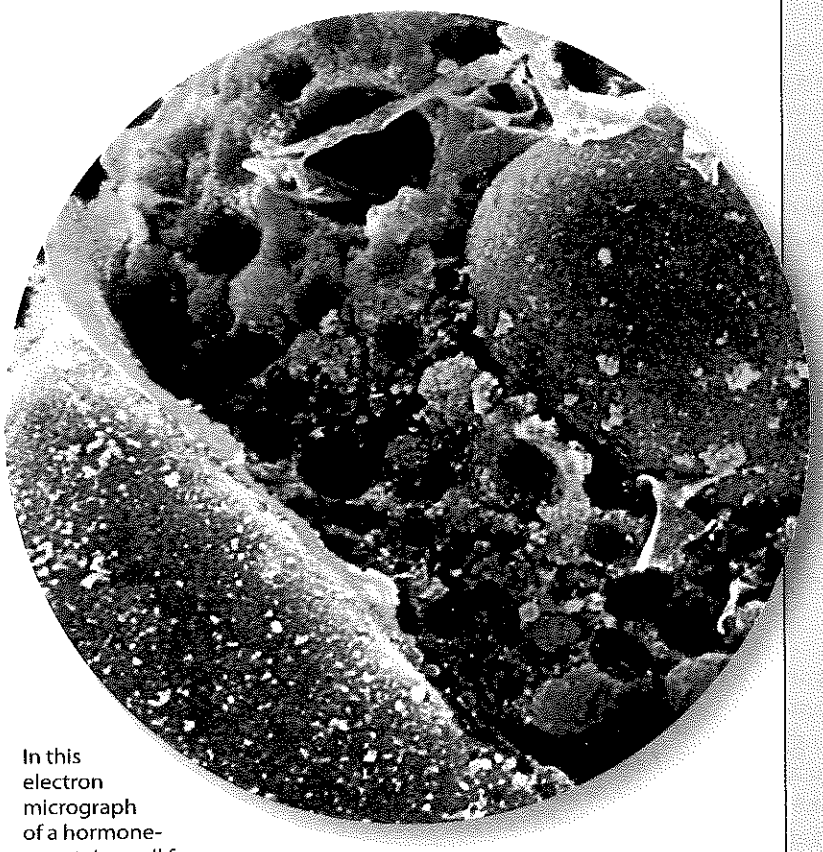
13 Endocrine System



In this electron micrograph of a hormone-secreteing cell from the adrenal cortex, the upper portion of the cell has been removed to reveal the nucleus (brown) and the edge of the cell membrane (grey) (14,400×).

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Module 8: Endocrine System

Learning Outcomes

After you have studied this chapter, you should be able to:

13.1 Introduction

1 Distinguish between endocrine and exocrine glands. (p. 488)

13.2 General Characteristics of the Endocrine System

2 Explain what makes a cell a target cell for a hormone. (p. 488)

3 List some important functions of hormones. (p. 489)

13.3 Hormone Action

4 Describe how hormones can be classified according to their chemical composition (p. 490)

5 Explain how steroid and nonsteroid hormones affect their target cells (p. 492)

13.4 Control of Hormonal Secretions

6 Discuss how negative feedback mechanisms regulate hormone secretion. (p. 496)

7 Explain how the nervous system controls hormone secretion. (p. 496)

13.5–13.10 Pituitary Gland–Other Endocrine Glands

8 Name and describe the locations of the major endocrine glands, and list the hormones that they secrete. (pp. 497–516)

9 Describe the actions of the various hormones and their contributions to homeostasis. (pp. 498–515)

10 Explain how the secretion of each hormone is regulated. (pp. 500–516)

13.11 Stress and Its Effects

11 Distinguish between physical and psychological stress. (p. 517)

12 Describe the general stress response. (p. 518)

13.12 Life-Span Changes

13 Describe some of the changes associated with aging of the endocrine system. (p. 519)

LEARN PRACTICE ASSESS

Understanding Words

cort-, bark, rind: adrenal *cort*ex—outer portion of an adrenal gland.

-crin, to secrete: endo*crine*—internal secretion.

diuret-, to pass urine: *diuret*ic—substance that promotes urine production.

endo-, inside: *endo*crine gland—gland that internally secretes into a body fluid.

exo-, outside: *exo*crine gland—gland that secretes to the outside through a duct.

horm-, impetus, impulse: *horm*one—substance that a cell secretes that affects another cell.

hyper-, above: *hyper*thyroidism—condition resulting from an above-normal secretion of thyroid hormone.

hypo-, below: *hypo*thyroidism—condition resulting from a below-normal secretion of thyroid hormone.

lact-, milk: pro*lact*in—hormone that promotes milk production.

med-, middle: adrenal *med*ulla—middle section of an adrenal gland.

para-, beside: *para*thyroid glands—set of glands near the surface of the thyroid gland.

toc-, birth: oxy*toc*in—hormone that stimulates the uterine muscles to contract during childbirth.

-tropic, influencing: adrenocortico*tropic* hormone—a hormone secreted by the anterior pituitary gland that stimulates the adrenal cortex.

vas-, vessel: *vas*opressin—substance that causes blood vessel walls to contract.

Human Pheromones in Sweat and Tears?

The endocrine system produces and secretes hormones, which are biochemicals that affect target cells within an individual. Less well understood are pheromones, which are chemical signals sent between members of a species. In rodents, pheromones stimulate social behavior, including mating. In humans, pheromones may act through sweat and tears.

Mice choose mates based on odor. Specific receptors in their olfactory epithelium respond to molecules in the urine of other mice that not only direct social behavior but reflect different strengths of an individual's immune system. By following their noses, mice end up mating in ways that maximize immunity in their pups. Humans also have these receptors.

To test whether people use the sense of smell to choose partners, researchers recruited forty-nine young women and forty-four young men, all heterosexual. Each donated DNA, which was typed for the human counterparts of genes that affect mating in mice. The women used a nasal spray for two weeks to clear their nasal passages. The men wore the same T-shirts on two consecutive days without using deodorant or soap. Each woman was then given three T-shirts from men genetically similar to her and three T-shirts from men genetically dissimilar to her, not knowing which shirts came from which men. The women sniffed the shirts, and rated the sweat stains on intensity, pleasantness, and sexiness. Like female mice, female humans preferred the sweaty T-shirts from the men least like them.

Human tears may also contain pheromones. Tears that are a response to eye irritation are chemically different from tears that are cried when a person is sad. Researchers conducted a series of experiments similar to the T-shirt study that suggest that females' emotional tears contain a chemical signal that seems to reduce sexual arousal in men.

In initial experiments, 24 young men were asked if tears cried when women watched a sad film smelled different from saline (salt water) that had been trickled down the women's faces. The men reported that the tears didn't smell different from the saline. Next, researchers taped a patch of cotton to each man's upper lip. The cotton bore either the saline that had been exposed to a woman's face ("trickled saline") or emotional tears. Although self-reporting did not indicate a pronounced effect on the men's sexual arousal, more objective measurements did. Specifically, the level of testosterone, the male sex hormone, in the saliva fell sharply after smelling emotional tears. Functional MRI scans of brain regions normally activated during sexual arousal confirmed the response of plummeting testosterone when sensing a woman in distress. In reality, the effect of emotional tears on sexual readiness may be even more pronounced because men would be in closer contact with women, and therefore to whatever potential pheromone is in tears. ■

13.1 INTRODUCTION

Maintaining homeostasis in the body is complex. Two organ systems function coordinately to enable body parts to communicate with each other and to adjust constantly to changing incoming signals. The nervous system is one biological communication system: it uses impulses and neurotransmitters. The other communication system is the endocrine system.

The **endocrine system** is so named because the cells, tissues, and organs that compose it, collectively called endocrine glands, secrete substances into the internal environment. (*Endocrine* means "internal secretion.") The secreted substances, called **hormones,** diffuse from the interstitial fluid into the bloodstream and eventually act on cells, called **target cells,** some distance away (fig. 13.1).

Other glands secrete substances into the internal environment that are not hormones by the traditional definition, but they function similarly as messenger molecules and are sometimes termed "local hormones." These include **paracrine** secretions, which enter the interstitial fluid but affect only neighboring cells, and **autocrine** secretions, which affect only the secreting cell.

Secretions from **exocrine glands** enter tubes or ducts that lead to body surfaces. In contrast to endocrine secretions, exocrine secretions are released externally. Two examples of exocrine secretions are stomach acid reaching the lumen of the digestive tract and sweat released at the skin's surface (fig. 13.1).

13.2 GENERAL CHARACTERISTICS OF THE ENDOCRINE SYSTEM

Cells of the endocrine system and the nervous system both communicate using chemical signals that bind to receptor molecules. Table 13.1 summarizes some similarities and differences between the two systems. In contrast to the nervous system, which releases neurotransmitter molecules into synapses, the endocrine system releases hormones into the bloodstream, which carries these messenger molecules everywhere. However, the endocrine system is also precise, because only target cells can respond to a hormone (fig. 13.2). A hormone's target cells have specific receptors that other cells lack. These receptors are proteins or glycoproteins with binding sites for a specific hormone. The other chemical messengers, paracrine and autocrine substances, also bind to specific receptors, and examples of these are included in the chapter.

Endocrine glands and their hormones help regulate metabolic processes. They control the rates of certain chemical reactions; aid in transporting substances through membranes; and help regulate water balance, electrolyte balance, and blood pressure. Endocrine hormones also play vital roles in reproduction, development, and growth.

Small groups of specialized cells produce some hormones. However, the larger endocrine glands—the pituitary gland, thyroid gland, parathyroid glands, adrenal glands, and pancreas—are the subject of this chapter (fig. 13.3).

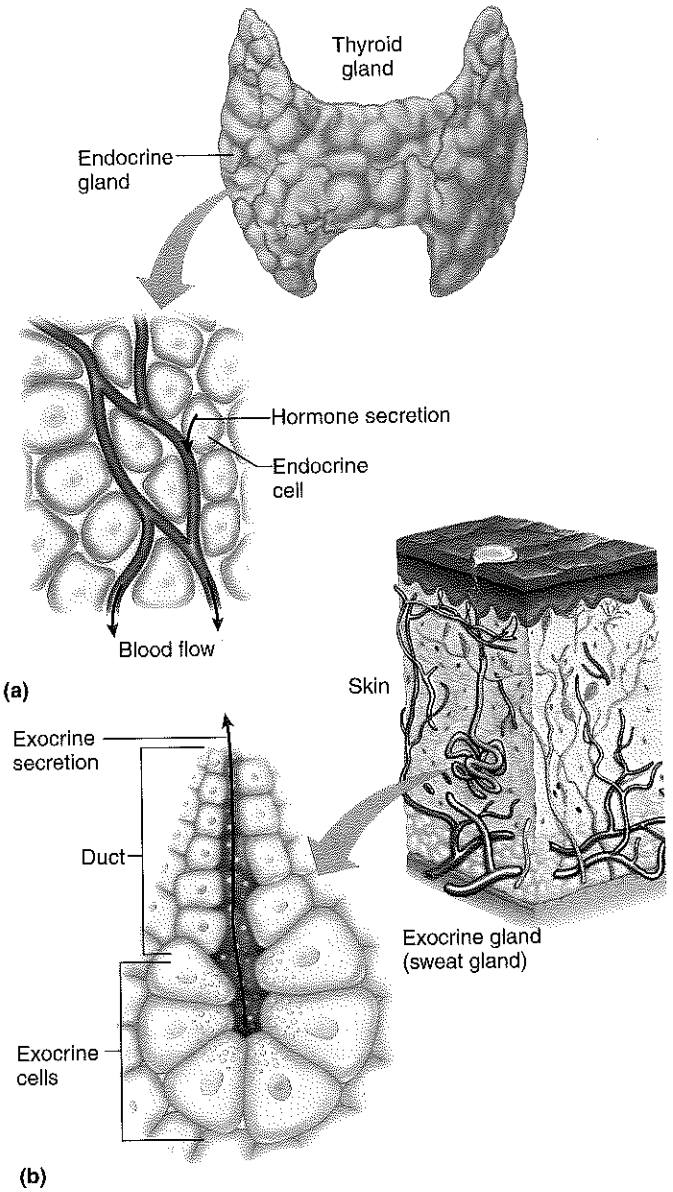


FIGURE 13.1 Types of glands. (*a*) Endocrine glands release hormones into the internal environment (body fluids). (*b*) Exocrine glands secrete to the outside environment through ducts that lead to body surfaces.

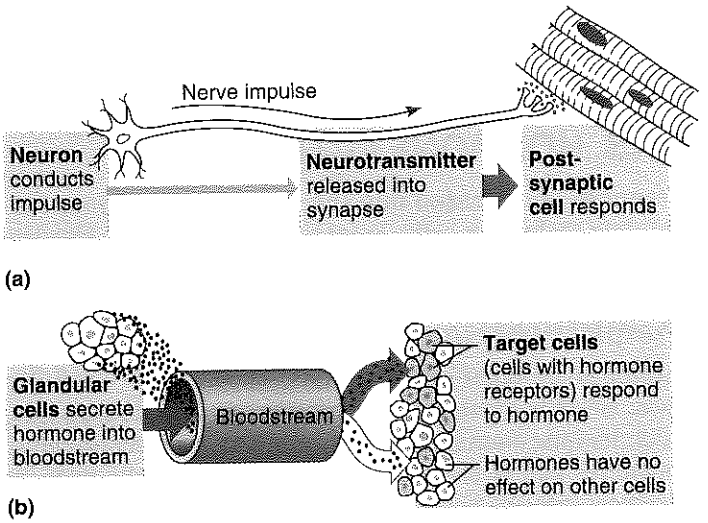


FIGURE 13.2 Chemical communication. (*a*) Neurons release neurotransmitters into synapses, affecting postsynaptic cells. (*b*) Glands release hormones into the bloodstream. Blood carries hormone molecules throughout the body, but only target cells respond.

Q: *Which is more specific in terms of which cells are affected, a neurotransmitter or a hormone?*

Answer can be found in Appendix G on page 938.

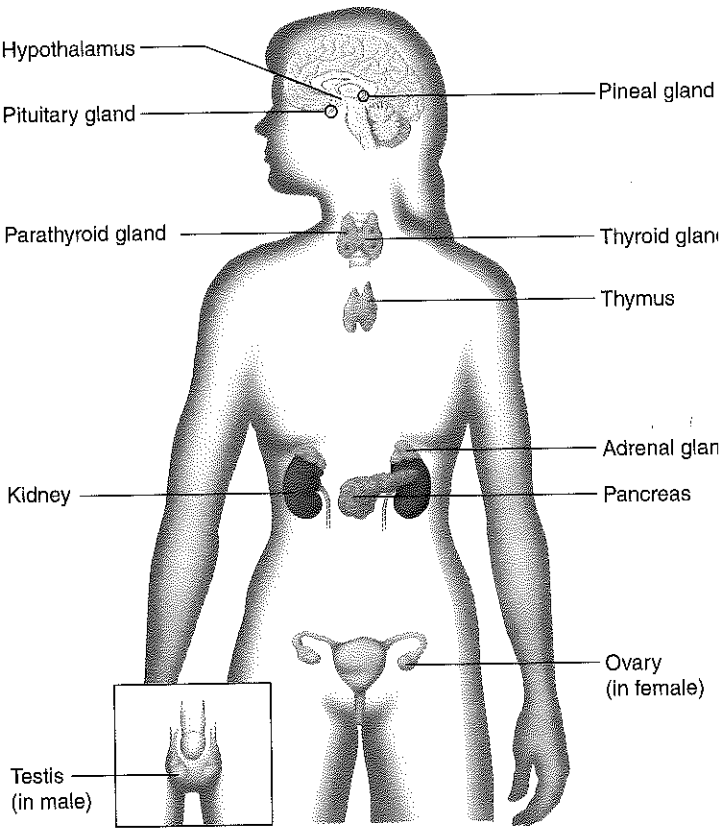


FIGURE 13.3 Locations of major endocrine glands.

TABLE 13.1 | A Comparison Between the Nervous System and the Endocrine System

	Nervous System	Endocrine System
Cells	Neurons	Glandular epithelium
Chemical signal	Neurotransmitter	Hormone
Specificity of action	Receptors on postsynaptic cell	Receptors on target cell
Speed of onset	Seconds	Seconds to hours
Duration of action	Very brief unless neuronal activity continues	May be brief or may last for days even if secretion ceases

Subsequent chapters discuss several other hormone-secreting glands and tissues.

13.3 HORMONE ACTION

Hormones are released into the extracellular spaces surrounding endocrine cells. From there, they diffuse into the bloodstream and are carried to all parts of the body.

Chemistry of Hormones

Hormones are organic compounds. They are of two major types: steroids, or steroidlike substances; and nonsteroids, which include amines, peptides, proteins, or glycoproteins. Hormones can stimulate changes in target cells even in extremely low concentrations.

Steroid Hormones

Steroids (ste'roidz) are lipids that include complex rings of carbon and hydrogen atoms (fig. 13.4*a*). Steroids differ by the types and numbers of atoms attached to these rings and the ways they are joined (see fig. 2.16, p. 73). All steroid hormones are derived from cholesterol (see chapter 2, p. 73). They include sex hormones such as testosterone and the estrogens, and secretions of the adrenal cortex (the outer portion of the adrenal gland), including aldosterone and cortisol. Vitamin D is a modified steroid and when converted to the active form in the kidneys and liver becomes a hormone (see "Parathyroid Hormone" on p. 507, and chapter 18, p. 707).

Nonsteroid Hormones

Hormones called *amines*, including norepinephrine and epinephrine, are derived from the amino acid tyrosine. These hormones are also synthesized in the adrenal medulla (the inner portion of the adrenal gland) (fig. 13.4*b*).

Protein hormones, like all proteins, are composed of long chains of amino acids that are linked and folded into specific molecular structures (see chapter 2, pp. 73–76, and fig. 13.4*c*). They include the hormone secreted by the parathyroid gland and some of those secreted by the anterior pituitary gland. Certain other hormones secreted from the anterior pituitary gland are *glycoproteins*, which consist of carbohydrates joined to proteins.

The *peptide* hormones are short chains of amino acids (fig. 13.4*d*). This group includes hormones associated with the posterior pituitary gland and some produced in the hypothalamus.

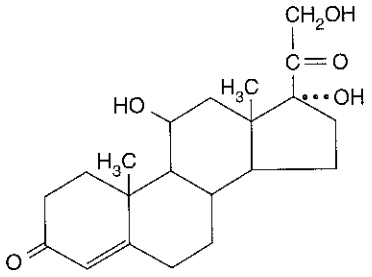
Another group of compounds, called *prostaglandins* (pros"tah-glan'dinz), are paracrine substances. They regulate neighboring cells. Prostaglandins are lipids (20-carbon fatty acids that include 5-carbon rings) and are synthesized from a type of fatty acid (arachidonic acid) in cell membranes (fig. 13.4*e*). Prostaglandins are produced in a wide variety of cells, including those of the liver, kidneys, heart, lungs, thymus, pancreas, brain, and reproductive organs.

Table 13.2 lists the names and abbreviations of some of the hormones discussed in this chapter. Table 13.3 and figure 13.4 summarize the chemical composition of hormones.

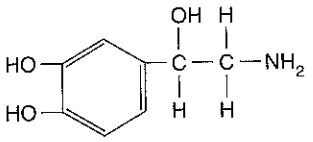
TABLE 13.2 | Hormone Names and Abbreviations

Source	Name	Abbreviation	Synonym
Hypothalamus	Corticotropin-releasing hormone	CRH	
	Gonadotropin-releasing hormone	GnRH	Luteinizing hormone-releasing hormone (LHRH)
	Somatostatin	SS	Growth hormone release-inhibiting hormone (GRIH)
	Growth hormone-releasing hormone	GHRH	
	Prolactin release-inhibiting hormone	PIH	Dopamine
	Prolactin-releasing factor*	PRF*	
	Thyrotropin-releasing hormone	TRH	
Anterior pituitary gland	Adrenocorticotropic hormone	ACTH	Corticotropin
	Follicle-stimulating hormone	FSH	Follitropin
	Growth hormone	GH	Somatotropin (STH)
	Luteinizing hormone	LH	Lutropin, interstitial cell-stimulating hormone (ICSH)
	Prolactin	PRL	
	Thyroid-stimulating hormone	TSH	Thyrotropin
Posterior pituitary gland	Antidiuretic hormone	ADH	Vasopressin
	Oxytocin	OT	
Thyroid gland	Calcitonin		
	Thyroxine	T_4	Tetraiodothyronine
	Triiodothyronine	T_3	
Parathyroid gland	Parathyroid hormone	PTH	Parathormone
Adrenal medulla	Epinephrine	EPI	Adrenalin
	Norepinephrine	NE	Noradrenalin
Adrenal cortex	Aldosterone		
	Cortisol		Hydrocortisone
Pancreas	Glucagon		
	Insulin		
	Somatostatin	SS	

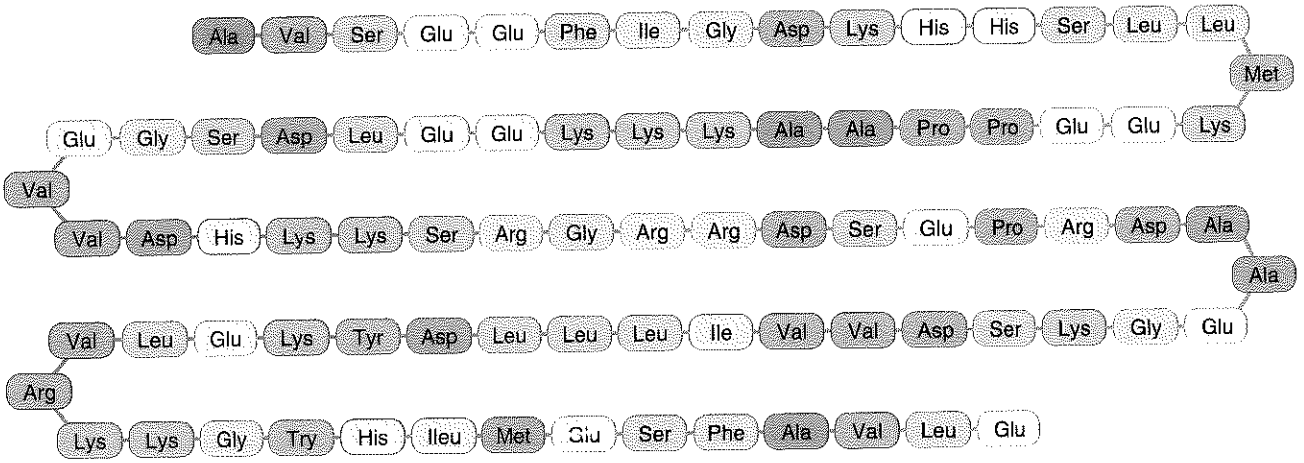
*"Factor" is used because specific prolactin-releasing hormones have not yet been identified.



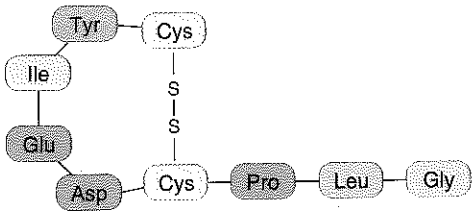
(a) Cortisol



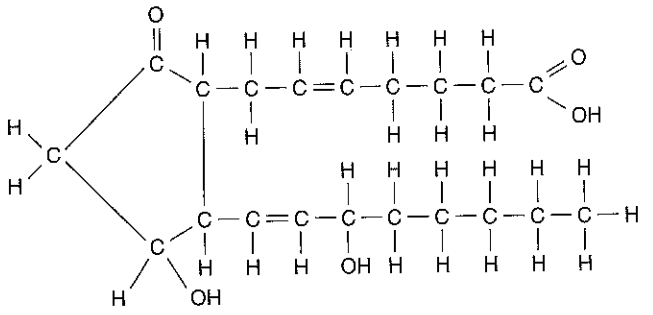
(b) Norepinephrine



(c) Parathyroid hormone (PTH)



(d) Oxytocin



(e) Prostaglandin PGE_2

FIGURE 13.4 Structural formulas of (*a*) a steroid hormone (cortisol) and (*b*) an amine hormone (norepinephrine). Amino acid sequences of (*c*) a protein hormone (PTH) and (*d*) a peptide hormone (oxytocin). Structural formula of (*e*) a prostaglandin (PGE_2).

TABLE 13.3 | Types of Hormones

Type of Compound	Formed from	Examples
Amines	Amino acids	Norepinephrine, epinephrine
Peptides	Amino acids	ADH, OT, TRH, SS, GnRH
Proteins	Amino acids	PTH, GH, PRL
Glycoproteins	Protein and carbohydrate	FSH, LH, TSH
Steroids	Cholesterol	Estrogens, testosterone, aldosterone, cortisol

PRACTICE

1. What is a hormone?
2. How do endocrine glands and exocrine glands differ?
3. How are hormones chemically classified?

Actions of Hormones

Hormones exert their effects by altering metabolic processes. A hormone might change the activity of an enzyme necessary for synthesizing a particular substance or alter the rate at

which particular chemicals are transported through cell membranes. A hormone delivers its message to a cell by uniting with the binding site of its receptor. The more receptors the hormone binds on its target cells, the greater the response.

The number of receptors on target cells may change. *Upregulation* is an increase in the number of receptors on a target cell, which often occurs as a response to a prolonged decrease in the level of a hormone. *Down-regulation* is the opposite, a decrease in the number of receptors in response to a prolonged increase in hormone levels. Therefore, the number of receptors changes in ways that maintain an appropriate response to hormone level.

Steroid Hormones and Thyroid Hormones

Steroid hormones and thyroid hormones are insoluble in water. They are carried in the bloodstream weakly bound to plasma proteins in a way that they are released in sufficient quantity to affect their target cells. However, unlike amine, peptide, and protein hormones, steroid and thyroid hormones are soluble in the lipids that make up the bulk of cell membranes. For this reason, these hormones can diffuse into cells relatively easily and are able to enter any cell in the body.

Once inside a target cell, steroid and thyroid hormones combine (usually in the nucleus) with specific protein receptors. The resulting *hormone-receptor complex* binds to particular DNA sequences, either activating or repressing specific genes. Activated genes are transcribed into messenger RNA (mRNA) molecules. The mRNAs enter the cytoplasm, where they direct the synthesis of specific proteins, which may be enzymes, transport proteins, or even hormone receptors. The activities of these hormones produce the cellular changes associated with the particular hormone (fig. 13.5, table 13.4, and Clinical Application 13.1). An example is the steroid hormone **aldosterone** (al'do-ster-ōn", al-dos'ter-ōn), from the adrenal gland, whose action is to stimulate the kidneys to retain

TABLE 13.4 | Sequence of Steroid Hormone Action

1. Endocrine gland secretes steroid hormone.
2. Steroid hormone diffuses through target cell membrane and enters cytoplasm or nucleus.
3. Hormone combines with a receptor molecule in the cytoplasm or nucleus.
4. Steroid hormone-receptor complex binds to DNA and promotes transcription of messenger RNA.
5. Messenger RNA enters the cytoplasm and directs protein synthesis.
6. Newly synthesized proteins produce the steroid hormone's specific effects.

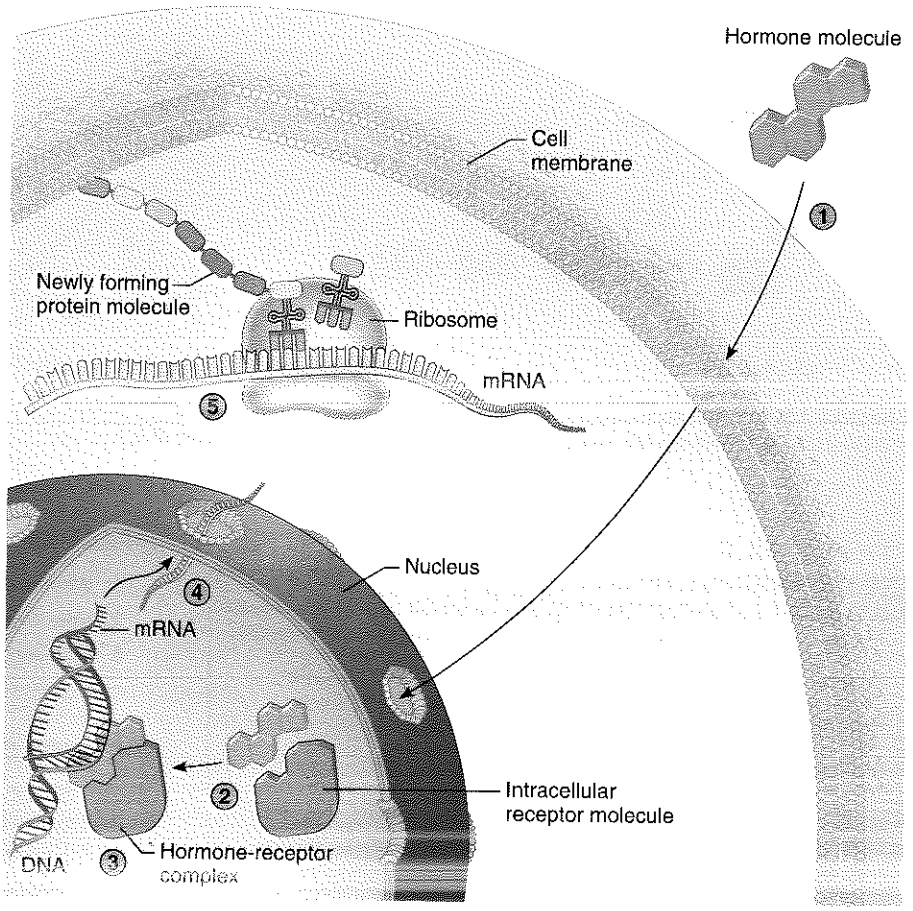
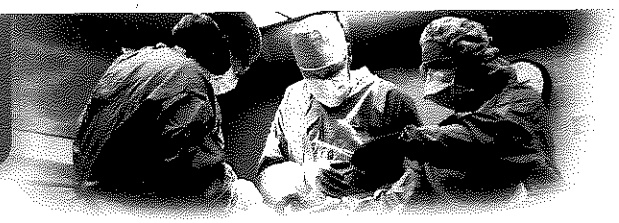


FIGURE 13.5 AP|R Steroid hormones. (*1*) A steroid hormone crosses a cell membrane and (*2*) combines with a protein receptor, usually in the nucleus. (*3*) The hormone-receptor complex activates transcription of specific messenger RNA (mRNA) molecules from DNA. (*4*) The mRNA molecules leave the nucleus and enter the cytoplasm (*5*) where they guide synthesis of their encoded proteins. In the bloodstream, most molecules of a particular steroid are bound to proteins. Only the few that are not bound are free to enter cells, as shown here.

13.1 CLINICAL APPLICATION



Abusing Hormones to Improve Athletic Performance

Abuse of performance-enhancing drugs among athletes, both amateur and professional, is a common problem and not new (Table 13A). Athletes have used drugs for a competitive edge since the earliest Olympics, when cocaine, heroin, morphine, and strychnine were the drugs of choice. Amphetamines joined the list after World War II, when soldiers took these stimulants to mask the fatigue that accompanies great exertion. The drugs boosted energy in sports too. Today, the general focus of performance enhancement is misuse of certain hormones. Three examples are described here.

TABLE 13A | List of Prohibited Drugs

Anabolic agents
Anabolic androgenic steroids
Other anabolic agents
Hormones and related substances
EPO
Growth factors
Gonadotropins (LH, hCG in males)
Insulin
Corticotropins
Beta-2 agonists
Hormone antagonists and modulators
Aromatase inhibitors
Selective estrogen receptor modulators
Other antiestrogens
Myostatin inhibitors
Diuretics

Source: World Anti-Doping Agency

Steroids

Athletes who abuse steroids seek the hormone's ability to increase muscular strength. Abusers are caught when the steroids or their metabolites are detected in urine or when natural testosterone levels plummet in a negative feedback response to the outside supply of the hormone.

Abusing steroids carries serious risks to health. Steroids hasten adulthood, stunting height and causing early hair loss. In males, excess steroid hormones lead to breast development, and in females to a deepened voice, hairiness, and a male physique. The kidneys, liver, and heart may be damaged, and atherosclerosis may develop because steroids raise LDL and lower HDL—the opposite of a healthy cholesterol profile. Steroids can also cause psychiatric symptoms, including delusions, depression, and violent behavior.

For some athletes, illicit steroid use cannot be detected because of a natural mutation that deletes part of a gene. The result is a block in the conversion of testosterone from fat soluble to water soluble, and the hormone is not excreted into the urine as it normally is. This mutation is responsible for variations seen in different populations in the amount of testosterone excreted in the urine. In one telling experiment, researchers in Sweden injected fifty-five male volunteers with a high dose of testosterone, and seventeen of the men showed no traces of the steroid in their urine!

The urine ratio of testosterone to an inactive form of the hormone called epitestosterone can reveal the taking of exogenous (outside) testosterone. The body normally produces testosterone and epitestosterone in about equal amounts. The presence of much more testosterone than epitestosterone therefore indicates "doping."

Growth Hormone

Some athletes take human growth hormone (HGH) preparations instead of, or to supplement, the effects of steroids. HGH enlarges muscles; steroids strengthen them. HGH has been available as a prescription drug since 1985, and it is used as such to treat children with certain forms of inherited dwarfism. However, HGH is available from other nations without prescription and can be obtained illegally to enhance athletic performance. Unlike steroids, HGH has a half-life of only seventeen to forty-five minutes, which means that it becomes so scant that it is undetectable in body fluids within an hour. At first only elite athletes abused HGH to enhance performance. One recent study of young weight lifters in the United States, however, found that 12% of them took HGH or insulin-like growth factor-1 (which HGH stimulates synthesis of in the body).

Erythropoietin

Increasing the number of red blood cells can increase oxygen delivery to muscles and thereby enhance endurance. Athletes introduced "blood doping" in 1972. The athletes would have blood removed a month or more prior to performance, then reinfuse the blood shortly before a competition, boosting the number of red blood cells. Easier than blood doping is to take erythropoietin (EPO), a hormone secreted from the kidneys that signals the bone marrow to produce more red blood cells. EPO is used to treat certain forms of anemia. Using it to improve athletic performance is ill advised. In 1987, EPO abuse led to heart attacks and death in twenty-six cyclists. Some runners and swimmers also abuse EPO.

Testing for drugs or for mutations that enable athletes to mask abuse is expensive. Testing for biomarkers that are the breakdown products of abused drugs may be a less costly approach. ■

sodium. In response to aldosterone, cells that form tubules in the kidney begin to synthesize more Na^+/K^+ pumps. These are the proteins that actively transport these ions across the cell membrane, in this case retaining sodium.

In some cases, steroid hormones may repress a particular gene, so it is not transcribed. The cellular response results from decreased levels of the encoded protein.

Nonsteroid Hormones

A nonsteroid hormone, such as an amine, peptide, or protein, usually combines with specific receptor molecules on the target cell membrane. Each receptor molecule is a protein that has a *binding site* and an *activity site.* The hormone combines with the binding site, which causes the receptor's activity site to interact with other membrane proteins. The hormone that triggers this cascade of biochemical activity is considered a *first messenger.* The biochemicals in the cell that induce the changes recognized as responses to the hormone are called *second messengers.*

Many hormones use **cyclic adenosine monophosphate** (cyclic AMP, or cAMP) as a second messenger. In this mechanism, a hormone binds to its receptor, and the resulting hormone-receptor complex activates a protein called a **G protein,** which then activates an enzyme called **adenylate cyclase**

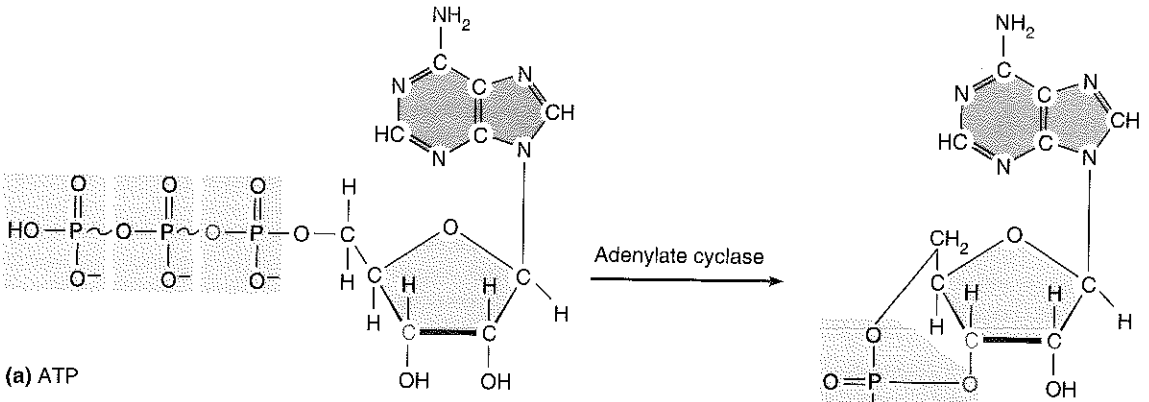


FIGURE 13.6 Adenylate cyclase catalyzes conversion of (*a*) ATP molecules into cyclic AMP (*b*). The atoms forming the new bond are shown in red.

(ah-den'ĭ-lāt si'klās), which is an integral membrane protein with its active site facing the inside of the cell. Activated adenylate cyclase removes two phosphates from ATP and reconnects the exposed oxygen, forming *cyclic AMP* (fig. 13.6). Cyclic AMP, in turn, activates another set of enzymes called **protein kinases** (ki'nās-ez). Protein kinases transfer phosphate groups from ATP molecules to protein substrate molecules. This phosphorylation alters the shapes of the substrate molecules, in some cases activating inactive forms.

The activated proteins then alter various cellular processes, bringing about the effect of that particular hormone (fig. 13.7). The response of a particular cell to such a hormone is determined by the type of membrane receptors present and by the types of protein substrate molecules in the cell. Table 13.5 summarizes these actions.

Cellular responses to second messenger activation include altering membrane permeabilities, activating enzymes, promoting synthesis of certain proteins, stimulating or inhibiting specific metabolic pathways, promoting cellular movements, and initiating secretion of hormones and other substances. A specific example is the action of epinephrine to raise blood sugar during periods of physical stress. Epinephrine acts through the second messenger cAMP to increase the activity of the enzyme that breaks down liver glycogen, increasing the number of glucose molecules that can diffuse out of liver cells and enter the bloodstream.

Another enzyme, phosphodiesterase, quickly and continuously inactivates cAMP, so its action is short-lived. For this reason, a continuing response in a target cell requires a continuing signal from hormone molecules binding receptors in the target cell membrane.

Hormones whose actions require cyclic AMP include releasing hormones from the hypothalamus; thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) from the anterior pituitary gland; antidiuretic hormone (ADH) from the posterior pituitary gland; parathyroid hormone (PTH) from the parathyroid glands; norepinephrine and epinephrine from the adrenal glands; calcitonin from the thyroid gland; and glucagon from the pancreas.

TABLE 13.5 | Sequence of Actions of Nonsteroid Hormone Using Cyclic AMP

1. Endocrine gland secretes nonsteroid hormone.
2. Body fluid carries hormone to its target cell.
3. Hormone combines with receptor site on membrane of its target cell, activating G protein.
4. Adenylate cyclase molecules are activated in target cell's membrane.
5. Adenylate cyclase converts ATP into cyclic AMP.
6. Cyclic AMP activates protein kinases.
7. Protein kinases activate protein substrates in the cell that change metabolic processes.
8. Cellular changes produce the hormone's effects.

An abnormality in cAMP-mediated signaling can lead to symptoms from many endocrine glands. In McCune-Albright syndrome, for example, a defect in the G protein that activates adenylate cyclase results in conversion of ATP to cAMP even without hormonal stimulation. As a result, cells in the pituitary, thyroid, gonads, and adrenal glands secrete hormones in excess. One symptom is precocious puberty. Infant girls menstruate, and boys as young as six years produce mature sperm.

Certain nonsteroid hormones use second messengers other than cAMP. For example, a second messenger called diacylglycerol (DAG), like cAMP, activates a protein kinase, leading to a cellular response.

In another mechanism, a hormone binding its receptor increases calcium ion concentration in the cell. Such a hormone may stimulate transport of calcium ions inward through the cell membrane or induce release of calcium ions from cellular storage sites via a second messenger called inositol triphosphate (IP3). The calcium ions combine with the

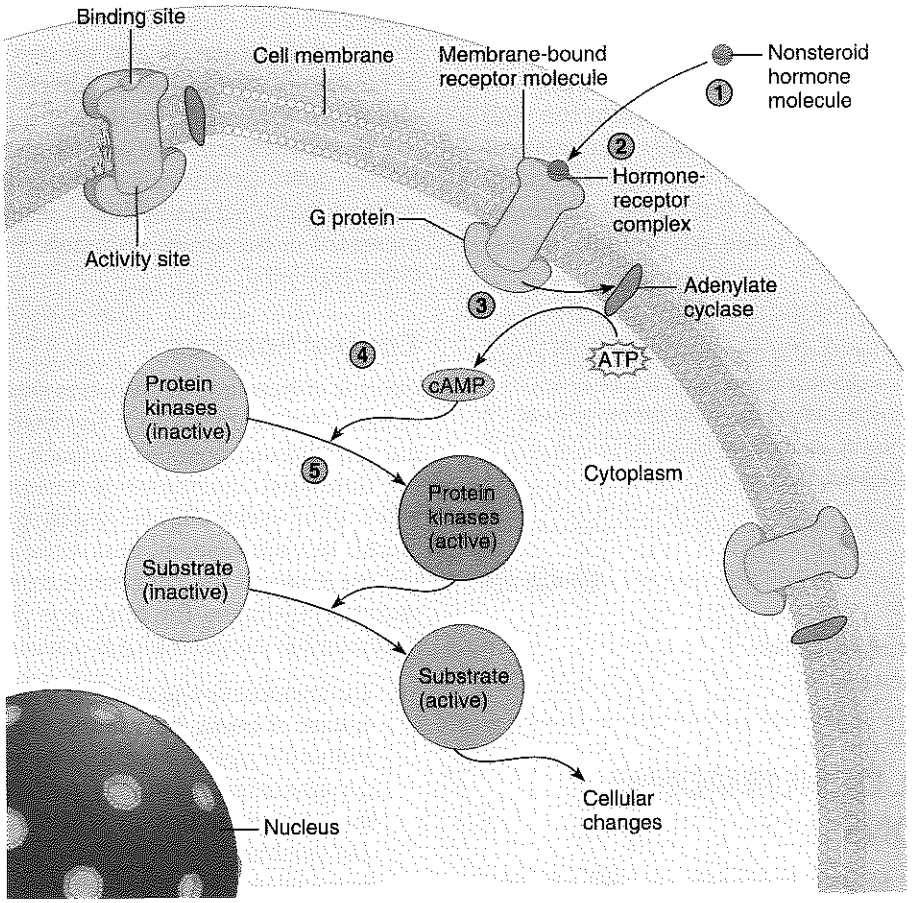


FIGURE 13.7 AP R Nonsteroid hormone action. (*1*) Body fluids carry nonsteroid hormone molecules to the target cell, where (*2*) they bind receptor molecules on the cell membrane. (*3*) This activates molecules of adenylate cyclase, which (*4*) catalyze conversion of ATP into cyclic adenosine monophosphate (cAMP). (*5*) The cAMP promotes a series of reactions leading to the cellular changes associated with the hormone's action.

protein *calmodulin* (see chapter 9, p. 309), altering its molecular structure in a way that activates the molecule. Activated calmodulin can then interact with enzymes, altering their activities and thus eliciting diverse responses.

Still another hormonal mechanism uses *cyclic guanosine monophosphate* (cyclic GMP, or cGMP). Like cAMP, cGMP is a nucleotide derivative and functions in much the same manner as a second messenger.

The cellular response to a hormone operating through a second messenger is greatly amplified. This is possible because many second messenger molecules can be activated in response to just a few hormone-receptor complexes, and the enzymes that are activated as a result can repeatedly catalyze reactions. Since existing proteins are being activated, the response is fast. Cells are highly sensitive to changes in the concentrations of nonsteroid hormones because of such rapid amplification. Cellular response to a steroid hormone (and thyroid hormones) is directly proportional to the number of hormone-receptor complexes that form. Some amplification does occur since more than one mRNA may be transcribed when a gene is activated, and each mRNA may be translated into multiple copies of a protein. The response is much slower than the response to hormones acting through second messengers, although the response is longer lasting.

PRACTICE

4 How does a steroid hormone act on its target cells?

5 How does a nonsteroid hormone act on its target cells?

6 What is a second messenger?

Prostaglandins

Prostaglandins are paracrine substances, acting locally, that are potent and present in small amounts. They are not stored in cells but are synthesized just before they are released. They are rapidly inactivated.

Some prostaglandins regulate cellular responses to hormones. For example, different prostaglandins can either activate or inactivate adenylate cyclase in cell membranes, thereby controlling production of cAMP and altering the cell's response to a hormone.

Prostaglandins produce a variety of effects. Some prostaglandins relax smooth muscle in the airways of the lungs and

in the blood vessels, dilating these passageways. Yet other prostaglandins can contract smooth muscle in the walls of the uterus, causing menstrual cramps and labor contractions. They stimulate secretion of hormones from the adrenal cortex and inhibit secretion of hydrochloric acid from the wall of the stomach. Prostaglandins also influence movements of sodium ions and water in the kidneys, help regulate blood pressure, and have powerful effects on both male and female reproductive physiology. When tissues are injured, prostaglandins promote inflammation.

Understanding prostaglandin function has medical applications. Drugs such as aspirin and certain steroids that relieve the joint pain of rheumatoid arthritis inhibit production of prostaglandins in the synovial fluid of affected joints. Daily low doses of aspirin may reduce the risk of heart attack by altering prostaglandin activity.

PRACTICE

7 What are prostaglandins?

8 Describe one function of prostaglandins.

9 List effects of prostaglandins.

13.4 CONTROL OF HORMONAL SECRETIONS

The body must be able to turn processes on and off. For example, removal of acetylcholine from the neuromuscular junction stops skeletal muscle contraction. In the case of hormones, a measurement called the half-life indicates rate of removal. Half-life is the time it takes for half of the hormone molecules to be removed from the plasma. For example, a hormone with a half-life of ten minutes would start out at 100% of its blood concentration, and if secretion were to stop, it would drop to 50% in ten minutes, 25% in another ten minutes, 12.5% in another ten minutes, and so on. Hormones with short half-lives (a few minutes) control body functions that turn on and off quickly, whereas the effects of hormones with longer half-lives, such as thyroid hormone and steroids, may last for days.

Hormones are continually excreted in the urine and broken down by enzymes, primarily in the liver. Therefore, increasing or decreasing blood levels of a hormone requires increased or decreased secretion. Hormone secretion is precisely regulated.

Control Sources

Control of hormone secretion is essential to maintaining the internal environment. In a few cases, primarily in the reproductive systems, positive feedback affects this control.

Generally, hormone secretion is controlled in three ways, all of which employ **negative feedback** (see chapter 1, p. 18). In each case, an endocrine gland or the system controlling it senses the concentration of the hormone the gland secretes, a process the hormone controls, or an action the hormone has on the internal environment (fig. 13.8).

1. The hypothalamus controls the anterior pituitary gland's release of **tropic hormones,** which stimulate other endocrine glands to release hormones (fig. 13.8*a*). The hypothalamus constantly receives information about the internal environment from neural connections and cerebrospinal fluid. This is possible because the hypothalamus is near the thalamus and the third ventricle (fig. 13.9).
2. The nervous system directly stimulates some glands. The adrenal medulla, for example, secretes its hormones (epinephrine and norepinephrine) in response to impulses from preganglionic sympathetic neurons. The secretory cells replace the postganglionic sympathetic neurons, which would normally secrete norepinephrine alone as a neurotransmitter (see fig. 13.8*b*).

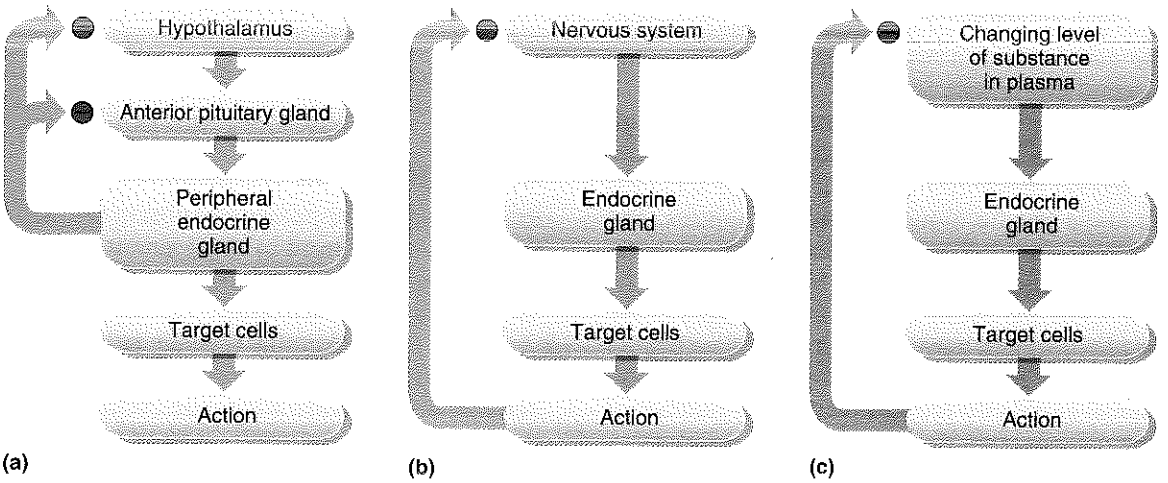


FIGURE 13.8 Examples of endocrine system control: (*a*) one way the hypothalamus controls the anterior pituitary, (*b*) the nervous system controls some glands directly, and (c) some glands respond directly to changes in the internal environment. ● indicates negative feedback inhibition.

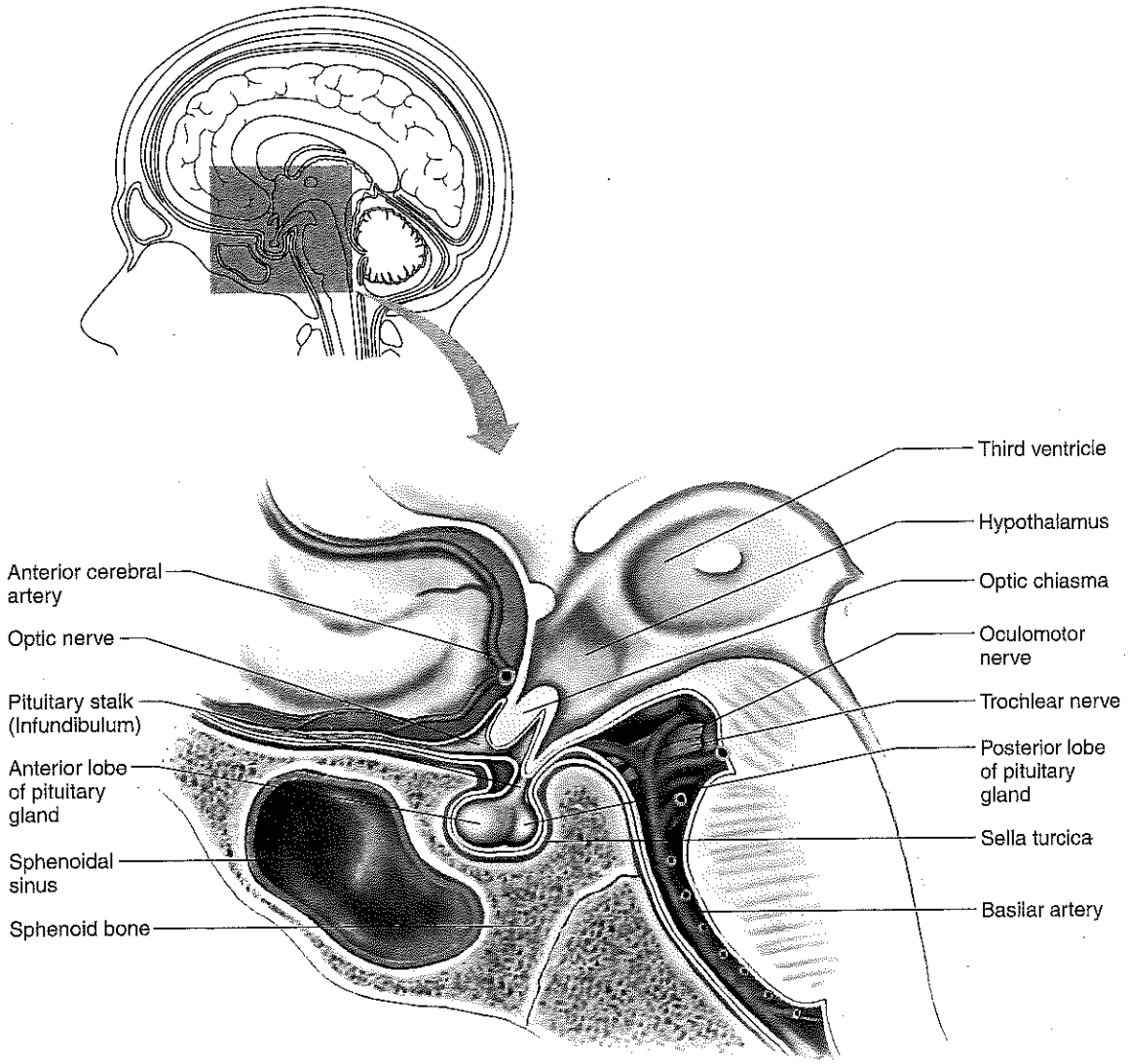


FIGURE 13.9 AP R The pituitary gland is attached to the hypothalamus and lies in the sella turcica of the sphenoid bone.

3. Another group of glands responds directly to changes in the composition of the internal environment. For example, when the blood glucose level rises, the pancreas secretes insulin, and when the blood glucose level falls, it secretes glucagon (see "Hormones of the Pancreatic Islets" on p. 514 and fig. 13.8c).

In each of these cases, as hormone levels rise in the blood and the hormone exerts its effects, negative feedback inhibits the system and hormone secretion decreases. Then, as hormone levels in the blood decrease and the hormone's effects wane, inhibition of the system ceases, and secretion of that hormone increases again (fig. 13.10). As a result of negative feedback, hormone levels in the bloodstream remain relatively stable, fluctuating slightly around an average value (fig. 13.11).

PRACTICE

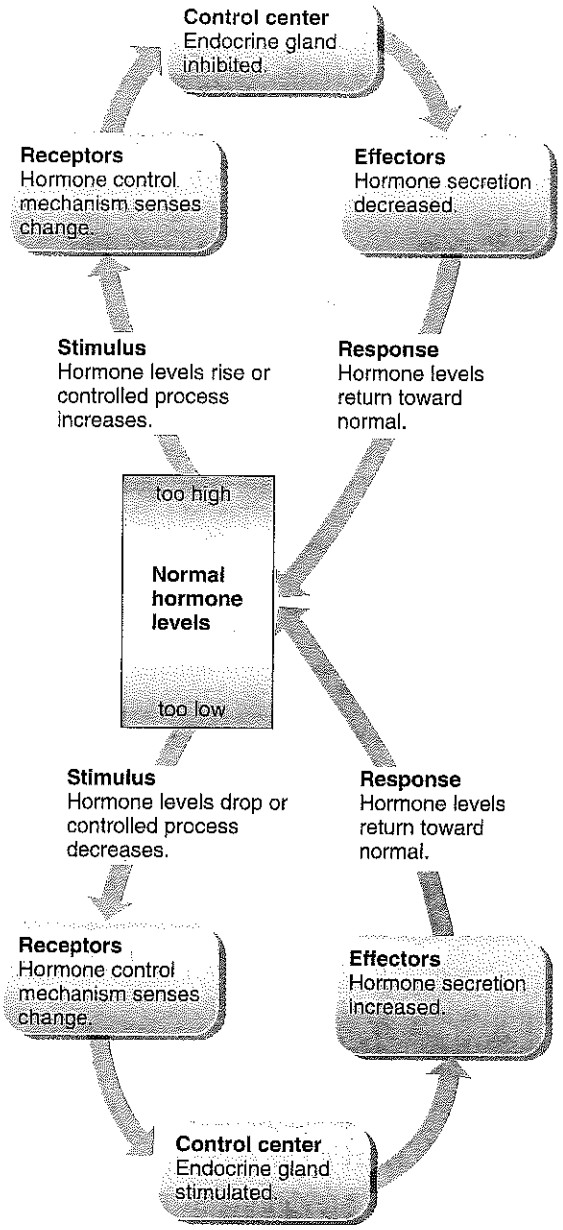
10 How does the nervous system help regulate hormonal secretions?

11 How does a negative feedback system control hormonal secretion?

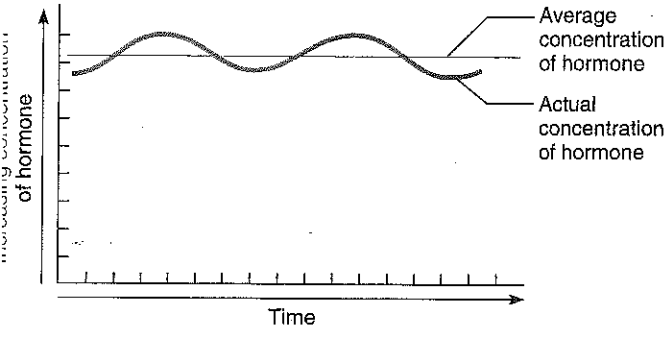
13.5 PITUITARY GLAND

The **pituitary** (pĭ-tu'ĭ-tār"e) **gland** (hypophysis), at the base of the brain, is about one centimeter in diameter. It is attached to the hypothalamus by the pituitary stalk, or *infundibulum,* and lies in the sella turcica of the sphenoid bone, as figure 13.9 shows.

The pituitary gland consists of two distinct portions: an *anterior lobe* (adenohypophysis) and a *posterior lobe* (neurohypophysis). The anterior lobe secretes a number of hormones, including growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). The cells that make up the posterior lobe (pituicytes) do not synthesize hormones. However, specialized neurons called neurosecretory cells, whose axon endings enter the posterior lobe of the pituitary, secrete into the bloodstream two important hormones: antidiuretic hormone (ADH) and oxytocin (OT). The cell bodies of these neurosecretory cells are in the hypothalamus.



GURE 13.10 Hormone secretion is under negative feedback control.



GURE 13.11 As a result of negative feedback, hormone concentrations nain relatively stable, although they may fluctuate slightly above and below erage concentrations.

In the fetus, a narrow region develops between the anterior and posterior lobes of the pituitary gland. Called the *intermediate lobe* (pars intermedia), it produces melanocyte-stimulating hormone (MSH), which regulates the synthesis of melanin—the pigment in skin and in parts of the eyes and brain. In most adults this intermediate lobe is no longer a distinct structure, but its secretory cells persist in the two remaining lobes.

The brain controls most of the pituitary gland's activities (fig. 13.12). The pituitary gland's posterior lobe releases hormones into the bloodstream in response to impulses conducted on the axons of the neurosecretory cells. A different mechanism controls the anterior lobe. Here, **releasing hormones** from the hypothalamus primarily control secretion. These releasing hormones are carried in the blood via a capillary bed associated with the hypothalamus. The vessels merge to form the **hypophyseal** (hi"po-fiz'e-al) **portal veins** that pass downward along the pituitary stalk and give rise to a second capillary bed in the anterior lobe. In this way, substances released into the blood from the hypothalamus are carried directly to the anterior lobe. The hypothalamus, therefore, is an endocrine gland, yet it also controls other endocrine glands. This is also true of the anterior pituitary.

The arrangement of two capillaries in series is unusual and is called a *portal system*. It exists in three places in the body: the hepatic portal vein connects intestinal capillaries to special liver capillaries called sinusoids, the efferent arteriole of kidney nephrons connects two sets of capillaries, and the hypophyseal portal vein gives rise to a capillary net in the anterior lobe of the pituitary gland.

Each of the hypothalamic releasing hormones acts on a specific population of cells upon reaching the anterior lobe of the pituitary gland. Some of the resulting actions are inhibitory (prolactin release-inhibiting hormone and somatostatin), but most stimulate the anterior pituitary to release hormones that stimulate the secretions of peripheral endocrine glands. In many of these cases, important negative feedback relationships regulate hormone levels in the bloodstream. Figure 13.13 shows this general relationship.

PRACTICE

12 Where is the pituitary gland?

13 List the hormones that the anterior and posterior lobes of the pituitary gland secrete.

14 Explain how the hypothalamus controls the actions of the pituitary gland.

Anterior Pituitary Hormones

The anterior lobe of the pituitary gland is enclosed in a dense capsule of collagenous connective tissue and largely consists of epithelial tissue organized in blocks around many thin-

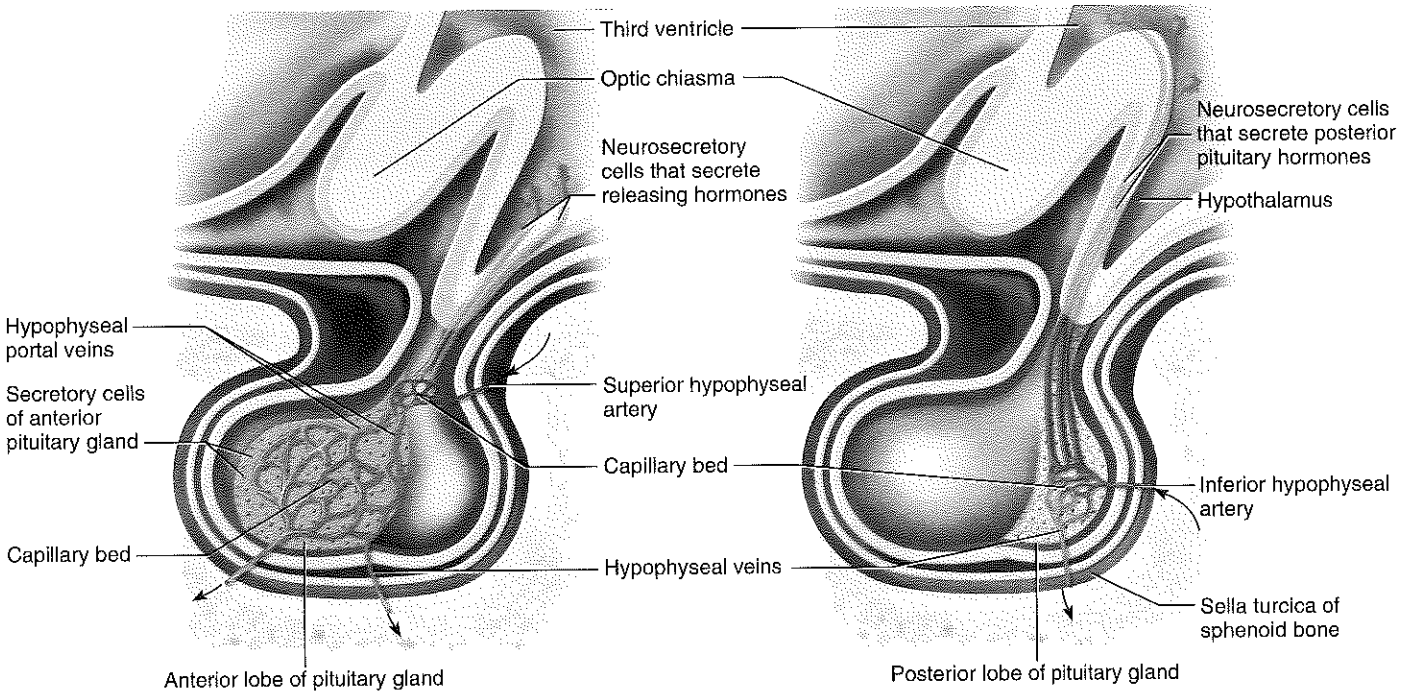


FIGURE 13.12 AP|R Hypothalamic releasing hormones stimulate cells of the anterior lobe to secrete hormones. Nerve impulses originating in the hypothalamus stimulate nerve endings in the posterior lobe of the pituitary gland to release hormones.

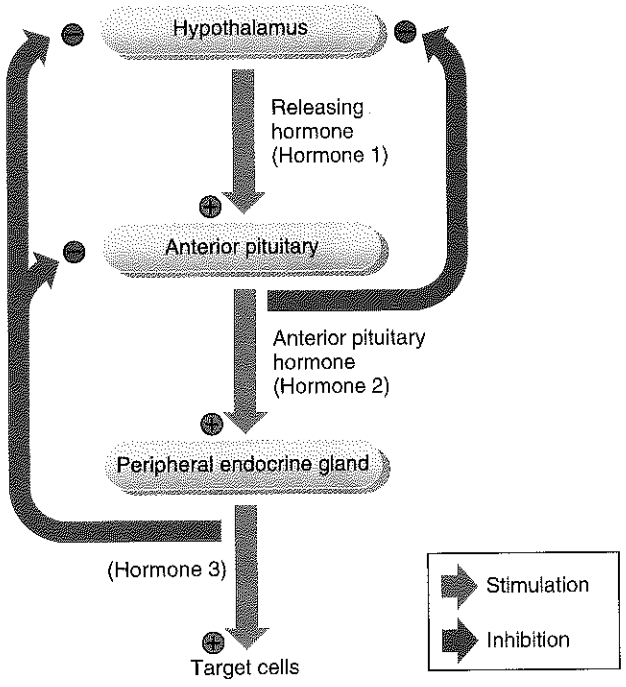


FIGURE 13.13 Hypothalamic control of the peripheral endocrine glands may use as many as three types of hormones, with multiple negative feedback controls. (⊕ = stimulation; ⊖ = inhibition)

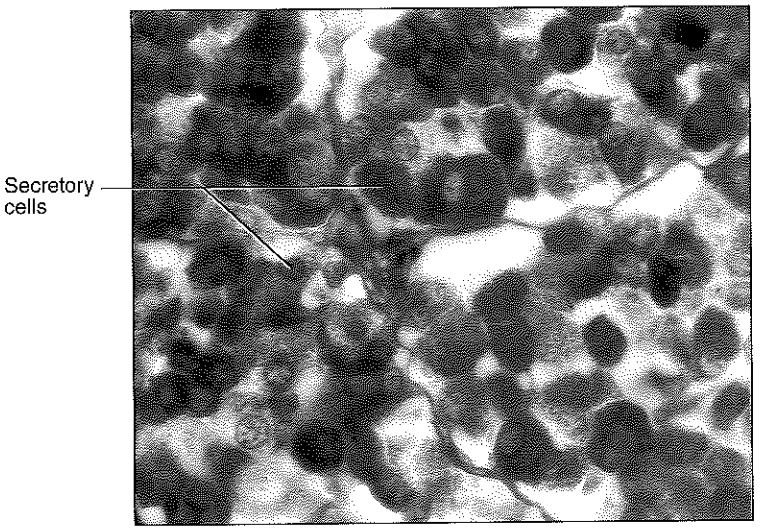


FIGURE 13.14 AP|R Light micrograph of the anterior pituitary gland (240×

walled blood vessels. The epithelial tissue has five types of secretory cells. They are *somatotropes* that secrete GH, *mammatropes* that secrete PRL, *thyrotropes* that secrete TSH, *corticotropes* that secrete ACTH, and *gonadotropes* that secrete FSH and LH (figs. 13.14 and 13.15). In males, LH (lutein-

izing hormone) is sometimes referred to as ICSH (interstitial cell-stimulating hormone) because it affects the interstitial cells of the testes (see chapter 22, p. 837).

Growth hormone, also called *somatotropin* (or somatotrophic hormone, STH), is a protein that stimulates cells to enlarge and more rapidly divide. It enhances the movement of amino acids through cell membranes and increases the rate of protein synthesis. GH also decreases the rate at which cells use carbohydrates and increases the rate at which they use fats.

Growth hormone secretion varies during the day, peaking during sleep. Two biochemicals from the hypothalamus control its secretion. They are released alternately, exerting opposite

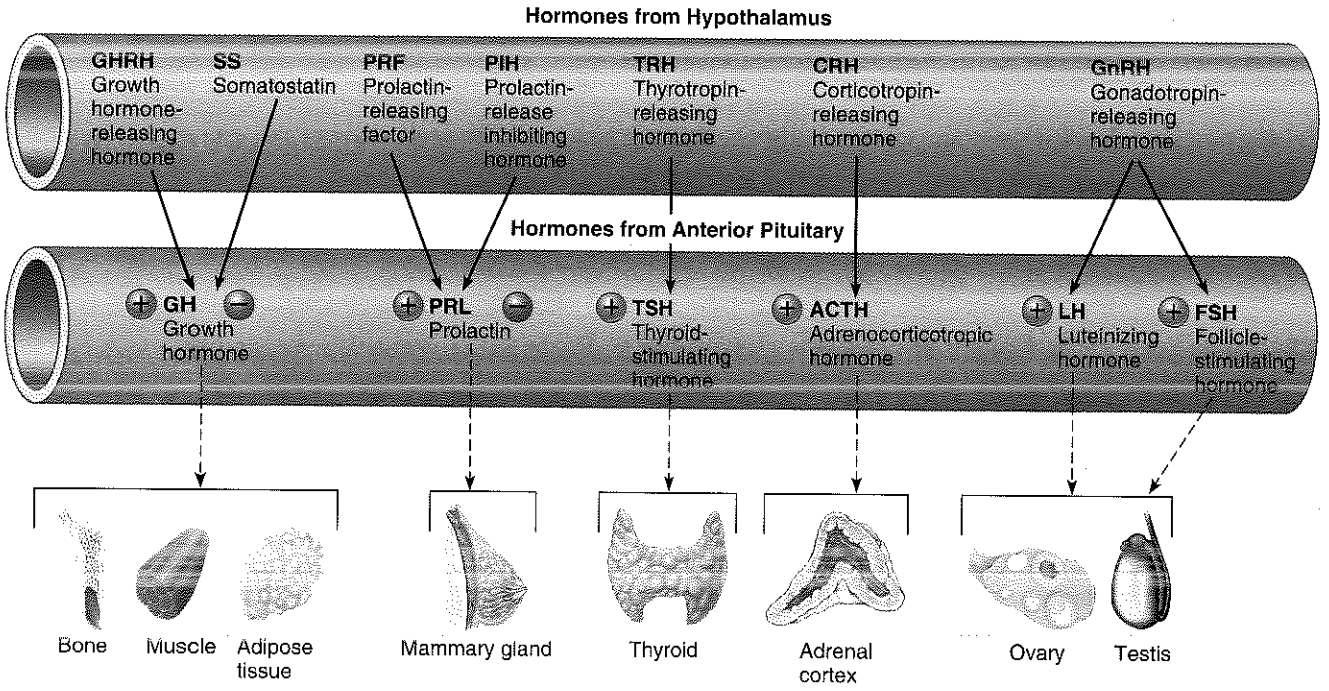


FIGURE 13.15 Hormones released from the hypothalamus, the corresponding hormones released from the anterior lobe of the pituitary gland, and their target organs.

effects. *Growth hormone-releasing hormone* (GHRH) stimulates secretion of GH, and *somatostatin* (SS) inhibits secretion.

Nutritional state can affect control of GH. More GH is released during periods of protein deficiency and abnormally low blood glucose concentration. Conversely, when blood protein and glucose concentrations increase, growth hormone secretion decreases. Apparently the hypothalamus can sense changes in the concentrations of certain blood nutrients and it releases GHRH in response to some of them.

Growth hormone can stimulate elongation of bone tissue directly, but its effect on cartilage requires a mediator protein, insulin-like growth factor-1 (IGF-1). Growth hormone releases IGF-1 from the liver and other tissues. Clinical Application 13.2 discusses some clinical uses of growth hormone.

Prolactin is a protein, and as its name suggests, it promotes milk production. No normal physiological role for this hormone in human males has been firmly established. Abnormally elevated levels of the hormone can disrupt sexual function in both sexes.

Prolactin secretion is mostly under inhibitory control by dopamine from the hypothalamus, which is also called *prolactin release-inhibiting hormone* (PIH). The hypothalamus likely releases more than one *prolactin-releasing factor* (PRF).

Thyroid-stimulating hormone, also called *thyrotropin*, is a glycoprotein. It controls secretion of certain hormones from the thyroid gland. TSH can also stimulate growth of the gland, and abnormally high TSH levels may lead to an enlarged thyroid gland, or *goiter.*

The hypothalamus partially regulates TSH secretion by producing thyrotropin-releasing hormone (TRH). Circulating thyroid hormones help regulate TSH secretion by inhibiting release of TRH and TSH. Therefore, as the blood concentration of thyroid hormones increases, secretion of TRH and TSH declines (fig. 13.16).

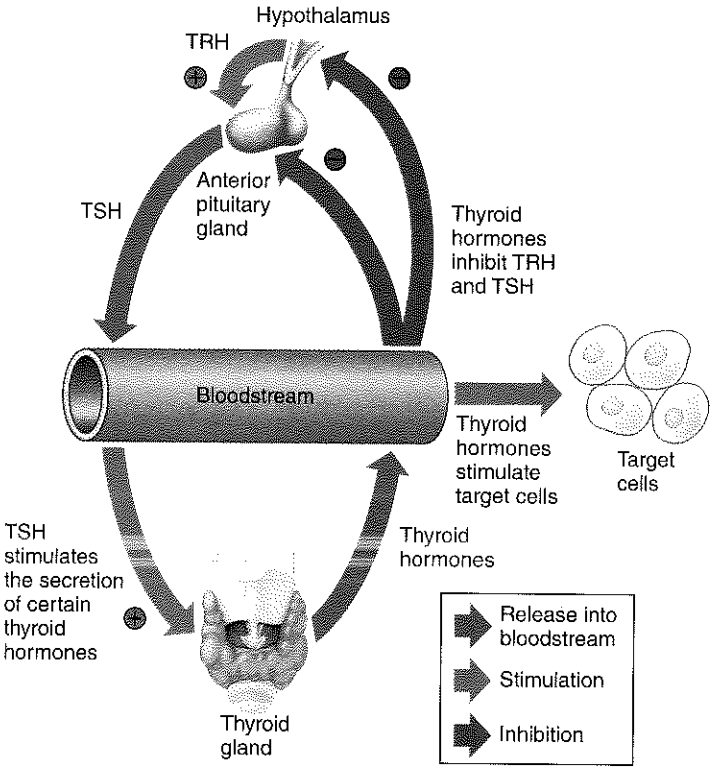


FIGURE 13.16 Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to release hormones. These thyroid hormones reduce the secretion of TSH and TRH by negative feedback. (⊕ = stimulation; ● = inhibition)

External factors influence release of TRH and TSH. Exposure to extreme cold, for example, increases hormonal secretion. Emotional stress can either increase or decrease TRH and TSH secretion, depending upon circumstances.

13.2 CLINICAL APPLICATION

Growth Hormone Ups and Downs

Insufficient secretion of human growth hormone (HGH) during childhood produces *hypopituitary dwarfism*. Body proportions and mental development are normal, but because secretion of other anterior pituitary hormones is also below normal, additional hormone deficiency symptoms may appear. For example, a child with growth hormone deficiency might not develop adult sexual features without hormone therapy.

HGH used as a drug can treat hypopituitary dwarfism if administration begins before the bones completely ossify. It is also used to treat conditions that include very short stature but in which HGH is not deficient, such as chronic renal failure, Turner syndrome, intrauterine growth retardation, and Prader-Willi syndrome. HGH may delay muscle wasting in people who have AIDS.

The reputation of HGH as an anti-aging agent stems from a 1990 study in which a dozen men over age sixty who received the hormone showed slight improvements in muscle mass and bone mineral density. Interpretation of this limited study to indicate that HGH reverses aging fueled claims that the hormone staves off the ravages of time. More recently studies have shown that although HGH given to older individuals can increase muscle mass and decrease fat, it does not improve strength. Taking HGH supplements could merely replace some fat with water. Excess HGH can cause joint pain and swelling and increased risk of diabetes mellitus. A long-term study of people with dwarfism due to a mutation in the gene that encodes the HGH receptor found that they do not develop diabetes or cancer, suggesting a possible protective effect of limiting exposure to the hormone.

Oversecretion of growth hormone in childhood may result in *gigantism*, in which height may eventually exceed 8 feet. Gigantism is usually caused by a tumor of the pituitary gland, which secretes excess pituitary hormones, including HGH. As a result, a person with gigantism may have other metabolic disturbances. An inherited form of gigantism is seen in families in Ireland.

Growth hormone oversecretion in an adult after the epiphyses of the long bones have ossified causes a condition called acromegaly. The person does not grow taller, but soft tissues continue to enlarge and bones thicken, producing a large tongue, nose, hands, and feet, and a protruding jaw. The heart and thyroid enlarge. Early symptoms include headache, joint pain, fatigue, and depression. A pituitary tumor or abuse of growth hormone (as a drug) can cause acromegaly (fig. 13A). ■

FIGURE 13A Natural oversecretion of growth hormone in adulthood causes acromegaly. Note the changes in this woman's facial features at ages (*a*) nine, (*b*) sixteen, (*c*) thirty-three, and (*d*) fifty-two.

After the thyroid gland is removed to treat cancer, an endocrinologist monitors a patient's TSH level to determine the appropriate daily dose of synthetic thyroid hormone. Enough thyroid hormone must be taken to suppress secretion of TSH. TSH is a useful marker for thyroid hormone levels because of negative feedback, even though TSH itself would be ineffectual because the thyroid gland is no longer present.

PRACTICE

15 How does growth hormone affect the cellular metabolism of carbohydrates, fats, and proteins?

16 What are the functions of prolactin?

17 How is TSH secretion regulated?

Adrenocorticotropic (ah-dre"no-kor"te-ko-trōp'ik) **hormone** is a peptide that controls the manufacture and secretion of certain hormones from the outer layer (cortex) of the adrenal gland. The secretion of ACTH is regulated in part by *corticotropin-releasing hormone* (CRH), which the hypothalamus releases in response to decreased concentrations of adrenal cortical hormones. Stress can increase secretion of ACTH by stimulating release of CRH.

Both **follicle-stimulating hormone** and **luteinizing** (lu'te'in-īz"ing) **hormone** are glycoproteins and are called *gonadotropins*, which means they act on the gonads or reproductive organs. FSH controls growth and development of follicles that house egg cells in the ovaries. It also stimulates the follicular cells to secrete a group of female sex hormones, collectively called *estrogen* (or estrogens).

In males, FSH stimulates the production of sperm cells in the testes. LH promotes secretion of sex hormones in both males and females and is essential for release of egg cells from the ovaries. Other functions of the gonadotropins and their interactions are discussed in chapter 22 (pp. 837, 847–849).

The mechanism that regulates secretion of gonadotropins is not well understood. However, starting at puberty, the hypothalamus secretes a *gonadotropin-releasing hormone* (GnRH). Gonadotropins are absent in the body fluids of infants and children.

PRACTICE

18 What is the function of ACTH?

19 What is a gonadotropin?

20 Describe the functions of FSH and LH in a female and in a male.

Posterior Pituitary Hormones

The posterior lobe of the pituitary largely consists of nerve fibers and neuroglia *(pituicytes)*. This is unlike the anterior lobe, which is primarily glandular epithelium. Neuroglia support the nerve fibers that originate in the hypothalamus. The hypothalamic cells that give rise to these fibers are called neurosecretory cells because their secretions function not as neurotransmitters but as hormones (see fig. 13.12).

Specialized neurons in the hypothalamus produce the two hormones associated with the posterior pituitary—**antidiuretic** (an″tĭ-di″u-ret′ik) **hormone** (also known as *vasopressin*) and **oxytocin** (ok″sĭ-to′sin). These hormones are transported down axons through the pituitary stalk to the posterior pituitary and are stored in vesicles (secretory granules) near the ends of the axons. The hormones are released into the blood in response to action potentials conducted on the axons of the neurosecretory cells. Therefore, posterior pituitary hormones are synthesized in the hypothalamus, and their secretion is controlled by the hypothalamus, but they are named for where they enter the bloodstream.

Antidiuretic hormone and oxytocin are short polypeptides with similar sequences (fig. 13.17). A *diuretic* is a chemical that increases urine production. An *antidiuretic*, then, is a chemical that decreases urine formation. ADH produces its antidiuretic effect by reducing the volume of water that the kidneys excrete. In this way, ADH plays an important role in regulating the concentration of body fluids (see chapter 20, pp. 787–789).

Frequent and copious urination often follows drinking alcoholic beverages, because ethyl alcohol inhibits ADH secretion. A person must replace the lost body fluid to maintain normal water balance. Drinking too much beer can actually lead to dehydration because the body loses more fluid than is being added.

Sufficient concentration of ADH contracts certain smooth muscles, including those in the walls of blood vessels. As a result, vascular resistance and blood pressure may increase.

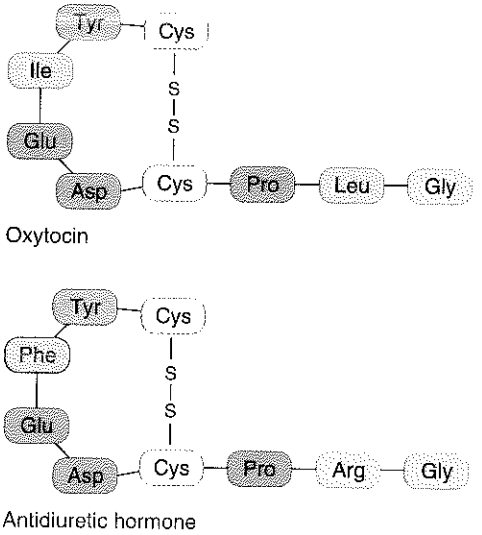


FIGURE 13.17 AP|R The structure of oxytocin differs from that of ADH by only two amino acids, yet they function differently.

(This is why ADH is also called vasopressin.) Although ADH is seldom at high enough levels to cause high blood pressure, its secretion increases following severe blood loss. In this situation, ADH's vasoconstrictor effect may help to minimize the drop in blood pressure that results from profuse bleeding and return blood pressure toward normal.

ADH's two effects—vasoconstriction and water retention—are possible because the hormone binds two different receptors on target cells. The binding of ADH to V1 receptors increases the concentration of the second messenger inositol triphosphate, which increases the intracellular calcium ion concentration in the smooth muscle of blood vessel walls, leading to vasoconstriction. The second receptor, V2, is on parts of the kidneys' microscopic tubules called collecting ducts. ADH binding there activates the cAMP second messenger system, which ultimately causes collecting duct cells to reabsorb water that would otherwise be excreted as urine.

The hypothalamus regulates ADH secretion. Certain neurons in this part of the brain, called *osmoreceptors*, sense changes in the concentration of body fluids. For example, if a person is dehydrating due to a lack of water intake, the solutes in blood become more concentrated. The osmoreceptors, sensing the resulting increase in osmotic pressure, signal the posterior pituitary to release ADH, which causes the kidneys to retain water. On the other hand, if a person drinks a large volume of water, body fluids become more dilute, which inhibits the release of ADH. In response, the kidneys excrete a more dilute urine until the concentration of body fluids returns to normal.

Blood volume also affects ADH secretion. Increased blood volume stretches the walls of certain blood vessels, stimulating volume receptors that signal the hypothalamus to inhibit release of ADH. However, if hemorrhage decreases blood volume, these receptors are stretched less and therefore send fewer inhibiting impulses. As a result, ADH secretion increases and the kidneys conserve water, countering further volume loss.

The baby first displayed symptoms at five months of age—he drank huge volumes of water. By thirteen months, he had become severely dehydrated, despite nearly continuous drinking. He had a form of *diabetes insipidus*, which impairs ADH regulation of water balance. The boy was drinking sufficient fluids, but his kidneys could not retain the water because ADH V2 receptors on the kidney collecting ducts were defective. The hormone could bind, but the receptor failed to trigger cAMP formation. The boy's ADH was still able to constrict blood vessels because the V1 receptors were unaffected. A high-calorie diet and providing lots of water preserved the boy's mental abilities, but he remained small for his age. Tumors and injury affecting the hypothalamus and posterior pituitary can also cause diabetes insipidus.

Oxytocin also has an antidiuretic action, but less so than ADH. In addition, oxytocin can contract smooth muscles in the uterine wall, playing a role in the later stages of childbirth. The uterus becomes more sensitive to oxytocin's effects during pregnancy. Stretching of uterine and vaginal tissues late in pregnancy, as the fetus grows, initiates sensory impulses to the hypothalamus, which then signals the posterior pituitary to release oxytocin, which, in turn, stimulates the uterine contractions of labor.

In the breasts, oxytocin contracts certain cells near the milk-producing glands and their ducts. In lactating breasts, this action forces liquid from the milk glands into the milk ducts and ejects the milk.

The mechanical stimulation of suckling initiates sensory impulses that travel to the mother's hypothalamus, which signals the posterior pituitary to release oxytocin, which, in turn, stimulates milk release. Milk is normally not ejected from the milk glands and ducts until the baby suckles. The fact that milk is ejected from both breasts in response to suckling is a reminder that all target cells respond to a hormone.

Oxytocin may be given intravenously to stimulate uterine contractions, inducing labor, if the uterus is not sufficiently contracting to expel a fully developed fetus. Oxytocin also may be administered to the mother following childbirth to ensure that the uterine muscles contract enough to squeeze broken blood vessels closed, minimizing bleeding.

Oxytocin has no established function in males, although it is present in the male posterior pituitary and it may stimulate the movement of certain fluids in the male reproductive tract during sexual activity. Oxytocin is also called the "cuddle hormone," because animal studies link it to bonding between mother and offspring. Studies on pregnant women also show that higher levels of the hormone during pregnancy correlate to more intense maternal bonding behavior with the infant, such as more eye contact, touching, and singing. Table 13.6 reviews the hormones of the pituitary gland.

PRACTICE

21 What is the function of ADH?

22 How is the secretion of ADH controlled?

23 What effects does oxytocin produce in females?

TABLE 13.6 | Hormones of the Pituitary Gland

Anterior Lobe	Action	Source of Control
Growth hormone (GH)	Stimulates increase in size and rate of division of body cells; enhances movement of amino acids through membranes; promotes growth of long bones	Secretion inhibited by somatostatin (SS) and stimulated by growth hormone-releasing hormone (GHRH) from the hypothalamus
Prolactin (PRL)	Sustains milk production after birth; amplifies the effect of LH in males	Secretion inhibited by prolactin release-inhibiting hormone (PIH) and may be stimulated by yet to be identified prolactin-releasing factor (PRF) from the hypothalamus
Thyroid-stimulating hormone (TSH)	Controls secretion of hormones from the thyroid gland	Thyrotropin-releasing hormone (TRH) from the hypothalamus
Adrenocorticotropic hormone (ACTH)	Controls secretion of certain hormones from the adrenal cortex	Corticotropin-releasing hormone (CRH) from the hypothalamus
Follicle-stimulating hormone (FSH)	Development of egg-containing follicles in ovaries; stimulates follicular cells to secrete estrogen; in males, stimulates production of sperm cells	Gonadotropin-releasing hormone (GnRH) from the hypothalamus
Luteinizing hormone (LH)	Promotes secretion of sex hormones; releases egg cell in females	Gonadotropin-releasing hormone (GnRH) from the hypothalamus
Posterior Lobe	**Action**	**Source of Control**
Antidiuretic hormone (ADH)	Causes kidneys to reduce water excretion; in high concentration, raises blood pressure	Hypothalamus in response to changes in body fluid concentration and blood volume
Oxytocin (OT)	Contracts muscles in uterine wall and those associated with milk-secreting glands	Hypothalamus in response to stretching uterine and vaginal walls and stimulation of breasts

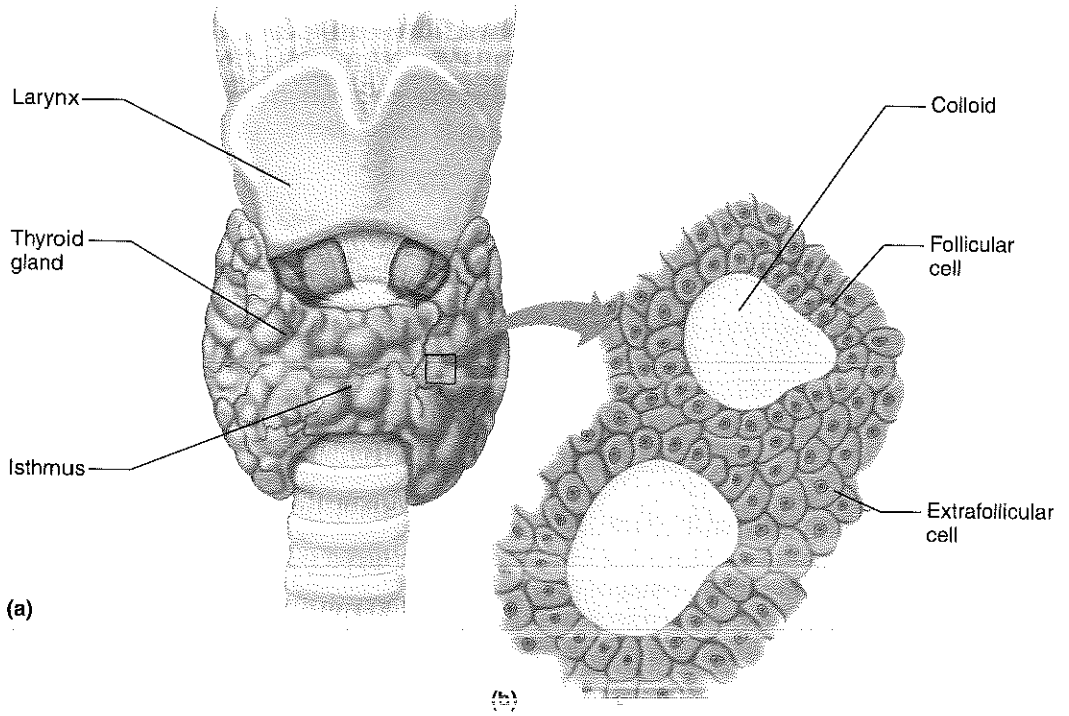


FIGURE 13.18 AP|R Thyroid gland. (*a*) The thyroid gland consists of two lobes connected anteriorly by an isthmus. (*b*) Follicular cells secrete thyroxine and triiodothyronine. Extrafollicular cells secrete calcitonin.

13.6 THYROID GLAND

The **thyroid gland** (thi'roid gland), as figure 13.18 shows, is a vascular structure that consists of two large lateral lobes connected by a broad **isthmus** (is'mus). The thyroid lies just below the larynx (voicebox) on either side and anterior to the trachea (windpipe). The gland is specialized to remove iodine from the blood.

Structure of the Gland

A capsule of connective tissue covers the thyroid gland, which is made up of many secretory parts called *follicles*. The follicles have cavities that are lined with a single layer of cuboidal epithelial cells, called follicular cells. These cavities are filled with a clear viscous substance called *colloid*, which consists primarily of a glycoprotein called *thyroglobulin*. The follicular cells produce and secrete hormones that are either stored in the colloid or released into nearby capillaries (fig. 13.19). Other hormone-secreting cells, called *extrafollicular cells* (C cells), lie outside the follicles.

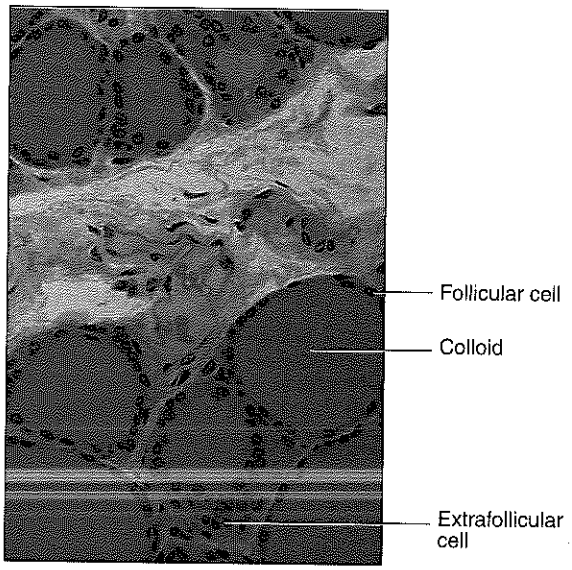
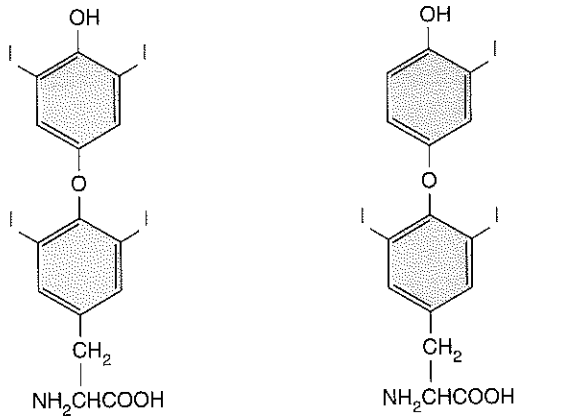


FIGURE 13.19 AP|R A light micrograph of thyroid gland tissue (240×). The open spaces that follicular cells surround are filled with colloid.

Thyroid Hormones

The thyroid gland produces three important hormones. The follicular cells synthesize two of these, which have marked effects on the metabolic rates of body cells. The extrafollicular cells produce the third type of hormone, which influences blood concentrations of calcium and phosphate ions.

The two important thyroid hormones that affect cellular metabolic rates are **thyroxine** (thi-rok'sin), or tetraiodothyronine, also called T_4 because it includes four atoms of iodine, and **triiodothyronine** (tri"i-o"do-thi'ro-nēn), also called T_3 because it includes three atoms of iodine (fig. 13.20). These hormones help regulate the metabolism of carbohydrates, lipids, and proteins. Specifically, thyroxine and triiodothyronine increase the rate at which cells release energy from carbohydrates, enhance the rate of protein synthesis, and stimulate breakdown and mobilization of lipids. These hormones are the major factors determining how many calories the body must consume at rest to maintain life, measured as



Thyroxine (T_4) Triiodothyronine (T_3)

FIGURE 13.20 The hormones thyroxine and triiodothyronine have very similar molecular structures.

the *basal metabolic rate* (BMR). They are essential for normal growth and development and for maturation of the nervous system. TSH from the anterior pituitary gland controls the levels of thyroid hormones.

Follicular cells require iodine salts (iodides) to produce thyroxine and triiodothyronine. Such salts are normally obtained from foods, and after they have been absorbed from the intestine, the blood carries some of them in the form of iodide (I^-) to the thyroid gland. An efficient active transport protein called the *iodide pump* moves the iodides into the follicular cells, where they are converted to iodine and concentrated. The iodine, with the amino acid tyrosine, is used to synthesize these thyroid hormones.

Follicular cells synthesize thyroglobulin, whose protein portion includes molecules of tyrosine, many of which have already had iodine attached by an enzymatic reaction. As the thyroglobulin protein twists and coils into its tertiary structure, bonds form between some of the tyrosine molecules, creating potential thyroid hormones waiting to be released. The follicular cells take up molecules of thyroglobulin by endocytosis, break down the protein, and release the individual thyroid hormones into the bloodstream. When the thyroid hormone levels in the bloodstream drop below a certain level, this process accelerates, returning thyroid hormone levels to normal.

Thyroxine (T_4) accounts for at least 95% of circulating thyroid hormones, but once in the blood, most of the T_3 and T_4 combine with blood proteins (alpha globulins). It is the small fraction of hormone molecules that are not protein-bound (so called "free" hormone) that act on target cells. Thus T_3, which has a 50-fold higher free concentration in the plasma, is physiologically more important. Additionally, T_3 is nearly five times more potent than T_4, and about a third of T_4 is converted to T_3 in peripheral tissues.

The thyroid gland produces **calcitonin**, which is usually not referred to as a "thyroid hormone" because it is synthesized by the C cells, distinct from the gland's follicles. Calcitonin plays a role in the control of blood calcium and phosphate ion concentrations. It helps lower concentrations of calcium and phosphate ions by decreasing the rate at which they leave the bones and enter extracellular fluids by inhibiting the bone-destroying activity of osteoclasts. At the same time, calcitonin increases the rate at which calcium and phosphate ions are deposited in bone matrix by stimulating activity of osteoblasts (see chapter 7, p. 211). Calcitonin also increases the excretion of calcium ions and phosphate ions by the kidneys.

A high blood calcium ion concentration stimulates calcitonin secretion. This may occur following absorption of calcium ions from a recent meal. Certain hormones also prompt calcitonin secretion, such as gastrin, released from active digestive organs. Calcitonin helps prevent prolonged elevation of the blood calcium ion concentration after eating.

Research suggests that calcitonin may be most important during early growth and physiological stress. In the young, calcitonin stimulates the increase in bone deposition associated with growth. In females, it helps protect bones from resorption during pregnancy and lactation, when calcium is required for growth of the fetus and synthesis of breast milk.

Table 13.7 summarizes the actions and sources of control of the thyroid hormones. From Science to Technology 2.1 (chapter 2, p. 62), table 13.8, and figures 13.21, 13.22, and 13.23 discuss disorders of the thyroid gland.

PRACTICE

24 Where is the thyroid gland located?

25 Which hormones of the thyroid gland affect carbohydrate metabolism, the mobilization of lipids, and protein synthesis?

26 What substance is essential for the production of thyroxine and triiodothyronine?

27 How does calcitonin influence the concentrations of blood calcium and phosphate ions?

TABLE 13.7 | Hormones of the Thyroid Gland AP|R

Hormone	Action	Source of Control
Thyroxine (T_4)	Increases rate of energy release from carbohydrates; increases rate of protein synthesis; accelerates growth; stimulates activity in the nervous system	TSH from the anterior pituitary gland
Triiodothyronine (T_3)	Same as above, but five times more potent than thyroxine	Same as above
Calcitonin	Lowers blood calcium and phosphate ion concentrations by inhibiting release of calcium and phosphate ions from bones and by increasing the rate at which calcium and phosphate ions are deposited in bones; increases excretion of calcium by the kidneys	Elevated blood calcium ion concentration, digestive hormones

TABLE **13.8** | Disorders of the Thyroid Gland

Condition	Mechanism/Symptoms
Hyperthyroid	
Hyperthyroidism	High metabolic rate, sensitivity to heat, restlessness, hyperactivity, weight loss, protruding eyes, goiter
Graves disease	Autoantibodies (against self) bind TSH receptors on thyroid cell membranes, mimicking action of TSH, overstimulating gland (hyperthyroidism); exopthalmia (protrusion of the eyes) and goiter
Hypothyroid	
Hashimoto disease	Autoantibodies (against self) destroy thyroid cells, resulting in hypothyroidism
Hypothyroidism (infantile)	Stunted growth, abnormal bone formation, intellectual disability, sluggishness
Hypothyroidism (adult)	Low metabolic rate, sensitivity to cold, sluggishness, poor appetite, swollen tissues, mental dullness
Simple goiter	Deficiency of thyroid hormones due to iodine deficiency; because no thyroid hormones inhibit pituitary release of TSH, thyroid is overstimulated and enlarges but functions below normal (hypothyroidism)

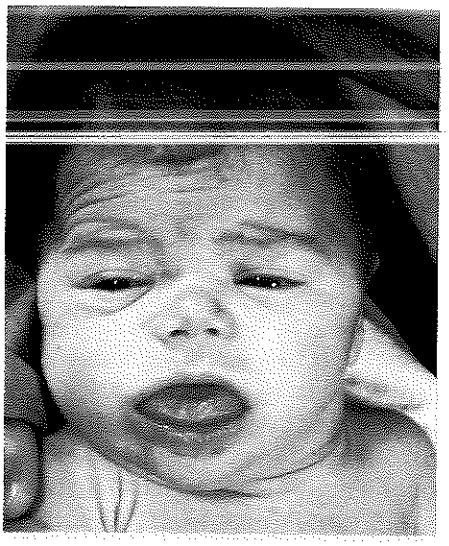


FIGURE 13.21 Infantile hypothyroidism is due to an underactive thyroid gland during infancy and childhood.

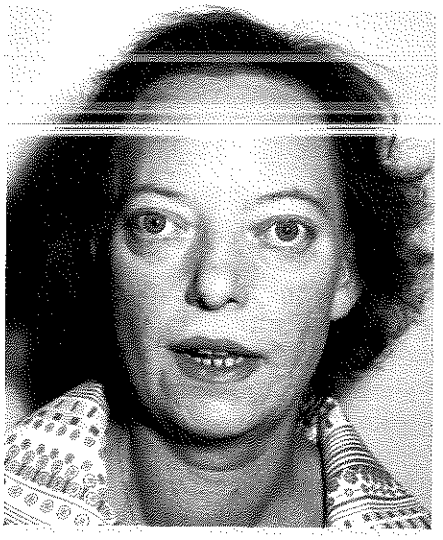


FIGURE 13.22 Graves disease may cause the eyes to protrude (exopthalmia).

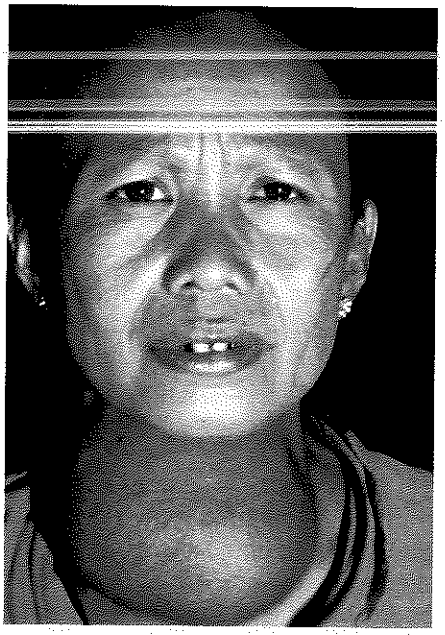


FIGURE 13.23 An iodine deficiency causes simple (endemic) goiter and results in high levels of TSH.

13.7 PARATHYROID GLANDS

The **parathyroid glands** (par″ah-thi′roid glandz) are on the posterior surface of the thyroid gland, as figure 13.24 shows. Usually there are four of them—a superior and an inferior gland associated with each of the thyroid's bilateral lobes. The parathyroid glands secrete a hormone that regulates the concentrations of calcium and phosphate ions in the blood.

Structure of the Glands

Each parathyroid gland is a small, yellowish brown structure covered by a thin capsule of connective tissue. The body of the gland consists of many tightly packed secretory cells closely associated with capillary networks (fig. 13.25).

Parathyroid Hormone

The parathyroid glands secrete a protein, **parathyroid hormone** (PTH), or *parathormone* (see fig. 13.4c). This hormone increases blood calcium ion concentration and decreases blood phosphate ion concentration through actions in the bones, kidneys, and intestines.

The extracellular matrix of bone tissue contains a considerable amount of calcium phosphate and calcium carbonate. PTH stimulates bone resorption by osteoclasts and inhibits the activity of osteoblasts (see chapter 7, p. 210). As bone resorption increases, calcium and phosphate ions are released into the blood. At the same time, PTH causes the kidneys to conserve blood calcium ions and to excrete more phosphate ions in the urine. PTH also indirectly stimulates

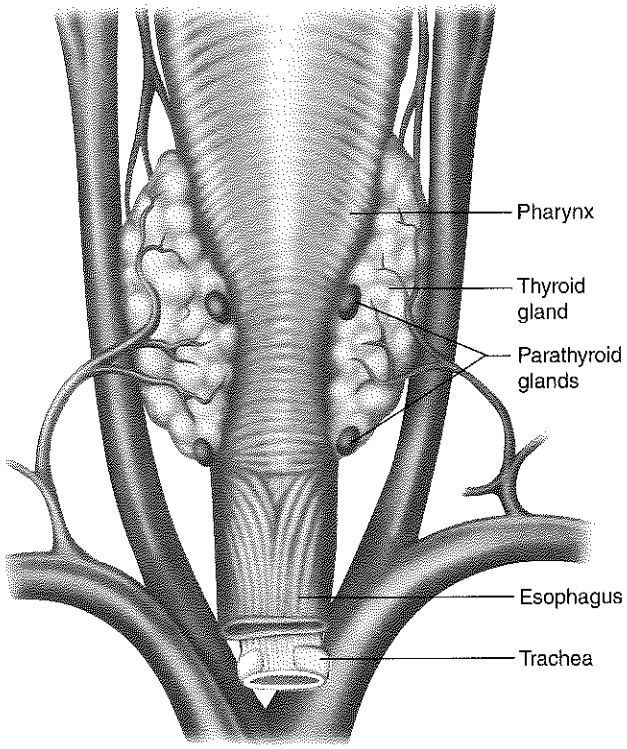


FIGURE 13.24 The parathyroid glands are embedded in the posterior surface of the thyroid gland.

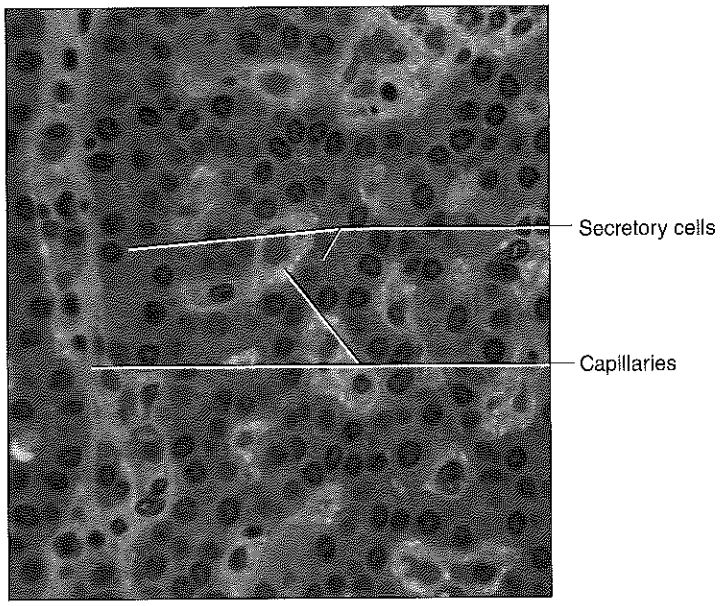


FIGURE 13.25 AP|R Light micrograph of the parathyroid gland (540×).

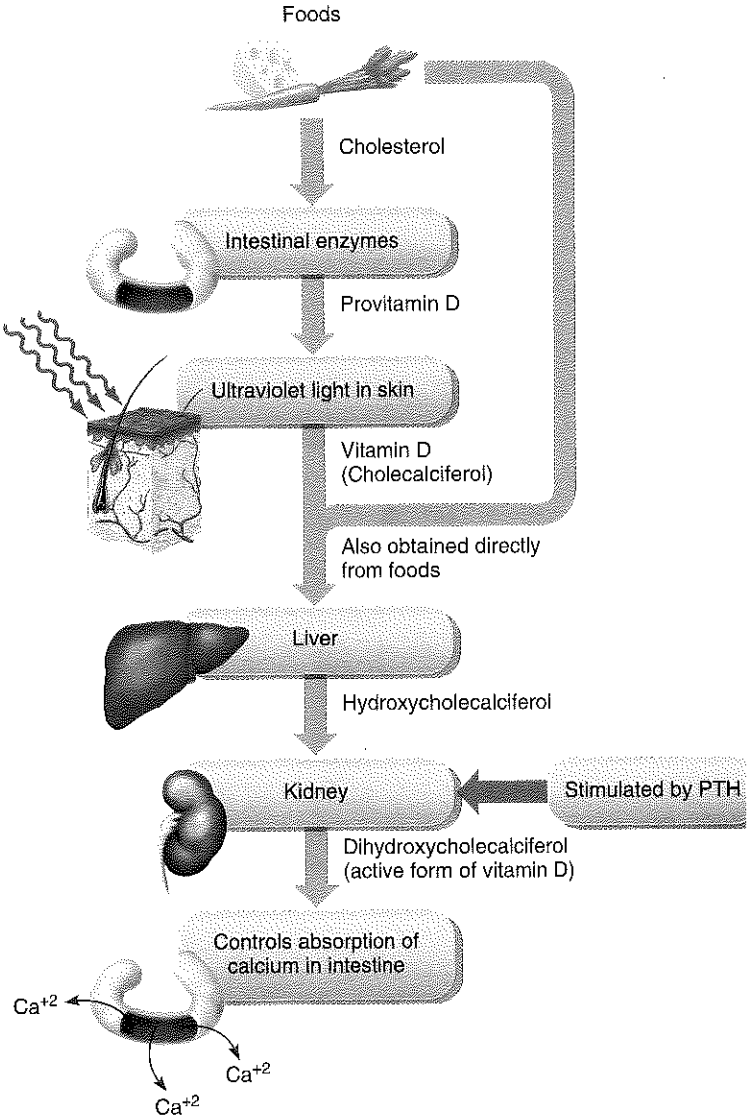


FIGURE 13.26 Mechanism by which PTH promotes calcium absorption in the intestine.

absorption of calcium ions from food in the intestine by influencing metabolism of vitamin D.

Vitamin D (cholecalciferol) is synthesized from dietary cholesterol, which intestinal enzymes convert into an inactive form called provitamin D (dehydrocholesterol). This provitamin is largely stored in the skin, and exposure to the ultraviolet wavelengths of sunlight changes it to vitamin D. Some vitamin D also comes from foods.

The liver changes vitamin D to hydroxycholecalciferol, which is carried in the bloodstream or stored in tissues. When PTH is present, hydroxycholecalciferol can be changed in the kidneys into the active form of vitamin D (dihydroxycholecalciferol), which controls absorption of calcium ions from the intestine (fig. 13.26).

A negative feedback mechanism operating between the parathyroid glands and the blood calcium ion concentration regulates secretion of PTH (fig. 13.27). As the concentration of blood calcium ions rises, less PTH is secreted; as the concentration of blood calcium ions drops, more PTH is released.

The opposite effects of calcitonin and PTH maintain calcium ion homeostasis. This is important in a number of physiological processes. For example, if the blood calcium ion concentration drops below the normal range (hypocalcemia), the nervous system becomes abnormally excitable, and

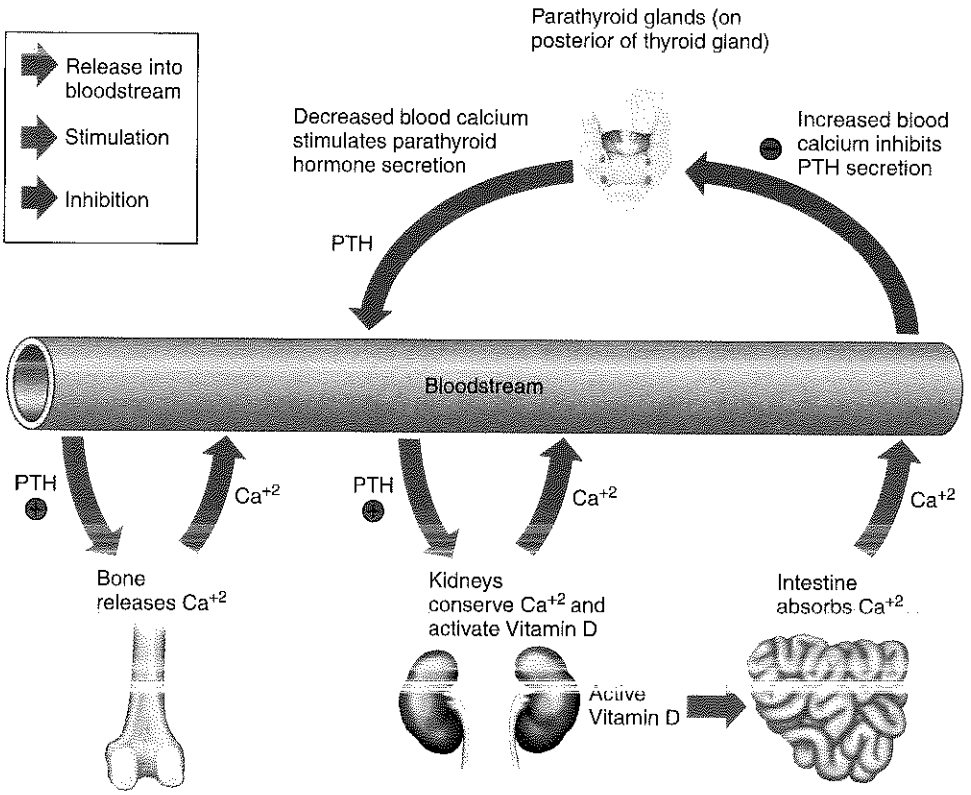


FIGURE 13.27 AP|R Parathyroid hormone (PTH) stimulates bone to release calcium (Ca^{+2}) and the kidneys to conserve calcium. It indirectly stimulates the intestine to absorb calcium. The resulting increase in blood calcium concentration inhibits secretion of PTH by negative feedback. (⊕ = stimulation; ⊖ = inhibition)

TABLE 13.9 | Disorders of the Parathyroid Glands

Condition	Symptoms/Mechanism	Cause	Treatment
Hyperparathyroidism	Fatigue, muscular weakness, painful joints, altered mental functions, depression, weight loss, bone weakening. Increased PTH secretion overstimulates osteoclasts.	Tumor	Remove tumor, correct bone deformities
Hypoparathyroidism	Muscle cramps and seizures. Decreased PTH secretion reduces osteoclast activity, diminishing blood calcium ion concentration.	Inadvertent surgical removal; injury	Calcium salt injections, massive doses of vitamin D

impulses may be triggered spontaneously. As a result, muscles, including the respiratory muscles, may undergo tetanic contractions, and the person may suffocate. In contrast, an abnormally high concentration of blood calcium ions (hypercalcemia) depresses the nervous system. Consequently, muscle contractions are weak, and reflexes are sluggish. Table 13.9 lists disorders of the parathyroid glands.

PRACTICE

28 Where are the parathyroid glands located?

29 How does parathyroid hormone help regulate the concentrations of blood calcium and phosphate ions?

30 How does the negative feedback system of the parathyroid glands differ from that of the thyroid gland?

13.8 ADRENAL GLANDS AP|R

The **adrenal glands** (suprarenal glands) are closely associated with the kidneys. A gland sits atop each kidney like a cap and is embedded in the mass of adipose tissue that encloses the kidney.

Structure of the Glands

The adrenal glands are shaped like pyramids. Each adrenal gland is vascular and consists of two parts. The central portion is the adrenal medulla, and the outer part is the adrenal cortex (fig. 13.28). These regions are not sharply divided, but they are distinct in that they secrete different hormones.

The **adrenal medulla** (ah-dre'nal me-dul'ah) consists of irregularly shaped cells grouped around blood vessels. These

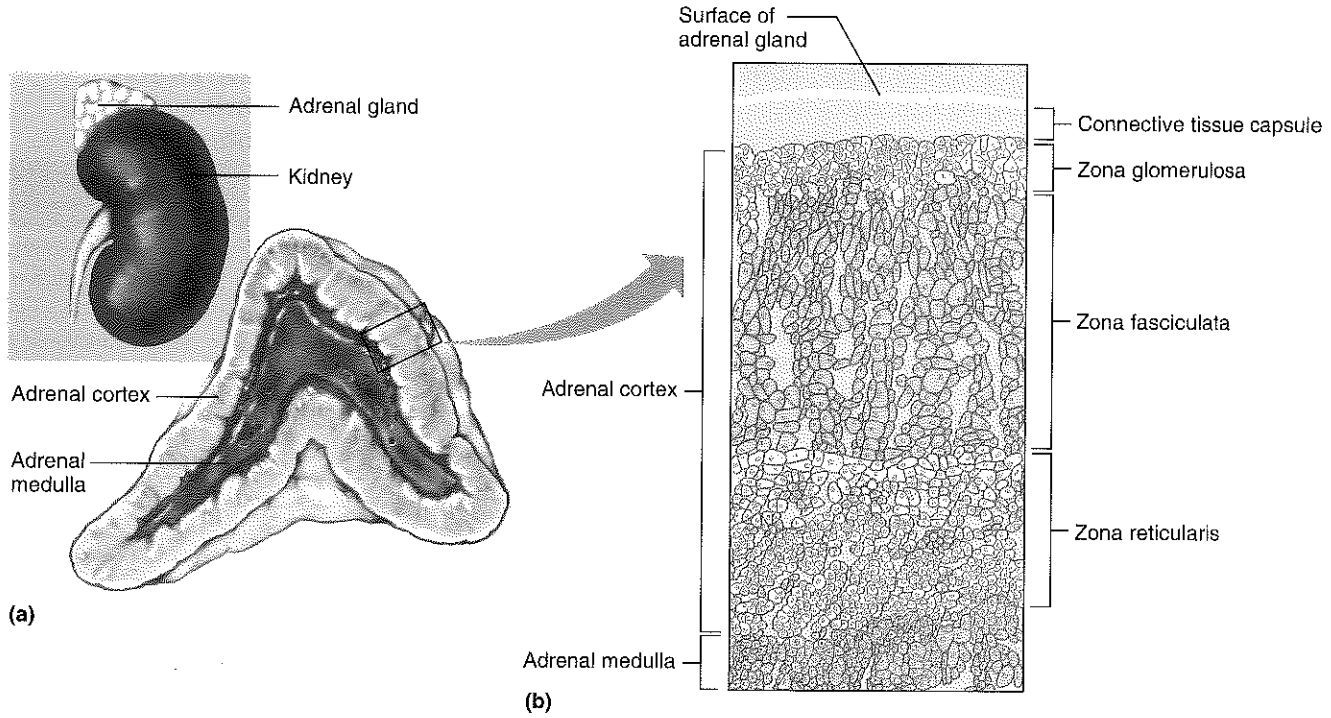


FIGURE 13.28 AP|R Adrenal glands. (*a*) An adrenal gland consists of an outer cortex and an inner medulla. (*b*) The cortex consists of three layers, or zones, of cells.

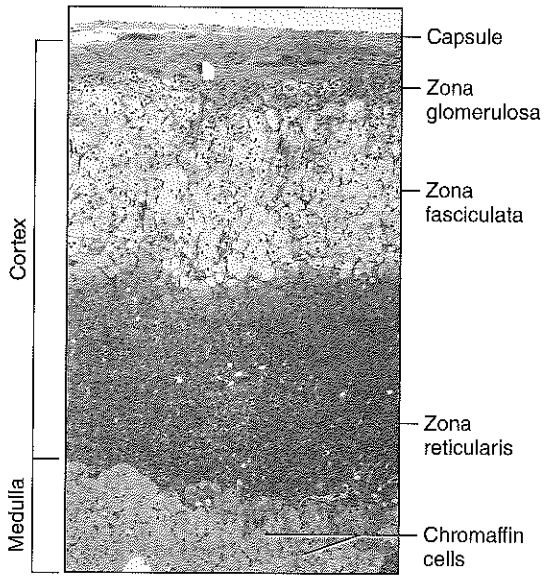


FIGURE 13.29 AP|R Light micrograph of the adrenal medulla and the adrenal cortex (75×).

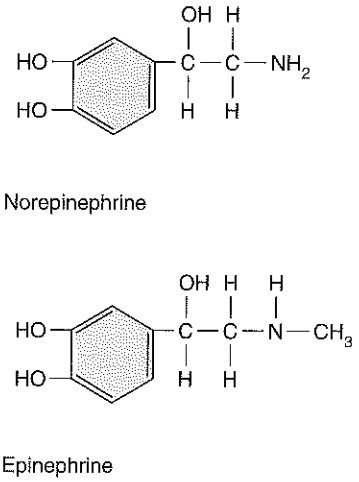


FIGURE 13.30 Epinephrine and norepinephrine have similar molecular structures and similar functions.

cells are intimately connected with the sympathetic division of the autonomic nervous system. The adrenal medullary cells (chromaffin cells) are modified postganglionic neurons, and preganglionic autonomic nerve fibers lead to them directly from the central nervous system (see chapter 11, p. 432).

The **adrenal cortex** (ah-dre'nal kor'teks) makes up the bulk of the adrenal gland. It is composed of closely packed masses of epithelial layers that form an outer, a middle, and an inner zone of the cortex—the zona glomerulosa, the zona fasciculata, and the zona reticularis, respectively (fig.13.28 and fig. 13.29).

Hormones of the Adrenal Medulla

The chromaffin cells of the adrenal medulla produce, store, and secrete two closely related hormones, **epinephrine** (ep"ĭ-nef'rin), also called adrenalin, and **norepinephrine** (nor"ep-ĭ-nef'rin), also called noradrenalin. Both of these substances are a type of amine called a *catecholamine*, and they have similar molecular structures and physiological functions (fig. 13.30). Epinephrine is synthesized from norepinephrine.

The synthesis of catecholamines begins with the amino acid tyrosine. In the first step of the pathway, an enzyme (tyrosine hydroxylase) in the secretory cells catalyzes a reaction that converts tyrosine into a substance called *dopa*. A second enzyme (dopa decarboxylase) catalyzes a reaction that

modifies dopa into dopamine, and a third enzyme (dopamine betahydroxylase) catalyzes a reaction that alters dopamine to form norepinephrine. Still another enzyme (phenylethanolamine N-methyltransferase) then catalyzes conversion of norepinephrine to epinephrine. About 15% of the norepinephrine is stored unchanged. The hormones occupy tiny vesicles (chromaffin granules), much like neurotransmitters are stored in vesicles in neurons.

The effects of the adrenal medullary hormones generally resemble those that result when sympathetic neurons stimulate their effectors: increased heart rate and force of cardiac muscle contraction, elevated blood pressure, increased breathing rate, and decreased digestive activity (see table 11.10, p. 436). The hormonal effects last up to ten times longer than the neurotransmitter effects because the hormones are slowly removed from the tissues.

The ratio of the two hormones in the adrenal medullary secretion varies with different physiological conditions, but usually it is about 80% epinephrine and 20% norepinephrine. Although these hormones' effects are generally similar, certain effector cells respond differently, due to the relative numbers of alpha and beta receptors in their membranes. Both hormones can stimulate both classes of receptors, but norepinephrine has a greater effect on alpha receptors.

Impulses arriving on sympathetic nerve fibers stimulate the adrenal medulla to release its hormones at the same time as sympathetic impulses stimulate other effectors. As a rule, all of these impulses originate in the hypothalamus in response to stress. Thus, the adrenal medullary secretions function together with the sympathetic division of the autonomic nervous system in preparing the body for energy-expending action—"fight or flight." Table 13.10 compares some of the differences in the effects of epinephrine and norepinephrine.

RECONNECT

To Chapter 11, Sympathetic Division, pages 430–432.

PRACTICE

31 Describe the location and structure of the adrenal glands.

32 Name the hormones the adrenal medulla secretes.

33 What general effects do hormones secreted by the adrenal medulla produce?

34 What usually stimulates release of hormones from the adrenal medulla?

Hormones of the Adrenal Cortex

The cells of the adrenal cortex produce more than thirty different steroids, including several hormones (corticosteroids). Unlike the adrenal medullary hormones, without which a person can survive, some of those released by the cortex are vital. In the absence of these adrenal cortical secretions, without extensive electrolyte therapy a person usually dies within a week. The most important adrenal cortical hormones are aldosterone, cortisol, and certain sex hormones.

TABLE **13.10** | Comparative Effects of Epinephrine and Norepinephrine

Structure or Function Affected	Epinephrine	Norepinephrine
Heart	Heart rate increases Force of contraction increases	Heart rate increases Force of contraction increases
Blood vessels	Vasodilation, especially important in skeletal muscle at onset of fight or flight	Vasoconstriction in skin and viscera shifts blood flow to other areas, such as exercising skeletal muscle
Systemic blood pressure	Some increase due to increased cardiac output	Some increase due to increased cardiac output and vasoconstriction (offset in some areas, such as exercising skeletal muscle, by local vasodilation due to other factors)
Airways	Dilation	Some dilation
Reticular formation of brainstem	Activated	Little effect
Liver	Promotes breakdown of glycogen to glucose, increasing blood sugar level	Little effect on blood glucose level
Metabolic rate	Increases	Increases

Aldosterone

Cells in the outer zone (zona glomerulosa) of the adrenal cortex synthesize **aldosterone.** This hormone is called a *mineralocorticoid* because it helps regulate the concentration of mineral electrolytes, such as sodium and potassium ions. Specifically, aldosterone causes the kidney to conserve sodium ions and to excrete potassium ions. The cells that secrete aldosterone respond directly to changes in the composition of blood plasma. However, whereas an increase in plasma potassium strongly stimulates these cells, a decrease in plasma sodium only slightly stimulates them. Control of aldosterone secretion is indirectly linked to plasma sodium level by the **renin-angiotensin system.**

Groups of specialized kidney cells (juxtaglomerular cells) are able to respond to changes in blood pressure and the plasma sodium ion concentration. If the level of either of these factors decreases, the cells release an enzyme called **renin** (re'nin). Renin reacts with a blood protein called **angiotensinogen** (an"je-o-ten-sin'o-jen) to release a peptide called **angiotensin I.** Another enzyme (angiotensin-converting enzyme, or ACE), found primarily in lung blood vessels, catalyzes a reaction that converts angiotensin I into another form, **angiotensin II,** which is carried in the bloodstream (fig. 13.31). When angiotensin II reaches the adrenal cortex, it stimulates the release of aldosterone. ACTH is necessary for the adrenal gland to respond to this and other stimuli.

Aldosterone, in conserving sodium ions, indirectly retains water by osmosis. This helps maintain both the blood sodium ion concentration and blood volume (fig. 13.31).

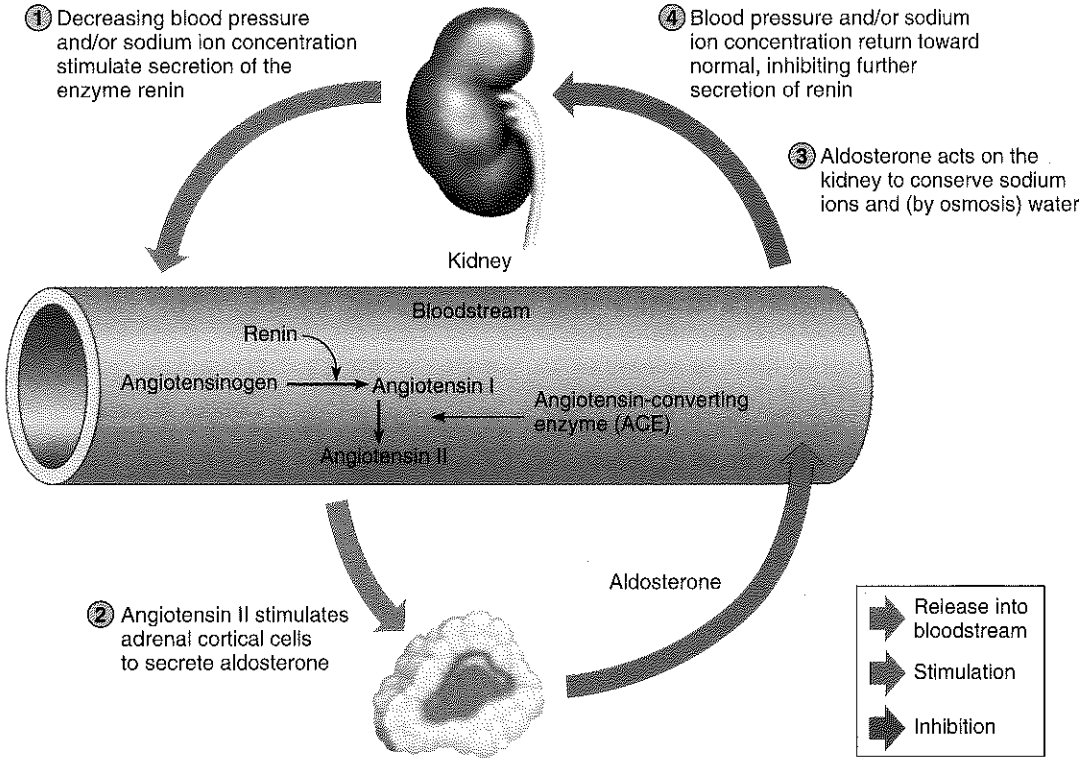


FIGURE 13.31 Aldosterone increases blood volume and pressure by promoting conservation of sodium ions and water (steps *1–4*).

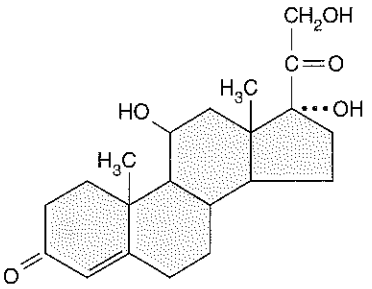
Angiotensin II is also a powerful vasoconstrictor and thereby helps maintain systemic blood pressure.

> ACE inhibitors are a class of drugs used to treat some forms of high blood pressure (hypertension). They work by binding to the active site on angiotensin-converting enzyme, blocking formation of angiotensin II and preventing inactivation of bradykinin, a vasodilator. Both effects dilate blood vessels, lowering blood pressure.

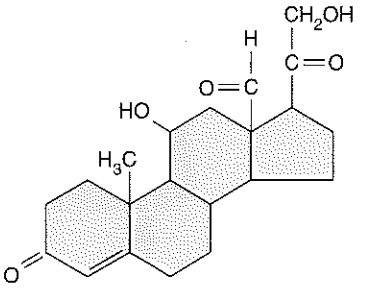
Cortisol

Cortisol (hydrocortisone) is a *glucocorticoid*, which means it affects glucose metabolism. It is produced in the middle zone (zona fasciculata) of the adrenal cortex and has a molecular structure similar to aldosterone (fig. 13.32). In addition to affecting glucose, cortisol influences protein and fat metabolism. Among the more important actions of cortisol are the following:

1. It inhibits the synthesis of protein in various tissues, increasing blood concentration of amino acids.
2. It promotes the release of fatty acids from adipose tissue, increasing the use of fatty acids and decreasing the use of glucose as energy sources.
3. It stimulates liver cells to synthesize glucose from noncarbohydrates (gluconeogenesis), such as circulating amino acids and glycerol, thus increasing blood glucose concentration.



Cortisol



Aldosterone

FIGURE 13.32 Cortisol and aldosterone are steroids with similar molecular structures.

Cortisol's actions help keep the blood glucose concentration within the normal range between meals. These actions are important because just a few hours without food can exhaust liver glycogen, which is another major source of glucose.

A negative feedback mechanism much like that controlling the thyroid hormones T_3 and T_4 regulates cortisol release. It involves the hypothalamus, anterior pituitary gland, and adrenal cortex. The hypothalamus secretes CRH (corticotropin-releasing hormone) into the hypophyseal portal veins, which carry the CRH to the anterior pituitary gland, stimulating it to secrete ACTH. In turn, ACTH stimulates the adrenal cortex to release cortisol. Cortisol inhibits release of both CRH and ACTH. As concentration of these substances falls, cortisol production drops.

The set point of the feedback loop controlling cortisol secretion changes, adapting hormone output to changing conditions. For example, under stress—injury, disease, extreme temperature, or emotional upset—information reaches the brain concerning the situation. In response, brain centers signal the hypothalamus to release more CRH, leading to a higher concentration of cortisol until the stress subsides (fig. 13.33).

Sex Hormones

Cells in the inner zone (zona reticularis) of the adrenal cortex produce sex hormones. These hormones are male (adrenal androgens), but some of them are converted into female hormones (estrogens) by the skin, liver, and adipose tissues. These hormones may supplement the supply of sex hormones from the gonads and stimulate early development of the reproductive organs. Adrenal androgens may also play a role in controlling the female sex drive. Table 13.11 summarizes the actions of the cortical hormones. Clinical Application 13.3 discusses some of the effects of a malfunctioning adrenal gland on health.

TABLE **13.11** | Hormones of the Adrenal Cortex AP|R

Hormone	Action	Factors Regulating Secretion
Aldosterone	Helps regulate the concentration of extracellular electrolytes by conserving sodium ions and excreting potassium ions	Electrolyte concentrations in body fluids and renin-angiotensin system
Cortisol	Decreases protein synthesis, increases fatty acid release, and stimulates glucose synthesis from noncarbohydrates	CRH from the hypothalamus and ACTH from the anterior pituitary gland
Adrenal androgens	Supplement sex hormones from the gonads; may be converted into estrogens	

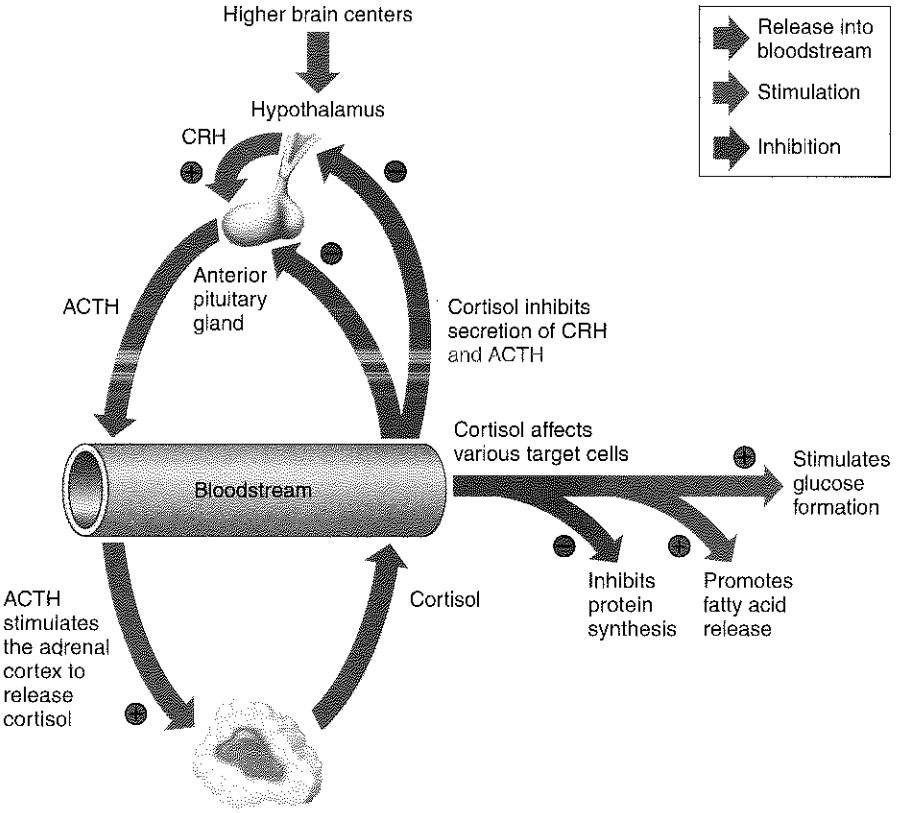
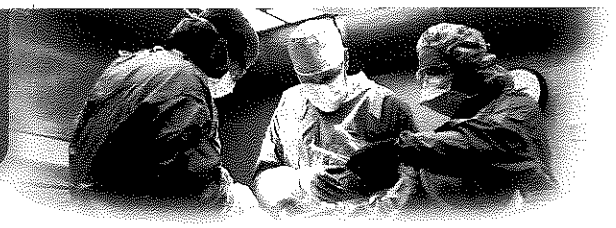


FIGURE 13.33 Negative feedback regulates cortisol secretion, similar to the regulation of thyroid hormone secretion (see fig. 13.16). (⊕ = stimulation; ⊖ = inhibition)

13.3 CLINICAL APPLICATION



Disorders of the Adrenal Cortex

President John F. Kennedy's bronze complexion may have resulted not from sunbathing, but from a disorder of the adrenal glands. When he ran for president in 1960, Kennedy knew he had *Addison disease,* but his staff kept his secret, for fear it would affect his career. Kennedy had almost no adrenal tissue, but he functioned by receiving mineralocorticoids and glucocorticoids, the standard treatment.

In Addison disease, the adrenal cortex does not secrete hormones sufficiently. This may be due to immune system attack (autoimmunity) or an infection such as tuberculosis. Signs and symptoms include decreased blood sodium, increased blood potassium, low blood glucose level (hypoglycemia), dehydration, low blood pressure, frequent infections, fatigue, nausea and vomiting, loss of appetite, and increased skin pigmentation. Some sufferers experience salt cravings—one woman reported eating many bowls of salty chicken noodle soup, with pickles and briny pickle juice added! Without treatment, death comes within days from severe disturbances in electrolyte balance.

Cushing syndrome is hypersecretion of cortisol from any cause, such as an adrenal tumor or oversecretion of ACTH by the anterior pituitary. The condition may also result from taking corticosteroid drugs for many years, such as to treat asthma or rheumatoid arthritis. Tissue protein level plummets, due to muscle wasting and loss of bone tissue. Blood glucose level remains elevated, and excess sodium is retained. As a result, tissue fluid increases, blood pressure rises, and the skin appears puffy. The skin may appear thin due to inhibition of collagen synthesis by the excess cortisol. Adipose tissue deposited in the face and back produce a characteristic "moon face" and "buffalo hump." Increase in adrenal sex hormone secretion may masculinize a female, causing growth of facial hair and a deepening voice. Other symptoms include extreme fatigue, sleep disturbances, skin rashes, headache, and leg muscle cramps.

Treatment of Cushing syndrome attempts to reduce ACTH secretion. This may entail removing a tumor in the pituitary gland or partially or completely removing the adrenal glands.

Both Addison disease and Cushing syndrome are rare, and for this reason, they are often misdiagnosed, or, in early stages, the patient's report of symptoms is not taken seriously. Addison disease affects thirty-nine to sixty people of every million, and Cushing syndrome affects five to twenty-five people per million. ■

Cortisol and related compounds are used as drugs to reduce inflammation. They relieve pain by:

- decreasing permeability of capillaries, preventing leakage of fluids that swell surrounding tissues
- stabilizing lysosomal membranes, preventing release of their enzymes, which destroy tissue
- inhibiting prostaglandin synthesis

Because the concentrations of cortisol compounds used to stifle inflammation have significant side effects, these drugs can be used for only a limited time. They are used to treat autoimmune disorders, allergies, asthma, and recipients of organ transplants or tissue grafts.

PRACTICE

35 Name the important hormones of the adrenal cortex.
36 What is the function of aldosterone?
37 What does cortisol do?
38 How are blood concentrations of aldosterone and cortisol regulated?

13.9 PANCREAS

The **pancreas** (pan'kre-as) consists of two major types of secretory tissues. The organization of the cell types reflects the dual function of the pancreas as an exocrine gland that secretes digestive juice through a duct, and an endocrine gland that releases hormones into body fluids.

Structure of the Gland

The pancreas is an elongated, somewhat flattened organ posterior to the stomach and behind the parietal peritoneum (fig. 13.34). A duct that attaches the pancreas to the first section of the small intestine (duodenum) transports its digestive juice into the intestine. Chapter 17 (p. 668) discusses the digestive functions of the pancreas.

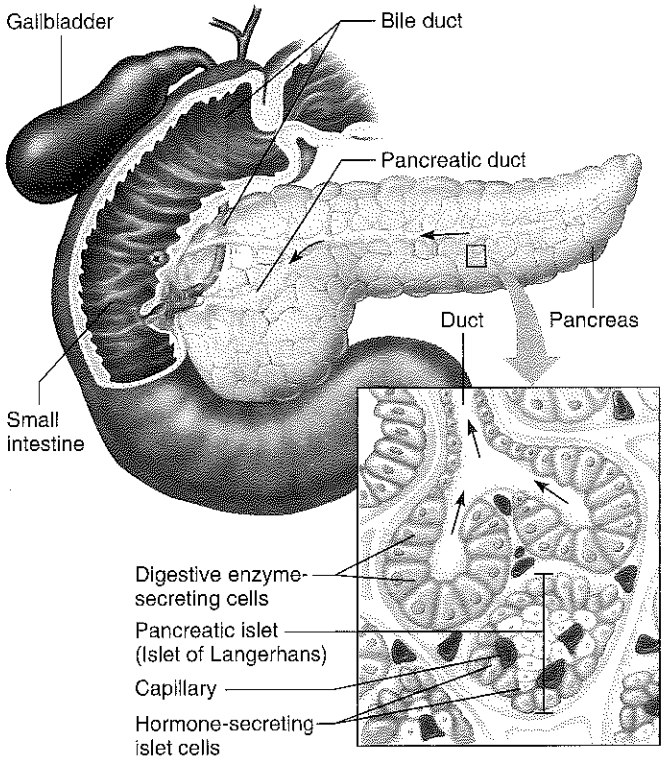


FIGURE 13.34 AP|R The hormone-secreting cells of the pancreas are grouped in clusters, or islets, closely associated with blood vessels. Other pancreatic cells secrete digestive enzymes into ducts.

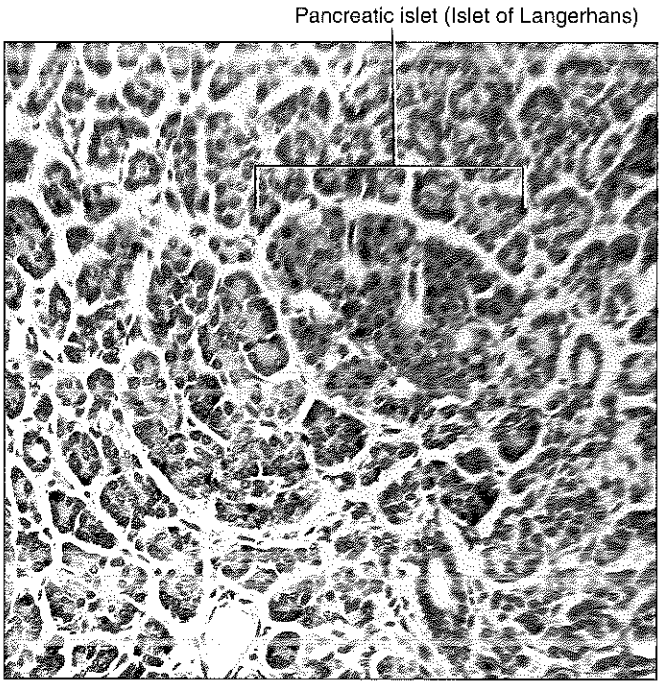


FIGURE 13.35 AP Light micrograph of pancreatic islets (200×).

The endocrine portion of the pancreas consists of cells grouped around blood vessels. These groups, called *pancreatic islets* (islets of Langerhans), include three distinct types of hormone-secreting cells—*alpha cells,* which secrete glucagon; *beta cells,* which secrete insulin; and *delta cells,* which secrete somatostatin (fig.13.34 and fig. 13.35).

Hormones of the Pancreatic Islets

Glucagon is a protein that stimulates the liver to break down glycogen into glucose (glycogenolysis) and to convert noncarbohydrates, such as amino acids, into glucose (gluconeogenesis). Glucagon also stimulates breakdown of fats into fatty acids and glycerol.

In a negative feedback system, a low concentration of blood glucose stimulates release of glucagon from the alpha cells. When blood glucose concentration returns toward normal, glucagon secretion decreases (fig. 13.36). This mechanism prevents hypoglycemia when glucose concentration is relatively low, such as between meals, or when glucose is being used rapidly, such as during exercise.

The hormone **insulin** is also a protein, and its main effect is exactly opposite that of glucagon. Insulin stimulates the liver to form glycogen from glucose and inhibits conversion of noncarbohydrates into glucose. Insulin also has the special effect of promoting the facilitated diffusion (see chapter 3, p. 101) of glucose through the membranes of cells bearing insulin receptors. These cells include those of adipose tissues, skeletal muscle, and cardiac muscle (although glucose uptake by active muscle is not dependent on insulin). Insulin action decreases the concentration of blood glucose, promotes transport of amino acids into cells, and increases protein synthesis. It also stimulates adipose cells to synthesize and store fat.

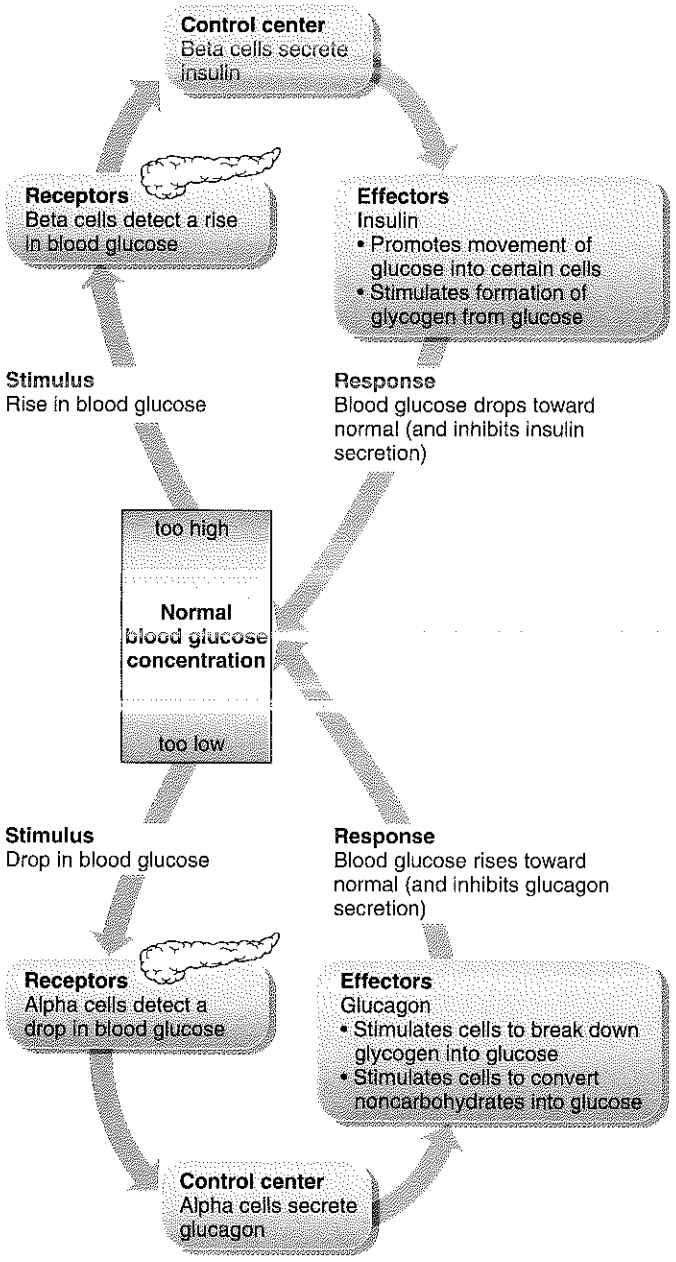


FIGURE 13.36 AP|R Insulin and glucagon function together to stabilize blood glucose concentration. Negative feedback responding to blood glucose concentration controls the levels of both hormones.

Q: *Four hours after a meal, would you expect blood levels of insulin to be high or low? What about blood levels of glucagon?*

Answers can be found in Appendix G on page 938.

An enzyme called glucokinase enables pancreatic cells to "sense" glucose level, which is important in regulating synthesis of glucagon and insulin. In one form of a rare type of diabetes mellitus, maturity-onset diabetes of the young (MODY), a mutation in a gene encoding glucokinase impairs the ability of beta cells to assess when to produce insulin. Other mutations that cause MODY alter insulin's structure, secretion, or cell surface receptors or the ability of liver cells to form glycogen in response to insulin. MODY is treated with drugs or dietary modification.

A negative feedback system sensitive to the concentration of blood glucose regulates insulin secretion. When glucose concentration is relatively high, such as after a meal, the beta cells release insulin. By promoting formation of glycogen in the liver and entrance of glucose into adipose and muscle cells, insulin helps prevent excessive rise in blood glucose concentration (hyperglycemia). Then, when the glucose concentration falls, between meals or during the night, insulin secretion decreases (fig. 13.36).

As insulin concentration falls, less glucose enters the adipose and muscle cells, and the glucose remaining in the blood is available for cells that lack insulin receptors, such as nerve cells. Neurons readily tap the energy in a continuous supply of glucose to produce ATP.

Hypoglycemia, or low blood glucose level due to excess insulin in the bloodstream, causes episodes of shakiness, weakness, and anxiety. Following a diet of frequent, small meals low in carbohydrates and high in protein can often control symptoms by preventing the surges of insulin that lower the blood glucose level. Hypoglycemia is most often seen when a person with diabetes mellitus injects too much insulin, but it can also reflect a tumor of the insulin-producing cells of the pancreas, or it may occur transiently following strenuous exercise.

Neurons, including those of the brain, obtain glucose by a facilitated diffusion mechanism not dependent on insulin, but rather only on the glucose concentration gradient. For this reason, neurons are particularly sensitive to changes in blood glucose concentration. Conditions that cause such changes—excess insulin secretion, for example—are likely to affect brain functions.

At the same time that the insulin concentration is decreasing, glucagon secretion is increasing. Therefore, these hormones function together to maintain a relatively constant blood glucose concentration, despite great variations in the amounts of ingested carbohydrates.

Somatostatin (similar to the hypothalamic hormone), which the delta cells release, helps regulate glucose metabolism by inhibiting secretion of glucagon and insulin. Table 13.12 summarizes the hormones of the pancreatic islets, and Clinical Application 13.4 and From Science to Technology 13.1 discuss diabetes mellitus, which is a disruption of the control of glucose metabolism that affects millions of people.

PRACTICE

39 Name the endocrine portion of the pancreas.

40 What is the function of glucagon?

41 What is the function of insulin?

42 How are the secretions of glucagon and insulin controlled?

43 Why are nerve cells particularly sensitive to changes in blood glucose concentration?

13.10 OTHER ENDOCRINE GLANDS

Additional organs produce hormones. These are part of the endocrine system too. They include the pineal gland; the thymus; reproductive organs; and certain cells of the digestive tract, the heart, and the kidneys.

The **pineal gland** (pin'e-al gland) is a small, oval structure deep between the cerebral hemispheres, where it attaches to the upper portion of the thalamus near the roof of the third ventricle. It largely consists of specialized *pineal cells* and supportive neuroglia (see fig. 11.20*b*, p. 414).

The pineal gland secretes a hormone, **melatonin,** that is synthesized from serotonin. Varying patterns of light and dark outside the body control the gland's activities. In the presence of light, action potentials from the retina travel to the hypothalamus, then to the reticular formation, and then downward into the spinal cord. From here, the impulses travel along sympathetic nerve fibers back into the brain, and finally they reach the pineal gland, where they decrease melatonin secretion. In the absence of light, impulses from the eyes decrease and secretion of melatonin increases.

Melatonin secretion is part of the regulation of **circadian rhythms,** which are patterns of repeated activity associated with cycles of day and night, such as sleep/wake rhythms. Melatonin binds to two types of receptors on brain neurons, one that is abundant and one that is scarce. The major receptors are on cells of the suprachiasmatic nucleus, a region that regulates the circadian clock. Binding to the second, less abundant receptors, however, induces sleepiness.

TABLE **13.12** | Hormones of the Pancreatic Islets

Hormone	Action	Source of Control
Glucagon	Stimulates the liver to break down glycogen and convert noncarbohydrates into glucose; stimulates breakdown of fats	Blood glucose concentration
Insulin	Promotes formation of glycogen from glucose, inhibits conversion of noncarbohydrates into glucose, and enhances movement of glucose through adipose and muscle cell membranes, decreasing blood glucose concentration; promotes transport of amino acids into cells; enhances synthesis of proteins and fats	Blood glucose concentration
Somatostatin	Helps regulate carbohydrates	Not determined

13.4 CLINICAL APPLICATION

Diabetes Mellitus

In the United States, nearly 26 million people have diabetes mellitus and 79 million have prediabetes, according to the Centers for Disease Control and Prevention. In addition, about 7 million people have diabetes but do not know it. In Latin, *diabetes* means "increased urine output," and *mellitus* means "honey," referring to the urine's sugar content.

In type 1 diabetes mellitus (juvenile or insulin-dependent diabetes mellitus), the pancreas cannot produce insulin. Symptoms usually begin before age twenty. About 15% of people with diabetes mellitus have this form. It is an autoimmune disorder in which the immune system attacks pancreatic beta cells, ultimately destroying them and halting insulin secretion. Lack of insulin decreases movement of glucose into skeletal muscle and adipose cells, inhibiting glycogen formation. As a result, blood glucose concentration rises (hyperglycemia), and when it reaches a certain level, the kidneys begin to excrete the excess. Glucose appears in the urine (glycosuria). Water follows the glucose by osmosis, causing dehydration and intense thirst.

Untreated type 1 diabetes decreases protein synthesis, shrinking tissues as glucose-starved cells use protein for energy. Weight falls, and wounds cannot heal. Fatty acids accumulate in the blood as a result of fat catabolism. Ketone bodies, acidic byproducts of fatty acid catabolism, also build up in the blood. Accumulation of ketones leads to metabolic acidosis, a condition that lowers the pH of body fluids.

Dehydration and acidosis adversely affect brain neurons. Without treatment (insulin replacement), the person becomes disoriented and may enter a diabetic coma and die.

Daily life for a person with type 1 diabetes mellitus means constant awareness of the illness—insulin delivery; frequent finger punctures to monitor blood glucose level; a restrictive diet; and concern over complications, which include loss of vision, leg ulcers, and kidney damage. The many symptoms reflect disturbances in carbohydrate, protein, and fat metabolism.

Type 2, or non-insulin-dependent, diabetes mellitus begins gradually, usually in people over forty. Cells lose insulin receptors and are less able to respond to insulin. Following a very structured diet and regularly exercising can delay or even prevent type 2 diabetes.

Prediabetes is an elevated blood glucose level after eating that is not high enough to be considered diabetes. However, organ damage may already be occurring. Adopting healthy diet and exercise habits can slow progression to type 2 diabetes.

The oral glucose tolerance test is used to diagnose both major types of diabetes mellitus and indicate prediabetes. The patient ingests a known quantity of glucose, and blood glucose concentration is measured at intervals to assess glucose use. If the person has diabetes, blood glucose concentration rises greatly and remains elevated for several hours. In a healthy person, glucose rise is less dramatic, and the level returns to normal in about an hour and a half. ■

Traveling across several time zones produces the temporary insomnia of jet lag. Melatonin supplements are advertised as preventing jet lag, based on anecdotal reports and small studies. However, the first large study, conducted on 257 doctors traveling from Norway to New York, testing three nightly doses of melatonin supplement versus placebo, showed no effect at all from melatonin in preventing or alleviating jet lag.

The **thymus** (thi'mus), which lies in the mediastinum posterior to the sternum and between the lungs, is large in young children but shrinks with age. This gland secretes a group of hormones, called **thymosins,** that affect production and differentiation of certain white blood cells (T lymphocytes). The thymus plays an important role in immunity and is discussed in chapter 16 (p. 623).

The reproductive organs that secrete important hormones include the **testes,** which produce testosterone; the **ovaries,** which produce estrogens and progesterone; and the **placenta,** which produces estrogens, progesterone, and a gonadotropin. Chapters 22 and 23 discuss these glands and their secretions (pp. 836, 848, and 874).

The digestive glands that secrete hormones are generally associated with the linings of the stomach and small intestine. The small intestine alone produces dozens of hormones, many of which have not been well studied. Chapter 17 (pp. 665 and 668–669) describes these structures and their secretions.

Other organs that produce hormones include the heart, which secretes *atrial natriuretic peptide* (chapter 15, p. 585), and the kidneys, which secrete *erythropoietin* that stimulates red blood cell production (chapter 14, p. 530). Clinical Application 13.1 discusses abuse of EPO to improve athletic performance.

PRACTICE

44 Where is the pineal gland located?

45 What is the function of the pineal gland?

46 Where is the thymus gland located?

13.11 STRESS AND ITS EFFECTS

Factors that change the body's internal or external environment are potentially life threatening. Sensory receptors detecting such changes provide information that reaches the hypothalamus, triggering physiological responses that resist a loss of homeostasis. These responses include increased activity in the sympathetic division of the autonomic nervous system and increased secretion of adrenal hormones. A factor capable of stimulating such a response is called a **stressor,** and the condition it produces in the body is called **stress.**

Types of Stress

Stressors may be physical or psychological. They may also be a combination.

13.1 FROM SCIENCE TO TECHNOLOGY

Treating Diabetes

The sweet-smelling urine that is the hallmark of type 1 diabetes mellitus was noted as far back as an Egyptian papyrus from 1500 B.C. In A.D. 96 in Greece, Aretaeus of Cappadocia described the condition as a "melting down of limbs and flesh into urine." One of the first people to receive insulin as a drug was a three-year-old boy whose body could not produce the hormone (fig. 13B). In December 1922, before treatment, he weighed only fifteen pounds. The boy rapidly improved after beginning insulin treatment, doubling his weight in just two months.

FIGURE 13B Before and after insulin treatment. The boy in his mother's arms is three years old but weighs only 15 pounds because he has untreated type 1 diabetes mellitus. The inset shows the same child after two months of receiving insulin. His weight had doubled!

In 1921, Canadian physiologists Sir Frederick Grant Banting and Charles Herbert Best discovered the link between lack of insulin and diabetes. They induced diabetes symptoms in dogs by removing their pancreases, then cured them by administering insulin from other dogs' healthy pancreases. A year later, people with diabetes began to receive insulin extracted from pigs or cattle. The medication allowed them to control their disease.

In 1982, pure human insulin became available by genetically altering bacteria to produce the human protein (recombinant DNA technology). Human insulin helps people with diabetes who are allergic to the product from pigs or cows. Today, people receive insulin in several daily injections, from an implanted insulin pump, and/or in aerosol form (fig. 13C).

Providing new pancreatic islets is a longer-lasting treatment for type 1 diabetes. Islet cell transplantation was first attempted in 1893, when an English surgeon transplanted bits of a sheep's pancreas into an adolescent near death. He died a few days later.

Interest in islet transplantation revived once researchers realized that the more frequent the daily doses of insulin, the healthier the patient. Islet transplants succeeded, in rats, in 1972, but difficulties arose in treating people. It was challenging to separate islets from cadaver pancreases, and then collect enough beta cells, which account for only 2% of pancreas cells. Many patients' immune systems rejected transplants. By the 1990s, automated islet isolation and new anti-rejection drugs helped. In 1996 in Germany, and then in 1999 in Edmonton, Canada, islet transplantation began.

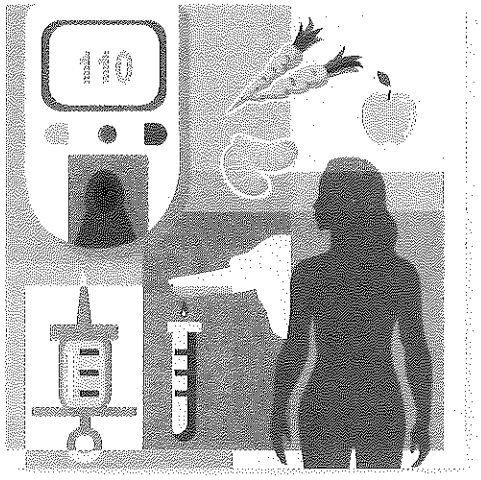


FIGURE 13C A person with either common form of diabetes mellitus must monitor his or her blood glucose level and be very diligent about proper diet and exercise.

Since 2000, several hundred people have received islet transplants in a procedure called the Edmonton protocol, which introduces islets into a vein in the liver. By a year after transplant, from 50% to 68% of patients do not need to receive additional insulin, but by five years after the procedure, fewer than 10% of total patients are free of daily insulin supplementation. The procedure is risky—12% of patients hemorrhage, and 4% develop blood clots in the liver vein. These risks, plus the apparent short-term improvement, have prompted physicians to carefully evaluate which patients are most likely to benefit from the few years of insulin independence that the procedure may offer. Researchers are also investigating implants of stem cells and progenitor cells from a patient's body.

A possible treatment for type 2 diabetes has come from an unexpected place—gastric bypass surgery, which removes parts of the stomach and small intestine to help people lose weight. Isolated reports since the 1950s noted cases of morbidly obese people with diabetes having gastric bypass surgery, and then, within days and with lasting effect, not needing to inject insulin. By the 1980s, doctors noticed that some patients who had normal regulation of blood glucose before the surgery, a few months after began to experience confusion, altered behavior, seizures, and unconsciousness—signs of low blood glucose. Today some surgeons are performing gastric bypass surgery on people who do not weigh as much as typical candidates for the surgery, but who have severe diabetes. Treating diabetes with weight-loss surgery is controversial, because the mechanism of how it corrects blood glucose regulation is not understood. ■

Physical stress threatens tissues. Extreme heat or cold, decreased oxygen concentration, infections, injuries, prolonged heavy exercise, and loud sounds inflict physical stress. Unpleasant or painful sensations often accompany physical stress.

Psychological stress results from thoughts about real or imagined dangers, personal losses, unpleasant social interactions (or lack of social interactions), or any threatening factors. Feelings of anger, fear, grief, anxiety, depression, and guilt cause psychological stress. Psychological stress may also stem from pleasant stimuli, such as friendly social contact, feelings of joy or happiness, or sexual arousal. The factors that produce psychological stress vary greatly from person to person. A situation that is stressful to one person may not affect another, and what is stressful at one time may not be at another time.

Responses to Stress

The hypothalamus controls the response to stress, termed the *general adaptation* (or *general stress*) *syndrome.* This response to stress of any type maintains homeostasis.

Recall that the hypothalamus receives information from nearly all body parts, including visceral receptors, the cerebral cortex, the reticular formation, and the limbic system. At times of stress, the hypothalamus responds to incoming impulses by activating the "fight-or-flight" response. Specifically, sympathetic impulses from the hypothalamus raise blood glucose concentration, the level of blood glycerol and fatty acids, heart rate, blood pressure and breathing rate, and dilate the air passages. The response also shunts blood from the skin and digestive organs into the skeletal muscles and increases secretion of epinephrine from the adrenal medulla. The epinephrine, in turn, intensifies these sympathetic responses and prolongs their effects (fig. 13.37).

At the same time that sympathetic activity increases, the hypothalamus's release of corticotropin-releasing hormone (CRH) stimulates the anterior pituitary gland to secrete ACTH, which increases the adrenal cortex's secretion of cortisol. Cortisol supplies cells with amino acids and extra energy sources and allows glucose to be spared for brain tissue (fig. 13.37). Stress can also stimulate release of glucagon from the pancreas, growth hormone (GH) from the anterior pituitary gland, antidiuretic hormone (ADH) from the posterior pituitary gland, and renin from the kidneys.

Glucagon and growth hormone help mobilize energy sources, such as glucose, glycerol, and fatty acids, and stimulate cells to take up amino acids, facilitating repair of injured tissues. ADH stimulates the kidneys to retain water. This action decreases urine output and helps to maintain blood volume, which is important if a person is bleeding or sweating heavily. Renin, by increasing angiotensin II levels, helps stimulate the kidneys to retain sodium (through aldosterone), and through the vasoconstrictor action of angiotensin II contributes to maintaining blood pressure. Table 13.13 summarizes the body's reactions to stress.

PRACTICE

47 What is stress?

48 Distinguish between physical stress and psychological stress.

49 Describe the general adaptation syndrome.

13.12 LIFE-SPAN CHANGES

With age, the glands of the endocrine system generally decrease in size and increase in the proportion of each gland that is fibrous in nature. At the cellular level, lipofuscin pigment accumulates as glands age. Functionally, hormone levels may change with advancing years. Treatments for endocrine disorders associated with aging supplement defi-

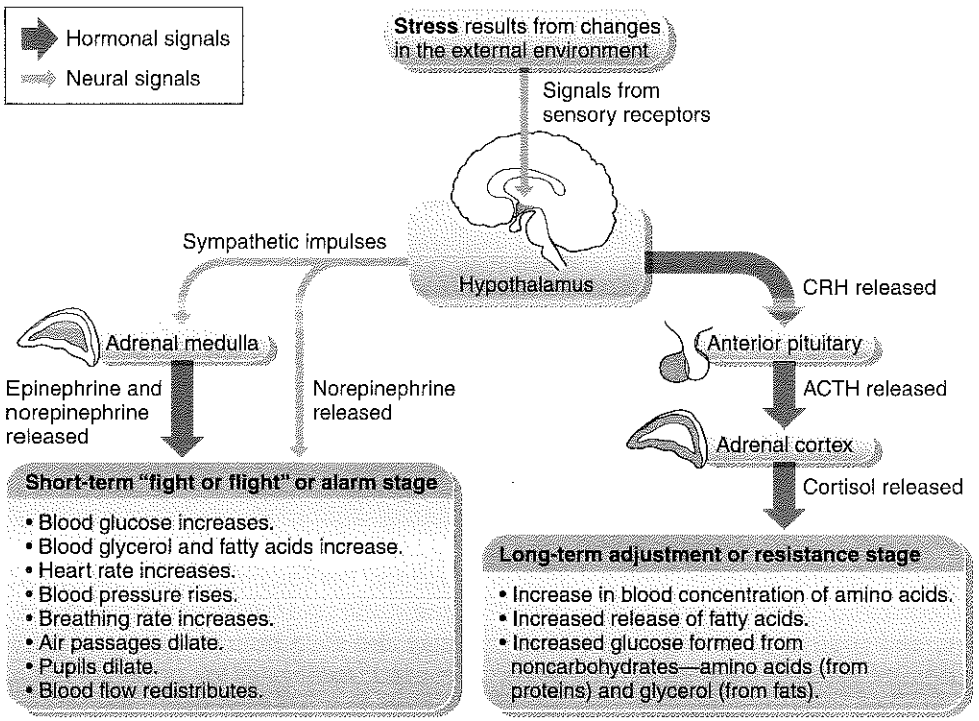


FIGURE 13.37 During stress, the hypothalamus helps prepare the body for "fight or flight" by triggering sympathetic impulses to various organs. It also stimulates epinephrine release, intensifying the sympathetic responses. The hypothalamus also stimulates the adrenal cortex to release cortisol, which promotes longer-term responses that resist the effects of stress.

TABLE 13.13 | Major Events in the General Stress Syndrome

1. In response to stress, impulses are conducted to the hypothalamus.
2. Sympathetic impulses originating from the hypothalamus increase blood glucose concentration, blood glycerol concentration, blood fatty acid concentration, heart rate, blood pressure, and breathing rate. They dilate air passages, shunt blood into skeletal muscles, and increase secretion of epinephrine from the adrenal medulla.
3. Epinephrine intensifies and prolongs sympathetic actions.
4. The hypothalamus secretes CRH, which stimulates secretion of ACTH by the anterior pituitary gland.
5. ACTH stimulates release of cortisol by the adrenal cortex.
6. Cortisol increases the concentration of blood amino acids, releases fatty acids, and stimulates formation of glucose from noncarbohydrate sources.
7. Secretion of glucagon from the pancreas and growth hormone from the anterior pituitary increase.
8. Glucagon and growth hormone aid mobilization of energy sources and stimulate uptake of amino acids by cells.
9. Secretion of ADH from the posterior pituitary increases.
10. ADH promotes the retention of water by the kidneys, which increases blood volume.
11. Renin increases blood levels of angiotensin II, which acts as a vasoconstrictor and also stimulates the adrenal cortex to secrete aldosterone.
12. Aldosterone stimulates sodium retention by the kidneys.

cient hormones, remove part of an overactive gland, or use drugs to block the action of an overabundant hormone.

Aging affects different hormones in characteristic ways. For growth hormone, the surge in secretion that typically occurs at night lessens somewhat with age. Lower levels of GH are associated with declining strength in the skeleton and muscles with advancing age. However, supplementing older people with GH in an attempt to duplicate the effects of exercise can dangerously raise blood pressure and blood glucose levels and enlarge the spleen, liver, and kidneys.

Levels of antidiuretic hormone increase with age, but this is due to slowed breakdown in the liver and kidneys, rather than increased synthesis. As a result, the kidneys are stimulated to reabsorb more water.

The thyroid gland shrinks with age, as individual follicles shrink and increasing amounts of fibrous connective tissue separate them. Thyroid nodules, which may be benign or cancerous, become more common with age, and are often first detected upon autopsy. Although blood levels of T_3 and T_4 may diminish with age, in general, the thyroid gland's control over the metabolism of various cell types is maintained throughout life. Calcitonin levels decline with age, which raises the risk of osteoporosis.

Parathyroid function differs between the sexes with age. Secretion peaks in males at about age fifty, whereas in women, the level of parathyroid hormone decreases until about age forty, after which it rises and contributes to osteoporosis risk. Fat accumulates between the cells of the parathyroid glands.

The adrenal glands illustrate the common theme of aging-related physical changes, yet continued function. Fibrous connective tissue, lipofuscin pigment, and increased numbers of abnormal cells characterize the aging adrenal glands. However, thanks to the fine-tuning of negative feedback systems, blood levels of glucocorticoids and mineralocorticoids usually remain within the normal range, although the ability to maintain homeostasis of osmotic pressure, blood pressure, acid/base balance, and sodium and potassium ion distributions may falter with age.

The most obvious changes in the aging endocrine system involve blood glucose regulation. The pancreas may be able to maintain secretion of insulin and glucagon, but lifestyle changes, such as increase in fat intake and less exercise, may increase the blood insulin level. The development of insulin resistance—the decreased ability of muscle, liver, and fat cells to take in glucose even in the presence of insulin—reflects impaired ability of these target cells to respond to the hormone, rather than compromised pancreatic function. Blood glucose buildup may signal the pancreas to secrete more insulin, setting the stage for type 2 diabetes mellitus.

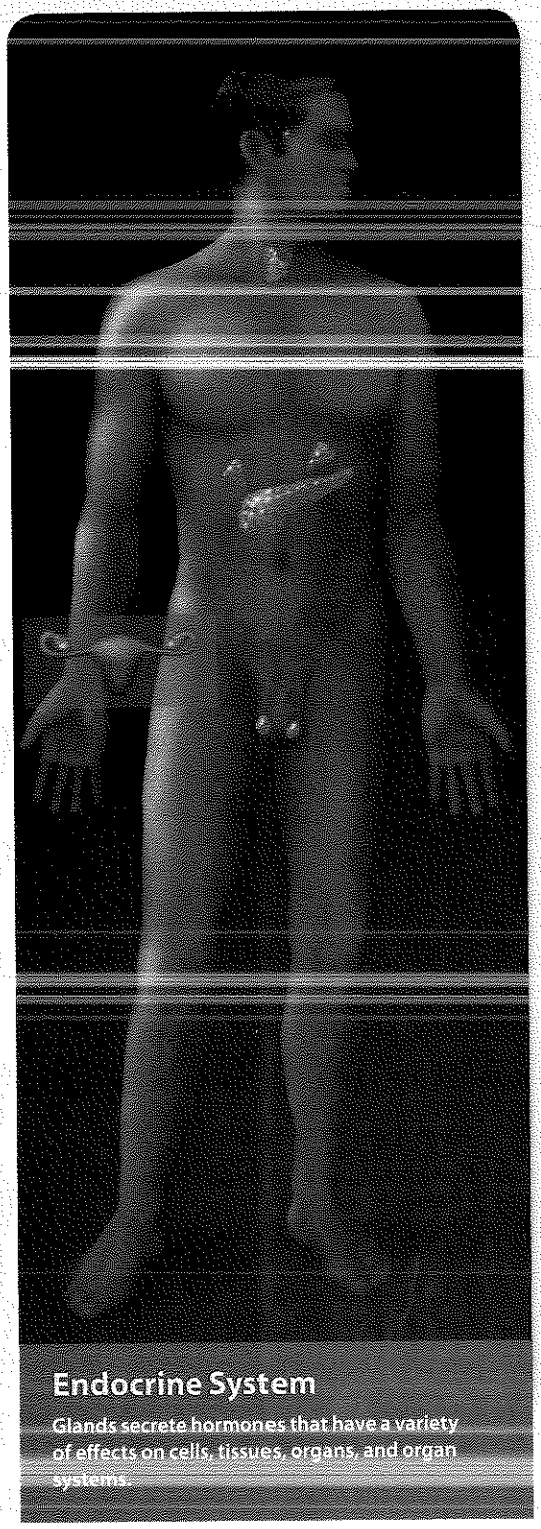
The daily fall and rise of melatonin levels may even out somewhat with age, which may alter control of the sleep/wake cycle. People usually require less sleep as they age. Changes to the tempo of the body clock may, in turn, affect secretion of other hormones.

The thymus begins to noticeably shrink before age twenty, with accompanying declining levels of thymosins. By age sixty, thymosin secretion is nil. The result is a slowing of the maturation of B and T cells, which increases susceptibility to infections as a person ages.

PRACTICE

50 What general types of changes occur in the glands of the endocrine system with aging?

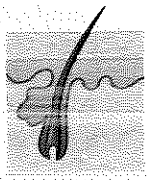
51 How do the structures and functions of particular endocrine glands change over a lifetime?



Endocrine System

Glands secrete hormones that have a variety of effects on cells, tissues, organs, and organ systems.

Integumentary System



Melanocytes produce skin pigment in response to hormonal stimulation.

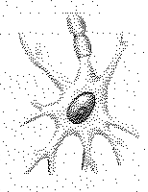
Skeletal System

Hormones act on bones to control calcium balance.

Muscular System

Hormones help increase blood flow to exercising muscles.

Nervous System



Neurons control the secretions of the anterior and posterior pituitary glands and the adrenal medulla.

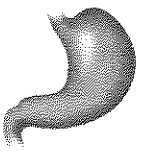
Cardiovascular System

Hormones are carried in the bloodstream; some have direct actions on the heart and blood vessels.

Lymphatic System

Hormones stimulate lymphocyte production.

Digestive System

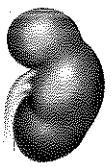


Hormones help control digestive system activity.

Respiratory System

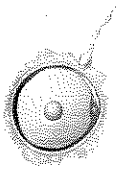
Decreased oxygen causes hormonal stimulation of red blood cell production.

Urinary System



Hormones act on the kidneys to help control water and electrolyte balance.

Reproductive System



Sex hormones play a major role in development of secondary sex characteristics, egg, and sperm.

CHAPTER SUMMARY

13.1 INTRODUCTION (PAGE 488)

The nervous system and the endocrine system work together to control body functions. Endocrine glands secrete their products into body fluids (the internal environment); exocrine glands secrete their products into ducts that lead to the outside of the body.

13.2 GENERAL CHARACTERISTICS OF THE ENDOCRINE SYSTEM (PAGE 488)

A hormone's target cells have specific receptors. Hormones from endocrine glands regulate metabolic processes.

13.3 HORMONE ACTION (PAGE 490)

Endocrine glands secrete hormones into the bloodstream, which carries them to all parts of the body.

1. Chemistry of hormones
   a. Steroid hormones are lipids that include complex rings of carbon and hydrogen atoms.
   b. Nonsteroid hormones are amines, peptides, and proteins.
2. Actions of hormones
   a. Steroid hormones and thyroid hormones
      (1) Steroid hormones and thyroid hormones enter target cells and combine with receptors to form complexes.
      (2) These complexes activate specific genes in the nucleus, which direct synthesis of specific proteins.
      (3) The degree of cellular response is proportional to the number of hormone-receptor complexes formed.
   b. Nonsteroid hormones
      (1) Nonsteroid hormones combine with receptors in the target cell membrane.
      (2) A hormone-receptor complex stimulates membrane proteins, such as adenylate cyclase, to induce the formation of second messenger molecules.
      (3) A second messenger, such as cAMP, activates protein kinases.
      (4) Protein kinases activate certain protein substrate molecules, which, in turn, change cellular processes.
      (5) The cellular response to a nonsteroid hormone is amplified because the enzymes induced by a small number of hormone-receptor complexes can catalyze formation of a large number of second messenger molecules.
3. Prostaglandins
   a. Prostaglandins are paracrine substances that have powerful hormonelike effects, even in small amounts.
   b. Prostaglandins modulate hormones that regulate formation of cyclic AMP.

13.4 CONTROL OF HORMONAL SECRETIONS (PAGE 496)

The concentration of each hormone in the body fluids is precisely regulated.

1. Some endocrine glands secrete hormones in response to releasing hormones the hypothalamus secretes.
2. Some endocrine glands secrete in response to nervous stimulation.
3. Some endocrine glands secrete in response to changes in the plasma concentration of a substance.
4. In a negative feedback system, a gland is sensitive to the physiological effect that its hormone brings about.
5. When the physiological effect reaches a certain level, it inhibits the gland.
6. As the gland secretes less hormone, the physiological effect is lessened.

13.5 PITUITARY GLAND (PAGE 497)

The pituitary gland, attached to the base of the brain, has an anterior lobe and a posterior lobe. Releasing hormones from the hypothalamus control most pituitary secretions.

1. Anterior pituitary hormones
   a. The anterior pituitary consists largely of epithelial cells, and it secretes GH, PRL, TSH, ACTH, FSH, and LH.
   b. Growth hormone (GH)
      (1) Growth hormone stimulates body cells to grow and divide.
      (2) Growth hormone-releasing hormone and somatostatin from the hypothalamus control GH secretion.
   c. Prolactin (PRL)
      (1) PRL promotes breast development and stimulates milk production.
      (2) A normal function of prolactin in males has not been established.
      (3) Prolactin release-inhibiting hormone from the hypothalamus restrains secretion of prolactin, whereas prolactin-releasing factors are thought to promote its secretion.
   d. Thyroid-stimulating hormone (TSH)
      (1) TSH controls secretion of hormones from the thyroid gland.
      (2) The hypothalamus, by secreting thyrotropin-releasing hormone, regulates TSH secretion.
   e. Adrenocorticotropic hormone (ACTH)
      (1) ACTH controls the secretion of certain hormones from the adrenal cortex.
      (2) The hypothalamus, by secreting corticotropin-releasing hormone, regulates ACTH secretion.
   f. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are gonadotropins that affect the reproductive organs.

2. Posterior pituitary hormones
   a. The posterior lobe of the pituitary gland largely consists of neuroglia and nerve fibers that originate in the hypothalamus.
   b. The two hormones of the posterior pituitary are produced in the hypothalamus.
   c. Antidiuretic hormone (ADH)
      (1) ADH causes the kidneys to excrete less water.
      (2) In high concentration, ADH constricts blood vessel walls, raising blood pressure.
      (3) The hypothalamus regulates ADH secretion.
   d. Oxytocin (OT)
      (1) OT has an antidiuretic effect and can contract muscles in the uterine wall.
      (2) OT also contracts certain cells associated with production and ejection of milk from the milk glands of the breasts.

13.6 THYROID GLAND (PAGE 504)

The thyroid gland is located in the neck and consists of two lateral lobes.

1. Structure of the gland
   a. The thyroid gland consists of many hollow secretory parts called follicles.
   b. The follicles are fluid filled and store the thyroxine and triiodothyronine the follicular cells secrete.
   c. Extrafollicular cells secrete calcitonin.
2. Thyroid hormones
   a. Thyroxine and triiodothyronine
      (1) These hormones increase the rate of metabolism, enhance protein synthesis, and stimulate lipid breakdown.
      (2) These hormones are needed for normal growth and development and for maturation of the nervous system.
   b. Calcitonin
      (1) Calcitonin lowers blood calcium and phosphate ion concentrations.
      (2) This hormone prevents prolonged elevation of calcium after a meal.

13.7 PARATHYROID GLANDS (PAGE 506)

The parathyroid glands are on the posterior surface of the thyroid.

1. Structure of the glands
   a. Each gland is small and yellow-brown, within a thin connective tissue capsule.
   b. Each gland consists of secretory cells well supplied with capillaries.
2. Parathyroid hormone (PTH)
   a. PTH increases blood calcium ion concentration and decreases blood phosphate ion concentration.
   b. PTH stimulates resorption of bone tissue, causes the kidneys to conserve calcium ions and excrete phosphate ions, and indirectly stimulates absorption of calcium ions from the intestine.
   c. A negative feedback mechanism operating between the parathyroid glands and the blood regulates these glands.

13.8 ADRENAL GLANDS (PAGE 508)

The adrenal glands are located atop the kidneys.

1. Structure of the glands
   a. Each adrenal gland consists of a medulla and a cortex.
   b. The adrenal medulla and adrenal cortex are distinct in that they secrete different hormones.
2. Hormones of the adrenal medulla
   a. The adrenal medulla secretes epinephrine and norepinephrine.
   b. These hormones are synthesized from tyrosine and are chemically similar.
   c. These hormones produce effects similar to those of the sympathetic nervous system.
   d. Sympathetic impulses originating from the hypothalamus stimulate secretion of these hormones.
3. Hormones of the adrenal cortex
   a. The cortex produces several types of steroids that include hormones.
   b. Aldosterone
      (1) It causes the kidneys to conserve sodium ions and water and to excrete potassium ions.
      (2) It is secreted in response to increased potassium ion concentration or presence of angiotensin II.
      (3) By conserving sodium ions and water, it helps maintain blood volume and pressure.
   c. Cortisol
      (1) It inhibits protein synthesis, releases fatty acids, and stimulates glucose formation from noncarbohydrates.
      (2) A negative feedback mechanism involving secretion of CRH from the hypothalamus and ACTH from the anterior pituitary gland controls its level.
   d. Sex hormones
      (1) These hormones are of the male type although some can be converted into female hormones.
      (2) They supplement the sex hormones produced by the gonads.

13.9 PANCREAS (PAGE 513)

The pancreas secretes digestive juices as well as hormones.

1. Structure of the gland
   a. The pancreas is posterior to the stomach and is attached to the small intestine.
   b. The endocrine portion, called the pancreatic islets (islets of Langerhans), secretes glucagon, insulin, and somatostatin.
2. Hormones of the pancreatic islets
   a. Glucagon stimulates the liver to produce glucose, increasing concentration of blood glucose. It also breaks down fat.
   b. Insulin activates facilitated diffusion of glucose through cell membranes, stimulates its storage, promotes protein synthesis, and stimulates fat storage.
   c. Facilitated diffusion of glucose into nerve cells does not depend on insulin.
   d. Somatostatin inhibits insulin and glucagon release.

13.10 OTHER ENDOCRINE GLANDS (PAGE 515)

1. Pineal gland
   a. The pineal gland is attached to the thalamus near the roof of the third ventricle.
   b. Postganglionic sympathetic nerve fibers innervate it.
   c. It secretes melatonin, which regulates some circadian rhythms.
2. Thymus
   a. The thymus lies posterior to the sternum and between the lungs.
   b. It shrinks with age.
   c. It secretes thymosin, which affects the production of certain lymphocytes that, in turn, provide immunity.
3. Reproductive organs
   a. The testes secrete testosterone.
   b. The ovaries secrete estrogens and progesterone.
   c. The placenta secretes estrogens, progesterone, and a gonadotropin.
4. The digestive glands include certain glands of the stomach and small intestine that secrete hormones.
5. Other hormone-producing organs include the heart and kidneys.

13.11 STRESS AND ITS EFFECTS (PAGE 516)

Stress occurs when the body responds to stressors that threaten the maintenance of homeostasis. Stress responses include increased activity of the sympathetic nervous system and increased secretion of adrenal hormones.

1. Types of stress
   a. Physical stress results from environmental factors that are harmful or potentially harmful to tissues.
   b. Psychological stress results from thoughts about real or imagined dangers. Factors that produce psychological stress vary with the individual and the situation.
2. Responses to stress
   a. Responses to stress maintain homeostasis.
   b. The hypothalamus controls a general adaptation (stress) syndrome.

13.12 LIFE-SPAN CHANGES (PAGE 518)

With age, endocrine glands shrink and accumulate fibrous connective tissue, fat, and lipofuscin, but hormonal activities usually remain within the normal range.

1. GH levels even out, as muscular strength declines.
2. ADH levels increase due to slowed breakdown.
3. The thyroid shrinks but control of metabolism continues.
4. Decreasing levels of calcitonin and increasing levels of parathyroid hormone increase osteoporosis risk.
5. The adrenal glands show aging-related changes, but negative feedback maintains functions.
6. Muscle, liver, and fat cells may develop insulin resistance.
7. Changes in melatonin secretion affect the body clock.
8. Thymosin production declines, hampering infectious disease resistance.

CHAPTER ASSESSMENTS

13.1 Introduction

1 Contrast the definitions of *endocrine gland* and *exocrine gland.* (p. 488)

13.2 General Characteristics of the Endocrine System

2 Explain the specificity of a hormone for its target cell. (p. 488)

3 List six general functions of hormones. (p. 489)

13.3 Hormone Action

4 Explain how hormones can be grouped on the basis of their chemical composition. (p. 490)

5 List the steps of steroid hormone action. (p. 492)

6 List the steps of the action of most nonsteroid hormones. (p. 493)

7 Explain how prostaglandins are similar to hormones and how they are different. (p. 495)

13.4 Control of Hormonal Secretions

8 Diagram the three mechanisms that control hormone secretion, including negative feedback in each mechanism. (p. 496)

13.5 Pituitary Gland

9 Describe the location and structure of the pituitary gland. (p. 497)

10 List the hormones that the anterior pituitary secretes. (p. 497)

11 Explain two ways that the brain controls pituitary gland activity. (p. 498)

12 Releasing hormones come from which one of the following? (p. 498)
   a. thyroid gland
   b. anterior pituitary gland
   c. posterior pituitary gland
   d. hypothalamus
   e. pineal gland

13 Match the following hormones with their actions: (pp. 499–502)

(1) growth hormone	A. milk synthesis
(2) thyroid stimulating hormone	B. cell division
(3) prolactin	C. metabolic rate
(4) adrenocorticotropic hormone	D. acts on gonads
(5) follicle-stimulating hormone	E. controls secretion of adrenal cortical hormones
(6) luteinizing hormone	

14 Explain how growth hormone produces its effects. (p. 499)

15 Describe the control of growth hormone secretion. (p. 499)

16 Describe the anatomical differences between the anterior and posterior lobes of the pituitary gland. (p. 502)

17 Name and describe the functions of the posterior pituitary hormones. (p. 502)

18 Under which of the following conditions would you expect an increase in antidiuretic hormone secretion? (p. 502)
   a. An individual ingests excess water.
   b. The posterior pituitary is removed because it has a tumor.
   c. An individual is rescued after three days in the desert without food or water.
   d. An individual receives an injection of synthetic antidiuretic hormone.
   e. none of the above

13.6 Thyroid Gland

19 Describe the location and structure of the thyroid gland. (p. 504)

20 Match the hormones from the thyroid gland with their descriptions. (p. 504)

(1) thyroxine	A. most potent at controlling metabolism
(2) triiodothyronine	B. regulates blood calcium
(3) calcitonin	C. has four iodine atoms

21 Define *iodide pump.* (p. 505)
22 Diagram the control of thyroid hormone secretion. (p. 505)

13.7 Parathyroid Glands

23 Describe the location and structure of the parathyroid glands. (p. 506)
24 Explain the general function of parathyroid hormone. (p. 506)
25 Diagram the regulation of parathyroid hormone secretion. (p. 507)

13.8 Adrenal Glands

26 Distinguish between the adrenal medulla and the adrenal cortex. (p. 508)
27 Match the adrenal hormones with their source and actions: (pp. 509-512)

(1) cortisol	A. cortex; sodium retention
(2) aldosterone	B. cortex; female sex hormones
(3) epinephrine	C. cortex; male sex hormones
(4) androgens	D. medulla; fight-or-flight response
(5) estrogens	E. cortex; gluconeogenesis

28 Diagram control of aldosterone secretion. (p. 510)
29 Diagram control of cortisol secretion. (p. 512)

13.9 Pancreas

30 Describe the location and structure of the pancreas. (p. 513)
31 List the hormones the pancreatic islets secrete and their general functions. (p. 514)
32 Diagram the control of pancreatic hormone secretion. (p. 514)

13.10 Other Endocrine Glands

33 Describe the location and general function of the pineal gland. (p. 515)
34 Describe the location and general function of the thymus. (p. 515)
35 Name five additional hormone-secreting organs. (p. 516)

13.11 Stress and Its Effects

36 Distinguish between a stressor and stress. (p. 516)
37 List several factors that cause physical and/or psychological stress. (p. 517)
38 Describe hormonal and nervous responses to stress. (p. 518)

13.12 Life-Span Changes

39 Levels of which hormones decrease with age? Which increase? (p. 519)

INTEGRATIVE ASSESSMENTS/CRITICAL THINKING

OUTCOMES 2.2, 13.3, 13.4, 13.5, 13.6

1. When a nuclear reactor explodes, a great plume of radioactive isotopes erupts into the air and may spread for thousands of miles. Most of the isotopes emitted immediately following the blast are of the element iodine. Which of the glands of the endocrine system would be most seriously—and immediately—affected by exposure to the isotopes, and how do you think this will become evident in the nearby population?

OUTCOMES 4.5, 13.4, 13.9

2. Why might oversecretion of insulin reduce glucose uptake by nerve cells?

OUTCOMES 13.3, 13.5, 13.11, 13.12

3. A young mother feels shaky, distracted, and generally ill. She lives with her mother, who is dying. A friend tells the young woman, "It's just stress, it's all in your head." Is it?

OUTCOMES 13.4, 13.5

4. Growth hormone is administered to people who have pituitary dwarfism. Parents wanting their normal children to be taller have requested the treatment for them. Do you think that this is a wise request? Why or why not?

OUTCOMES 13.4, 13.5, 13.6, 13.8, 13.10

5. An adult has had her anterior pituitary removed. Which hormone supplements will she require?

OUTCOMES 13.5, 13.8

6. The adrenal cortex of a patient who has lost a large volume of blood will increase secretion of aldosterone. What effect will this increased secretion have on the patient's blood concentrations of sodium and potassium ions?

OUTCOMES 13.5, 13.8, 13.11

7. What problems might result from the prolonged administration of cortisol to a person with severe inflammatory disease?