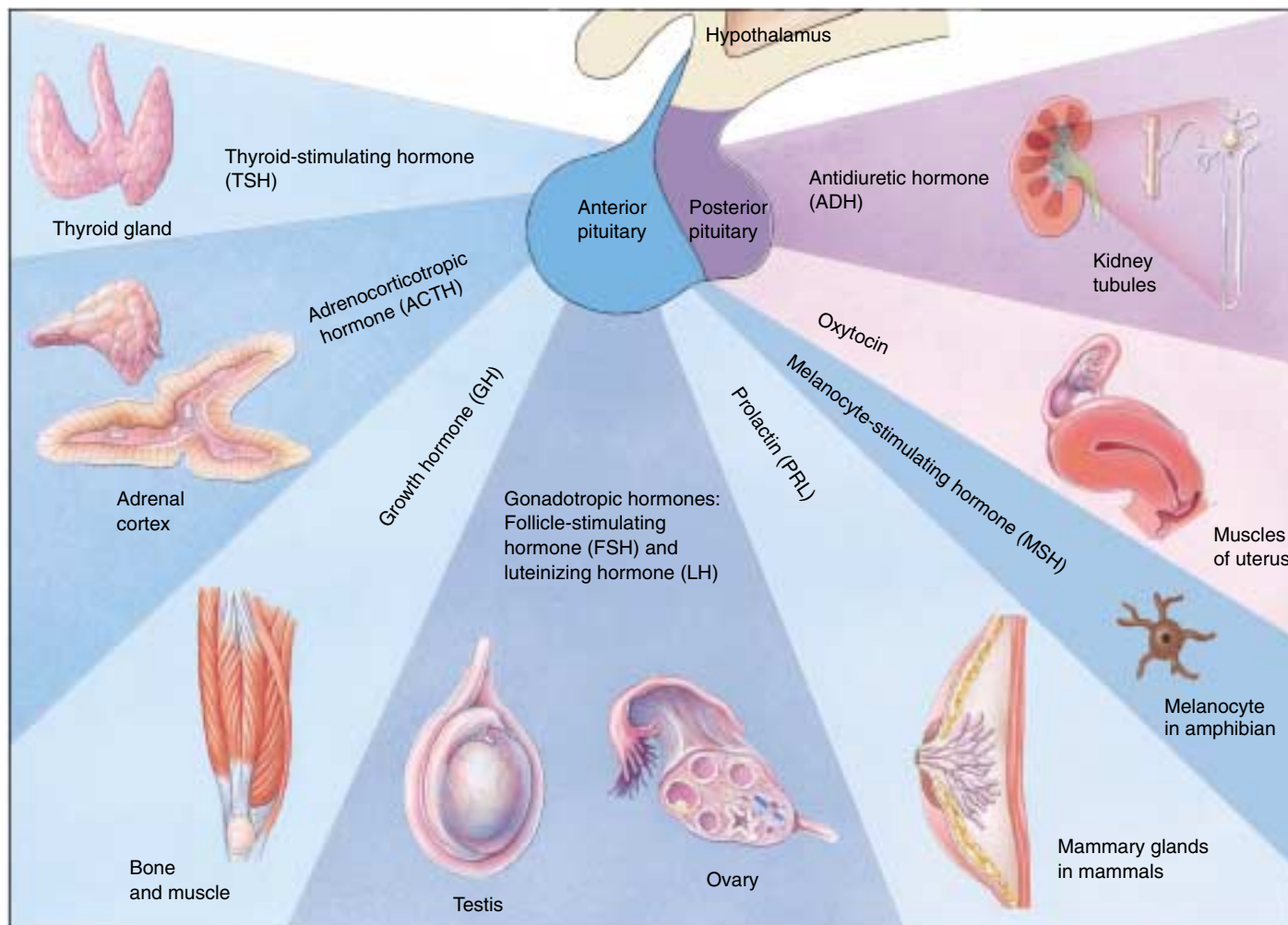


FIGURE 56.11
The major hormones of the anterior and posterior pituitary glands. Only a few of the actions of these hormones are shown.

5. **Follicle-stimulating hormone (FSH)** is required for the development of ovarian follicles in females. In males, it is required for the development of sperm. FSH and LH are both referred to as *gonadotropins*.
6. **Prolactin (PRL)** stimulates the mammary glands to produce milk in mammals. It also helps regulate kidney function in vertebrates, the production of “crop milk” (nutritional fluid fed to chicks by regurgitation) in some birds, and acts on the gills of fish that travel from salt to fresh water to promote sodium retention.
7. **Melanocyte-stimulating hormone (MSH)** stimulates the synthesis and dispersion of melanin pigment, which darken the epidermis of some fish, amphibians, and reptiles. MSH has no known specific function in mammals, but abnormally high amounts of ACTH can cause skin darkening because it contains the amino acid sequence of MSH within its structure.

Growth Hormone

The importance of the anterior pituitary gland first became understood in 1909, when a 38-year-old South Dakota farmer was cured of the growth disorder *acromegaly* by the surgical removal of a pituitary tumor. Acromegaly is a form of gigantism in which the jaw begins to protrude and other facial features thicken. It was discovered that gigantism is almost always associated with pituitary tumors. Robert Wadlow, born in 1928 in Alton, Illinois, stood 8 feet, 11 inches tall and weighed 485 pounds before he died from infection at age 22 (figure 56.12). He was the tallest human being ever recorded, and he was still growing the year he died.

We now know that gigantism is caused by the excessive secretion of growth hormone (GH) by the anterior pituitary gland in a growing child. GH stimulates protein synthesis and growth of muscles and connective tissues; it also indirectly promotes the elongation of bones by stimulating cell division in the cartilaginous epiphyseal growth plates of bones. Researchers found that this stimulation does not occur in the absence of blood plasma, suggesting that bone cells lack receptors for GH and that the stimulation by GH was indirect. We now know that GH stimulates the production of **insulin-like growth factors**, which are produced by the liver and secreted into the blood in response to stimulation by GH. The insulin-like growth factors then stimulate growth of the epiphyseal growth plates and thus elongation of the bones.

When a person’s skeletal growth plates have converted from cartilage into bone, however, GH can no longer cause an increase in height. Therefore, excessive GH secretion in an adult produces bone and soft tissue deformities in the condition called acromegaly. A deficiency in GH secretion during childhood results in pituitary dwarfism, a failure to achieve normal growth.



FIGURE 56.12

The Alton giant. This photograph of Robert Wadlow of Alton, Illinois, taken on his 21st birthday, shows him at home with his father and mother and four siblings. Born normal size, he developed a growth hormone–secreting pituitary tumor as a young child and never stopped growing during his 22 years of life.

Other Anterior Pituitary Hormones

Prolactin is like growth hormone in that it acts on organs that are not endocrine glands. In addition to its stimulation of milk production in mammals and “crop milk” production in birds, prolactin has varied effects on electrolyte balance by acting on the kidneys, the gills of fish, and the salt glands of marine birds (discussed in chapter 58). Unlike growth hormone and prolactin, the other anterior pituitary hormones act on specific glands.

Some of the anterior pituitary hormones that act on specific glands have common names, such as thyroid-stimulating hormone (TSH), and alternative names that emphasize the tropic nature of the hormone, such as thyrotropin. TSH stimulates only the thyroid gland, and adrenocorticotropic hormone (ACTH) stimulates only the adrenal cortex (outer portion of the adrenal glands). Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) act only on the gonads (testes and ovaries); hence, they are collectively called *gonadotropic hormones*. Although both FSH and LH act on the gonads, they each act on different target cells in the gonads of both females and males.

Hypothalamic Control of Anterior Pituitary Gland Secretion

The anterior pituitary gland, unlike the posterior pituitary, is not derived from the brain and does not receive an axon tract from the hypothalamus. Nevertheless, the hypothalamus controls production and secretion of the anterior pituitary hormones. This control is exerted hormonally rather than by means of nerve axons. Neurons in the hypothalamus secrete releasing hormones and inhibiting hormones into blood capillaries at the base of the hypothalamus (figure 56.13). These capillaries drain into small veins that run within the stalk of the pituitary to a second bed of capillaries in the anterior pituitary. This unusual system of vessels is known as the hypothalamohypophyseal portal system (another name for the pituitary is the hypophysis). It is called a portal system because it has a second capillary bed downstream from the first; the only other body location with a similar system is the liver, where capillaries receive blood drained from the gastrointestinal tract (via the hepatic portal vein—see chapter 52). Because the second bed of capillaries receives little oxygen from such vessels, the vessels must be delivering something else of importance.

Each releasing hormone delivered by the hypothalamohypophyseal system regulates the secretion of a specific anterior pituitary hormone. For example, *thyrotropin-releasing hormone (TRH)* stimulates the release of TSH, *corticotropin-releasing hormone (CRH)* stimulates the release of ACTH, and *gonadotropin-releasing hormone (GnRH)* stimulates the release of FSH and LH. A releasing hormone for growth hormone, called *growth hormone-releasing hormone (GHRH)* has also been discovered, and a releasing hormone for prolactin has been postulated but has thus far not been identified.

The hypothalamus also secretes hormones that *inhibit* the release of certain anterior pituitary hormones. To date, three such hormones have been discovered: *somatostatin* inhibits the secretion of GH; *prolactin-inhibiting factor (PIF)*, found to be the neurotransmitter dopamine, inhibits the secretion of prolactin; and *melanotropin-inhibiting hormone (MIH)* inhibits the secretion of MSH.

Negative Feedback Control of Anterior Pituitary Gland Secretion

Because hypothalamic hormones control the secretions of the anterior pituitary gland, and the anterior pituitary hormones control the secretions of some other endocrine glands, it may seem that the hypothalamus is in charge of hormonal secretion for the whole body. This idea is not valid, however, for two reasons. First, a number of endocrine organs, such as the adrenal medulla and the pancreas, are not directly regulated by this control system. Second, the hypothalamus and the anterior pituitary gland are themselves partially controlled by the very hormones whose secretion they stimulate! In most cases this is an in-

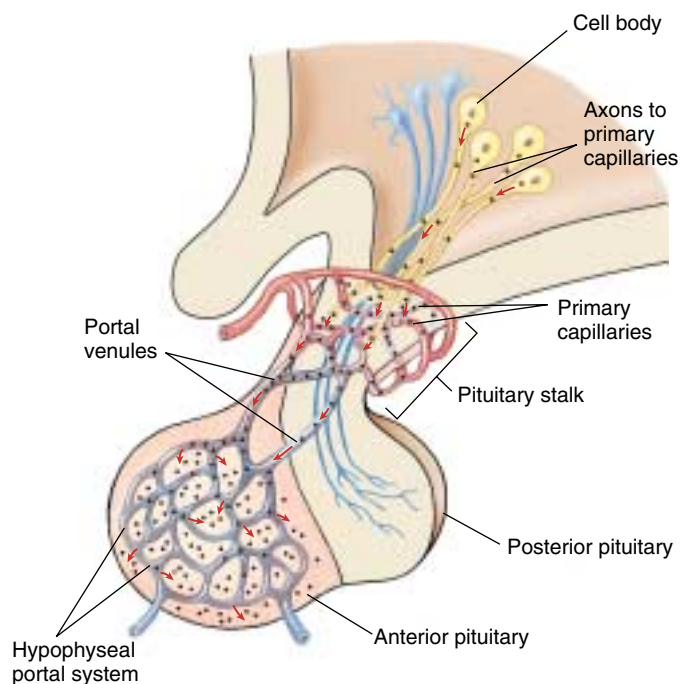


FIGURE 56.13
Hormonal control of the anterior pituitary gland by the hypothalamus. Neurons in the hypothalamus secrete hormones that are carried by short blood vessels directly to the anterior pituitary gland, where they either stimulate or inhibit the secretion of anterior pituitary hormones.

hibitory control, where the target gland hormones inhibit the secretions of the hypothalamus and anterior pituitary (figure 56.14). This type of control system is called negative feedback inhibition and acts to maintain relatively constant levels of the target cell hormone.

Let's consider the hormonal control of the thyroid gland. The hypothalamus secretes TRH into the hypothalamohypophyseal portal system, which stimulates the anterior pituitary gland to secrete TSH, which in turn stimulates the thyroid gland to release thyroxine. Among thyroxine's many target organs are the hypothalamus and the anterior pituitary gland themselves. Thyroxine acts upon these organs to inhibit their secretion of TRH and TSH, respectively (figure 56.15). This negative feedback inhibition is essential for homeostasis because it keeps the thyroxine levels fairly constant.

To illustrate the importance of negative feedback inhibition, we will examine a person who lacks sufficient iodine in the diet. Without iodine, the thyroid gland cannot produce thyroxine (which contains four iodines per molecule). As a result, thyroxine levels in the blood fall drastically, and the hypothalamus and anterior pituitary receive far less negative feedback inhibition than is normal. This reduced inhibition causes an elevated secretion of TRH and TSH. The high levels of TSH stim-

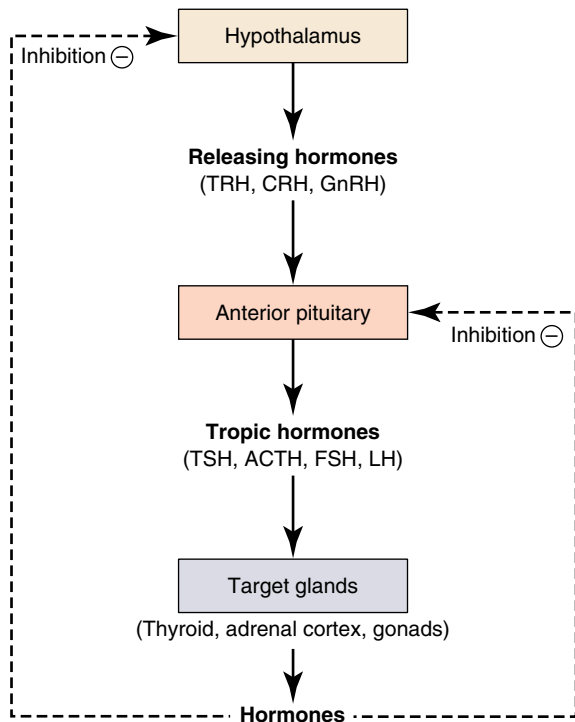


FIGURE 56.14
Negative feedback inhibition. The hormones secreted by some endocrine glands feed back to inhibit the secretion of hypothalamic releasing hormones and anterior pituitary tropic hormones.

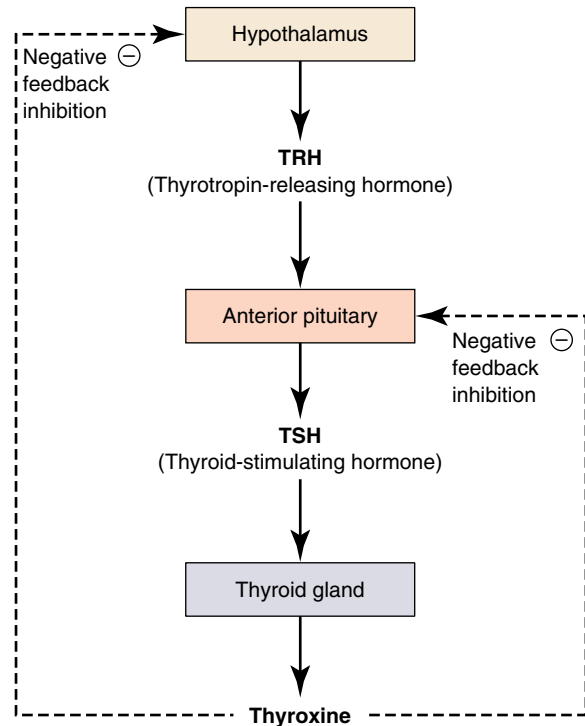


FIGURE 56.15
Regulation of thyroxine secretion. The hypothalamus secretes TRH, which stimulates the anterior pituitary to secrete TSH. The TSH then stimulates the thyroid to secrete thyroxine, which exerts negative feedback control of the hypothalamus and anterior pituitary.

ulate the thyroid gland to grow, but it still cannot produce thyroxine without iodine. The consequence of this interruption of the normal inhibition by thyroxine is an enlarged thyroid gland, a condition known as a goiter (figure 56.16).

Positive feedback in the control of the hypothalamus and anterior pituitary by the target glands is not common because positive feedback cannot maintain constancy of the internal environment (homeostasis). Positive feedback accentuates change, driving the change in the same direction. One example of positive control involves the control of ovulation, an explosive event that culminates in the expulsion of the egg cell from the ovary. In that case, an ovarian hormone, estradiol, actually stimulates the secretion of an anterior pituitary hormone, LH. This will be discussed in detail in chapter 59.

The hypothalamus controls the anterior pituitary gland by means of hormones, and the anterior pituitary gland controls some other glands through the hormones it secretes. However, both the hypothalamus and the anterior pituitary gland are controlled by other glands through negative feedback inhibition.



FIGURE 56.16
A person with a goiter. This condition is caused by a lack of iodine in the diet. As a result, thyroxine secretion is low, so there is less negative feedback inhibition of TSH. The elevated TSH secretion, in turn, stimulates the thyroid to grow and produce the goiter.

56.4 Endocrine glands secrete hormones that regulate many body functions.

The Thyroid and Parathyroid Glands

The endocrine glands that are regulated by the anterior pituitary, and those endocrine glands that are regulated by other means, help to control metabolism, electrolyte balance, and reproductive functions. Some of the major endocrine glands will be considered in this section.

The Thyroid Gland

The thyroid gland (Greek *thyros*, “shield”) is shaped like a shield and lies just below the Adam’s apple in the front of the neck. We have already mentioned that the thyroid gland secretes thyroxine and smaller amounts of triiodothyronine (T_3), which stimulate oxidative respiration in most cells in the body and, in so doing, help set the body’s basal metabolic rate (see chapter 51). In children, these thyroid hormones also promote growth and stimulate maturation of the central nervous system. Children with underactive thyroid glands are therefore stunted in their growth and suffer severe mental retardation, a condition called cretinism. This differs from pituitary dwarfism, which results from inadequate GH and is not associated with abnormal intellectual development.

People who are hypothyroid (whose secretion of thyroxine is too low) can take thyroxine orally, as pills. Only thyroxine and the steroid hormones (as in contraceptive pills), can be taken orally because they are nonpolar and can pass through the plasma membranes of intestinal epithelial cells without being digested.

There is an additional function of the thyroid gland that is unique to amphibians—thyroid hormones are needed for the metamorphosis of the larvae into adults (figure 56.17). If the thyroid gland is removed from a tadpole, it will not change into a frog. Conversely, if an immature tadpole is fed pieces of a thyroid gland, it will undergo premature metamorphosis and become a miniature frog!

The thyroid gland also secretes calcitonin, a peptide hormone that plays a role in maintaining proper levels of calcium (Ca^{++}) in the blood. When the blood Ca^{++} concentration rises too high, calcitonin stimulates the uptake of Ca^{++} into bones, thus lowering its level in the blood. Although calcitonin may be important in the physiology of some vertebrates, its significance in normal human

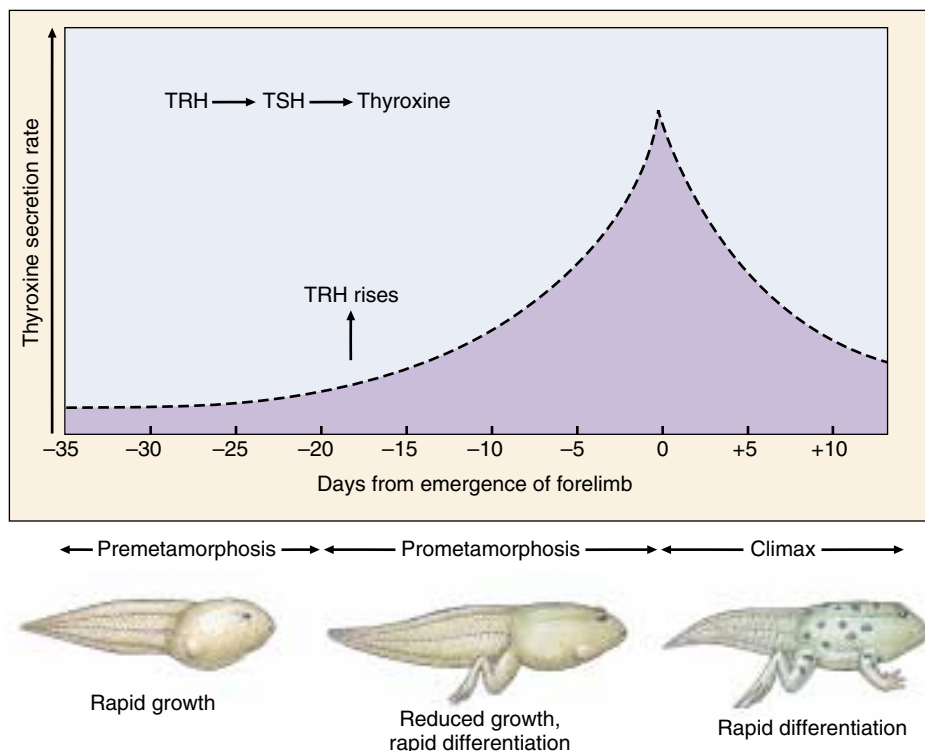


FIGURE 56.17

Thyroxine triggers metamorphosis in amphibians. In tadpoles at the premetamorphic stage, the hypothalamus releases TRH (thyrotropin-releasing hormone), which causes the anterior pituitary to secrete TSH (thyroid-stimulating hormone). TSH then acts on the thyroid gland, which secretes thyroxine. The hindlimbs then begin to form. As metamorphosis proceeds, thyroxine reaches its maximal level, after which the forelimbs begin to form.

physiology is controversial, and it appears less important in the day-to-day regulation of Ca^{++} levels. A hormone that plays a more important role in Ca^{++} homeostasis is secreted by the parathyroid glands, described in the next section.

The Parathyroid Glands and Calcium Homeostasis

The parathyroid glands are four small glands attached to the thyroid. Because of their size, researchers ignored them until well into this century. The first suggestion that these organs have an endocrine function came from experiments on dogs: if their parathyroid glands were removed, the Ca^{++} concentration in the dogs’ blood plummeted to less than half the normal value. The Ca^{++} concentration returned to normal when an extract of parathyroid gland was administered. However, if too much of the extract was administered, the dogs’ Ca^{++} levels rose far above normal as the calcium phosphate crystals in their bones was dissolved. It was clear that the parathyroid glands produce a hormone that stimulates the release of Ca^{++} from bone.

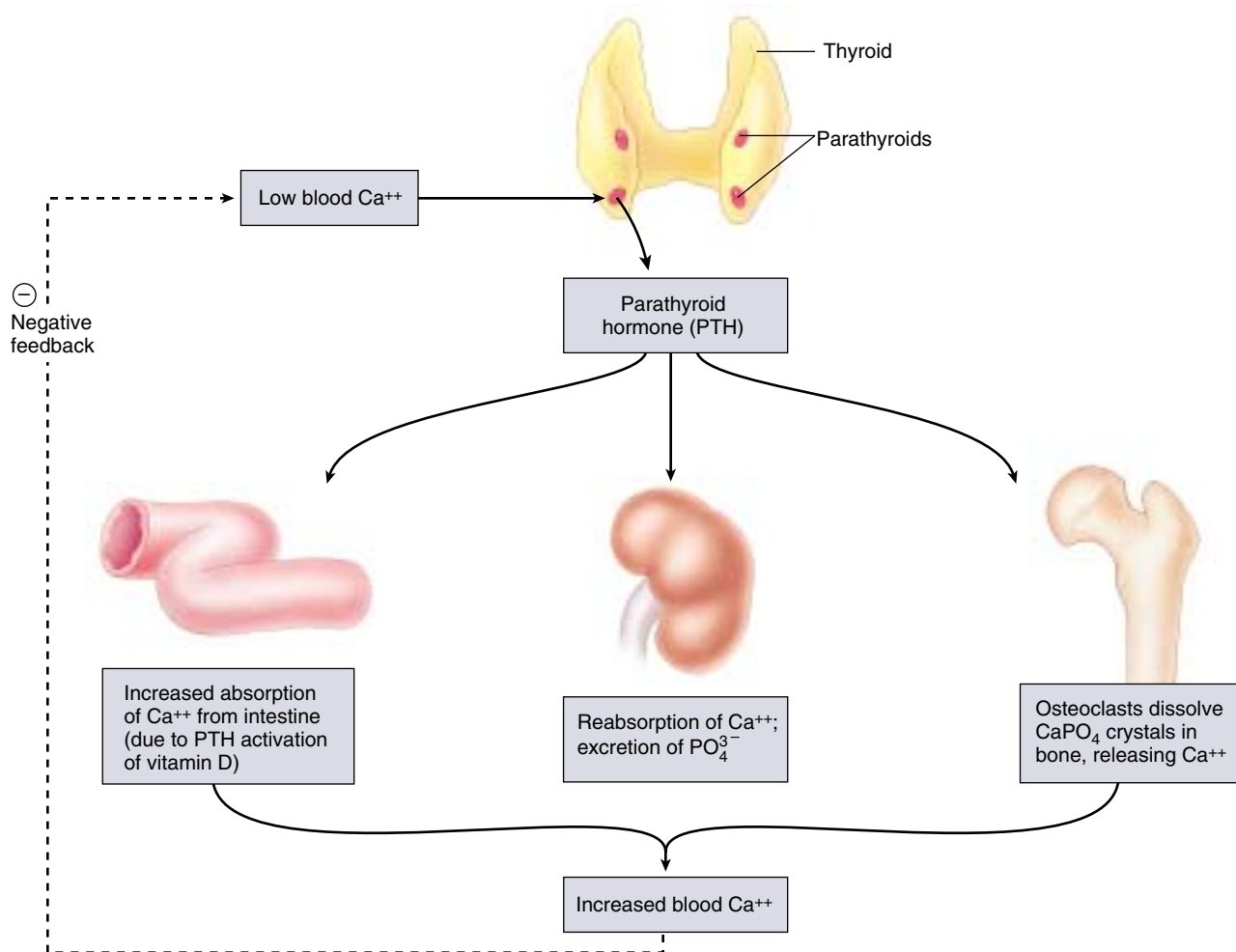


FIGURE 56.18

Regulation of blood Ca^{++} levels by parathyroid hormone (PTH). When blood Ca^{++} levels are low, parathyroid hormone (PTH) is released by the parathyroid glands. PTH directly stimulates the dissolution of bone and the reabsorption of Ca^{++} by the kidneys. PTH indirectly promotes the intestinal absorption of Ca^{++} by stimulating the production of the active form of vitamin D.

The hormone produced by the parathyroid glands is a peptide called parathyroid hormone (PTH). It is one of only two hormones in humans that are absolutely essential for survival (the other is aldosterone, which will be discussed in the next section). PTH is synthesized and released in response to falling levels of Ca^{++} in the blood. This cannot be allowed to continue uncorrected, because a significant fall in the blood Ca^{++} level can cause severe muscle spasms. A normal blood Ca^{++} is important for the functioning of muscles, including the heart, and for proper functioning of the nervous and endocrine systems.

PTH stimulates the osteoclasts (bone cells) in bone to dissolve the calcium phosphate crystals of the bone matrix and release Ca^{++} into the blood (figure 56.18). PTH also stimulates the kidneys to reabsorb Ca^{++} from the urine and leads to the activation of vitamin D, needed for the absorption of Ca^{++} from food in the intestine.

Vitamin D is produced in the skin from a cholesterol derivative in response to ultraviolet light. It is called a vitamin

because a dietary source is needed to supplement the amount that the skin produces. Secreted into the blood from the skin, vitamin D is actually an inactive form of a hormone. In order to become activated, the molecule must gain two hydroxyl groups ($-\text{OH}$); one of these is added by an enzyme in the liver, the other by an enzyme in the kidneys. The enzyme needed for this final step is stimulated by PTH, thereby producing the active form of vitamin D known as 1, 25-dihydroxyvitamin D. This hormone stimulates the intestinal absorption of Ca^{++} and thereby helps to raise blood Ca^{++} levels so that bone can become properly mineralized. A diet deficient in vitamin D thus leads to poor bone formation, a condition called rickets.

Thyroxine helps to set the basal metabolic rate by stimulating the rate of cell respiration throughout the body; this hormone is also needed for amphibian metamorphosis. Parathyroid hormone acts to raise the blood Ca^{++} levels, in part by stimulating osteoclasts to dissolve bone.

The Adrenal Glands

The adrenal glands are located just above each kidney (figure 56.19). Each gland is composed of an inner portion, the adrenal medulla, and an outer layer, the adrenal cortex.

The Adrenal Medulla

The adrenal medulla receives neural input from axons of the sympathetic division of the autonomic nervous system, and it secretes epinephrine and norepinephrine in response to stimulation by these axons. The actions of these hormones trigger “alarm” responses similar to those elicited by the sympathetic division, helping to prepare the body for “fight or flight.” Among the effects of these hormones are an increased heart rate, increased blood pressure, dilation of the bronchioles, elevation in blood glucose, and reduced blood flow to the skin and digestive organs. The actions of epinephrine released as a hormone supplement those of norepinephrine released as a sympathetic nerve neurotransmitter.

The Adrenal Cortex: Homeostasis of Glucose and Na^+

The hormones from the adrenal cortex are all steroids and are referred to collectively as *corticosteroids*. Cortisol (also called hydrocortisone) and related steroids secreted by the adrenal cortex act on various cells in the body to maintain glucose homeostasis. In mammals, these hormones are referred to as glucocorticoids. The glucocorticoids stimulate the breakdown of muscle protein into amino acids, which are carried by the blood to the liver. They also stimulate the liver to produce the enzymes needed for gluconeogenesis, the conversion of amino acids into glucose. This creation of glucose from protein is particularly important during very long periods of fasting or exercise, when blood glucose levels might otherwise become dangerously low.

In addition to regulating glucose metabolism, the glucocorticoids modulate some aspects of the immune response. Glucocorticoids are given medically to suppress the immune system in persons with immune disorders, such as rheumatoid arthritis. Derivatives of cortisol, such as prednisone, have widespread medical use as antiinflammatory agents.

Aldosterone, the other major corticosteroid, is classified as a mineralocorticoid because it helps regulate mineral balance through two functions. One of the functions of aldosterone is to stimulate the kidneys to reabsorb Na^+ from the urine. (Urine is formed by filtration of blood plasma, so the blood levels of Na^+ will decrease if Na^+ is not reabsorbed from the urine; see chapter 58.) Sodium is the major extracellular solute and is needed for the maintenance of normal blood volume and pressure. Without aldosterone, the kidneys would lose excessive amounts of blood Na^+ in the urine, followed by Cl^- and water; this would cause the blood volume and pressure to fall. By stimulating the kidneys to reabsorb salt and water, aldosterone thus maintains the normal blood volume and pressure essential to life.

The other function of aldosterone is to stimulate the kidneys to secrete K^+ into the urine. Thus, when aldosterone levels are too low, the concentration of K^+ in the blood may rise to dangerous levels. Because of these essential functions performed by aldosterone, removal of the adrenal glands, or diseases that prevent aldosterone secretion, are invariably fatal without hormone therapy.

The adrenal medulla is stimulated by sympathetic neurons to secrete epinephrine and norepinephrine during the fight-or-flight reaction. The adrenal cortex is stimulated to secrete its steroid hormones by ACTH from the anterior pituitary. Cortisol helps to regulate blood glucose and aldosterone acts to regulate blood Na^+ and K^+ levels.

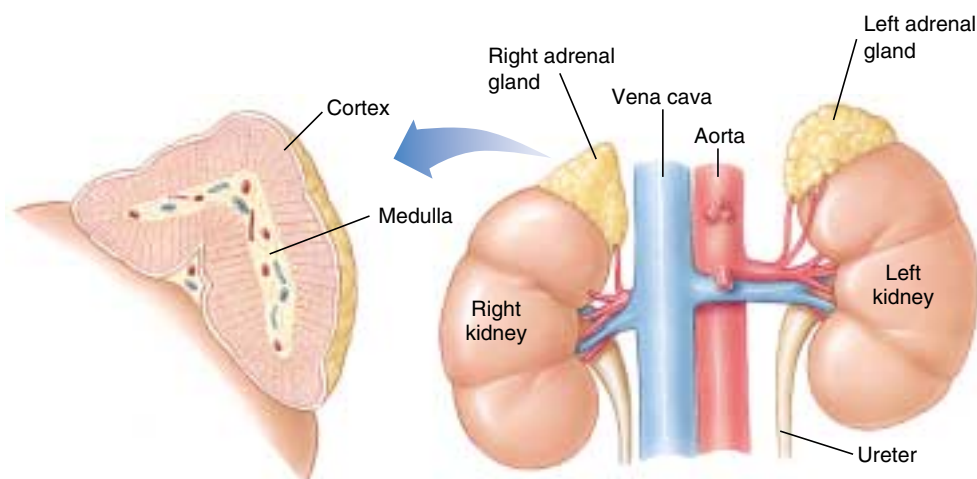


FIGURE 56.19

The adrenal glands. The inner portion of the gland, the adrenal medulla, produces epinephrine and norepinephrine, which initiate a response to stress. The outer portion of the gland, the adrenal cortex, produces steroid hormones that influence blood glucose levels.

The Pancreas

The pancreas is located adjacent to the stomach and is connected to the duodenum of the small intestine by the pancreatic duct. It secretes bicarbonate ions and a variety of digestive enzymes into the small intestine through this duct (see chapter 51), and for a long time the pancreas was thought to be solely an exocrine gland. In 1869, however, a German medical student named Paul Langerhans described some unusual clusters of cells scattered throughout the pancreas; these clusters came to be called islets of Langerhans. Laboratory workers later observed that the surgical removal of the pancreas caused glucose to appear in the urine, the hallmark of the disease diabetes mellitus. This suggested that the pancreas, specifically the islets of Langerhans, might be producing a hormone that prevents this disease.

That hormone is insulin, secreted by the beta (β) cells of the islets. Insulin was not isolated until 1922, when two young doctors working in a Toronto hospital succeeded where many others had not. On January 11, 1922, they injected an extract purified from beef pancreas into a 13-year-old diabetic boy, whose weight had fallen to 65 pounds and who was not expected to survive. With that single injection, the glucose level in the boy's blood fell 25%. A more potent extract soon brought the level down to near normal. The doctors had achieved the first instance of successful insulin therapy.

Two forms of diabetes mellitus are now recognized. People with *type I*, or insulin-dependent diabetes mellitus, lack the insulin-secreting β cells. Treatment for these patients therefore consists of insulin injections. (Because insulin is a peptide hormone, it would be digested if taken orally and must instead be injected into the blood.) In the past, only insulin extracted from the pancreas of pigs or cattle was available, but today people with insulin-dependent diabetes can inject themselves with human insulin produced by genetically engineered bacteria. Active research on the possibility of transplanting islets of Langerhans holds much promise of a lasting treatment for these patients. Most diabetic patients, however, have *type II*, or non-insulin-dependent diabetes mellitus. They generally have normal or even above-normal levels of insulin in their blood, but their cells have a reduced sensitivity to insulin. These

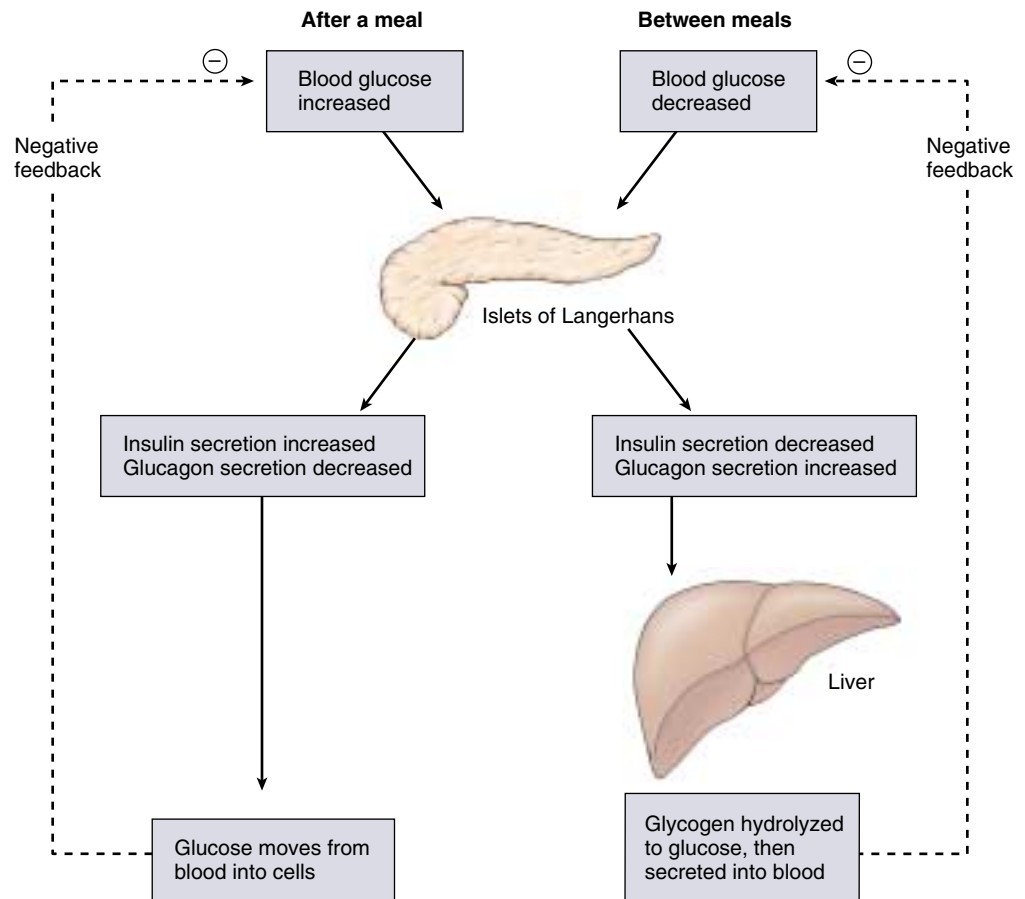


FIGURE 56.20

The antagonistic actions of insulin and glucagon on blood glucose. Insulin stimulates the cellular uptake of blood glucose into skeletal muscles and the liver after a meal. Glucagon stimulates the hydrolysis of liver glycogen between meals, so that the liver can secrete glucose into the blood. These antagonistic effects help to maintain homeostasis of the blood glucose concentration.

people do not require insulin injections and can usually control their diabetes through diet and exercise.

The islets of Langerhans produce another hormone; the alpha (α) cells of the islets secrete glucagon, which acts antagonistically to insulin (figure 56.20). When a person eats carbohydrates, the blood glucose concentration rises. This stimulates the secretion of insulin by β cells and inhibits the secretion of glucagon by the α cells. Insulin promotes the cellular uptake of glucose into liver and muscle cells, where it is stored as glycogen, and into adipose cells, where it is stored as fat. Between meals, when the concentration of blood glucose falls, insulin secretion decreases and glucagon secretion increases. Glucagon promotes the hydrolysis of stored glycogen in the liver and fat in adipose tissue. As a result, glucose and fatty acids are released into the blood and can be taken up by cells and used for energy.

The β cells of the islets of Langerhans secrete insulin, and the α cells secrete glucagon. These two hormones have antagonistic actions on the blood glucose concentration; insulin lowers and glucagon raises blood glucose.

Other Endocrine Glands

Sexual Development, Biological Clocks, and Immune Regulation in Vertebrates

The ovaries and testes are important endocrine glands, producing the steroid sex hormones called androgens (including estrogens, progesterone, and testosterone), to be described in detail in chapter 59. During embryonic development, testosterone production in the embryo is critical for the development of male sex organs. In mammals, androgens are responsible for the development of secondary sexual characteristics at puberty. These characteristics include breasts in females, body hair, and increased muscle mass in males. Because of this, some bodybuilders illegally take androgens to increase muscle mass. In addition to being illegal, this practice can cause liver disorders as well as a number of other serious side effects. In females, androgens are especially important in maintaining the sexual cycle. Estrogen and progesterone produced in the ovaries are critical regulators of the menstrual and ovarian cycles. During pregnancy, estrogen production in the placenta maintains the uterine lining, which protects and nourishes the developing embryo.

Another major endocrine gland is the pineal gland, located in the roof of the third ventricle of the brain in most vertebrates (see figure 54.27). It is about the size of a pea and is shaped like a pine-cone (hence its name). The pineal gland evolved from a median light-sensitive eye (sometimes called a “third eye,” although it could not form images) at the top of the skull in primitive vertebrates. This pineal eye is still present in primitive fish (cyclostomes) and some reptiles. In other vertebrates, however, the pineal gland is buried deep in the brain and functions as an endocrine gland by secreting the hormone melatonin. One of the actions of melatonin is to cause blanching of the skin of lower vertebrates by reducing the dispersal of melanin granules.

The secretion of melatonin is stimulated by activity of the *suprachiasmatic nucleus* (SCN) of the hypothalamus. The SCN is known to function as the major biological clock in vertebrates, entraining (synchronizing) various body processes to a circadian rhythm (one that repeats every 24 hours). Through regulation by the SCN, the secretion of melatonin by the pineal gland is entrained to cycles of light and dark, decreasing during the day and increasing at night. This daily cycling of melatonin release regulates body cycles such as sleep/wake cycles and temperature cycles. In some vertebrates, melatonin helps to regulate reproductive physiology in species with distinct breeding seasons, but the role of melatonin in human reproduction is controversial.

There are a variety of hormones secreted by non-endocrine organs. The thymus is the site of production of particular lymphocytes called T cells, and it secretes a number of hormones that function in the regulation of the immune system. The right atrium of the heart secretes atrial natriuretic hormone, which stimulates the



FIGURE 56.21

A molting cicada. This adult insect is emerging from its old cuticle.

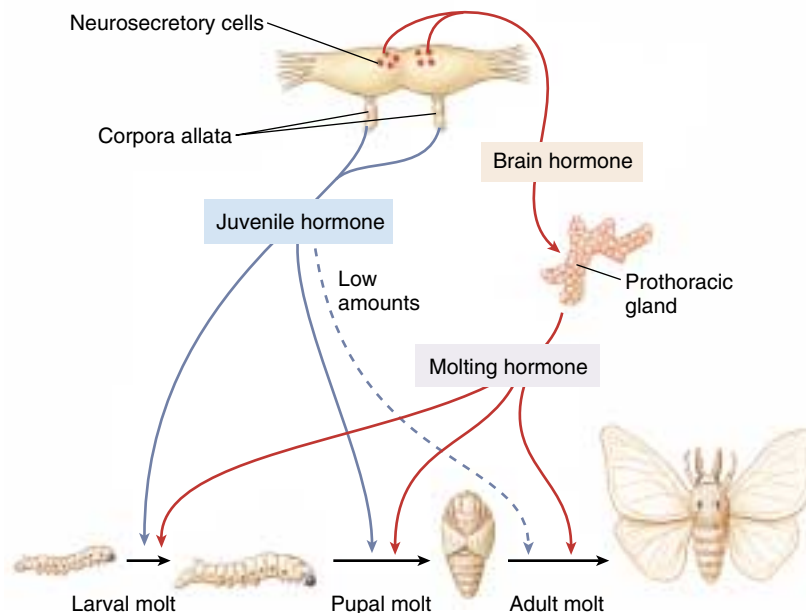
kidneys to excrete salt and water in the urine. This hormone, therefore, acts antagonistically to aldosterone, which promotes salt and water retention. The kidneys secrete erythropoietin, a hormone that stimulates the bone marrow to produce red blood cells. Other organs such as the liver, stomach, and small intestines secrete hormones; even the skin has an endocrine function: it secretes vitamin D. The gas nitric oxide, made by many different cells, controls blood pressure by dilating arteries. The drug sildenafil (Viagra) counters impotence by causing nitric oxide to dilate the blood vessels of the penis.

Molting and Metamorphosis in Insects

As insects grow during postembryonic development, their hardened exoskeletons do not expand. To overcome this problem, insects undergo a series of molts wherein they shed their old exoskeleton (figure 56.21) and secrete a new,

FIGURE 56.22
The hormonal control of metamorphosis in the silkworm moth, *Bombyx mori*.

While molting hormone (ecdysone), produced by the prothoracic gland, triggers when molting will occur, juvenile hormone, produced by bodies near the brain called the corpora allata, determines the result of a particular molt. High levels of juvenile hormone inhibit the formation of the pupa and adult forms. At the late stages of metamorphosis, therefore, it is important that the corpora allata not produce large amounts of juvenile hormone.



larger one. In one molt, a juvenile insect, or larvae, often undergoes a radical transformation to the adult. This process is called metamorphosis. Hormonal secretions influence both molting and metamorphosis in insects. Prior to molting, neurosecretory cells on the surface of the brain secrete a small peptide, **brain hormone**, which in turn stimulates a gland in the thorax called the prothoracic gland to produce *molting hormone*, or *ecdysone* (figure 56.22). High levels of ecdysone bring about the biochemical and behavioral changes that cause molting to occur. Another pair of endocrine glands near the brain called the corpora allata produce a hormone called **juvenile hormone**. High levels of juvenile hormone prevent the transformation to the adult and result in a larval to larval molt. If the level of juvenile hormone is low, however, the molt will result in metamorphosis.

Endocrine Disrupting Chemicals

Because target cells are very sensitive to hormones, these hormones are in very low concentrations in the blood. Therefore, small changes in concentrations can make a big difference in how the target organs function. Unfortunately, scientists are now finding that the endocrine system is not sufficiently protected from the outside world. Some man-made chemicals (and even a few plant-produced chemicals) can enter the body and interrupt normal endocrine function. These chemicals may be ones we manufacture for some other purpose and accidentally leak into the environment, ones that are industrial waste products which we “throw away” into the environment, or ones we purposefully release into the environment such as pesticides. These environmental contaminants get into the food

we eat and the air we breathe. They are everywhere on earth and cannot be avoided. Some can last for years in the environment, and just as long in an animal’s body. Those chemicals that interfere with hormone function are called *endocrine disrupting chemicals*.

Any chemical that can bind to receptor proteins and mimic the effects of the hormone is called a hormone *agonist*. Any chemical that binds to receptor proteins and has no effect but blocks the hormone from binding is called a hormone *antagonist*. Endocrine disrupting chemicals can also interfere by binding to the hormone’s protein carriers in the blood. So far, endocrine disrupting chemicals have been shown to interfere with reproductive hormones, thyroid hormones, and the immune system chemical messengers. These effects are not lethal, but may make individuals vulnerable in their environment. If they are having problems reproducing, maintaining the proper metabolic rate, or fighting off infections, then their numbers will decrease (perhaps even leading to extinction). These environmental contaminants may be harming humans in addition to other species. Laws have been passed requiring the testing of thousands of chemicals to see if they have endocrine disrupting potential, and the Environmental Protection Agency (EPA) must include this testing in their standard protocols before approving any new compounds.

Sex steroid hormones from the gonads regulate reproduction, melatonin secreted by the pineal gland helps regulate circadian rhythms, and thymus hormones help regulate the vertebrate immune system. Molting hormone, or ecdysone, and juvenile hormone regulate metamorphosis and molting in insects.



Chapter 56

Summary Questions Media Resources

56.1 Regulation is often accomplished by chemical messengers.

- Endocrine glands secrete hormones into the blood, which are then transported to target cells.
- Hormones may be lipophilic, such as the steroid hormones and thyroxine, or polar, such as amine, polypeptide, and glycoprotein hormones.
- Prostaglandins and other paracrine regulatory molecules are produced by one cell type and regulate different cells within the same organ.

1. What is the definition of a hormone? How do hormones reach their target cells? Why are only certain cells capable of being target cells for a particular hormone?
2. How do hormones and paracrine regulators differ from one another?



- Art Activity:
–Endocrine System



- Endocrine System Regulation

56.2 Lipophilic and polar hormones regulate their target cells by different means.

- Lipid-soluble hormones enter their target cells, bind to intracellular receptor proteins, and the complex then binds to hormone response elements on the DNA, activating specific genes.
- Polar hormones do not enter their target cells, but instead bind to receptor proteins on the cell membrane and activate second-messenger systems or control ion channels.

3. How does epinephrine result in the production of cAMP in its target cells? How does cAMP bring about specific changes inside target cells?



- Peptide Hormone Action



- Activity:
–Peptide Hormones
–Steroid Hormones
• Types of Hormones

56.3 The hypothalamus controls the secretions of the pituitary gland.

- Axons from neurons in the hypothalamus enter the posterior pituitary, carrying ADH and oxytocin; the posterior pituitary stores these hormones and secretes them in response to neural activity.
- The anterior pituitary produces and secretes a variety of hormones, many of which control other endocrine glands; the anterior pituitary, however, is itself controlled by the hypothalamus via releasing and inhibiting hormones secreted by the hypothalamus.

4. Where are hormones secreted by the posterior pituitary gland actually *produced*?
5. Why are the hormones of the anterior pituitary gland called tropic hormones?
6. How does the hypothalamus regulate the secretion of the anterior pituitary?



- Portal System



- Hypothalamus
• Pituitary Gland

56.4 Endocrine glands secrete hormones that regulate many body functions.

- The thyroid secretes thyroxine and triiodothyronine, which set the basal metabolic rate by stimulating the rate of cell respiration in most cells of the body.
- The adrenal cortex secretes cortisol, which regulates glucose balance, and aldosterone, which regulates Na⁺ and K⁺ balance.
- The β cells of the islets of Langerhans in the pancreas secrete insulin, which lowers the blood glucose; glucagon, secreted by the α cells, raises the blood glucose level.

7. What hormones are produced by the adrenal cortex? What functions do these hormones serve? What stimulates the secretion of these hormones?
8. What pancreatic hormone is produced when the body's blood glucose level becomes elevated?



- Parathyroid Hormone
• Glucose Regulation



- Thyroid Gland
• Parathyroid Glands
• Adrenal Glands
• Pancreas

