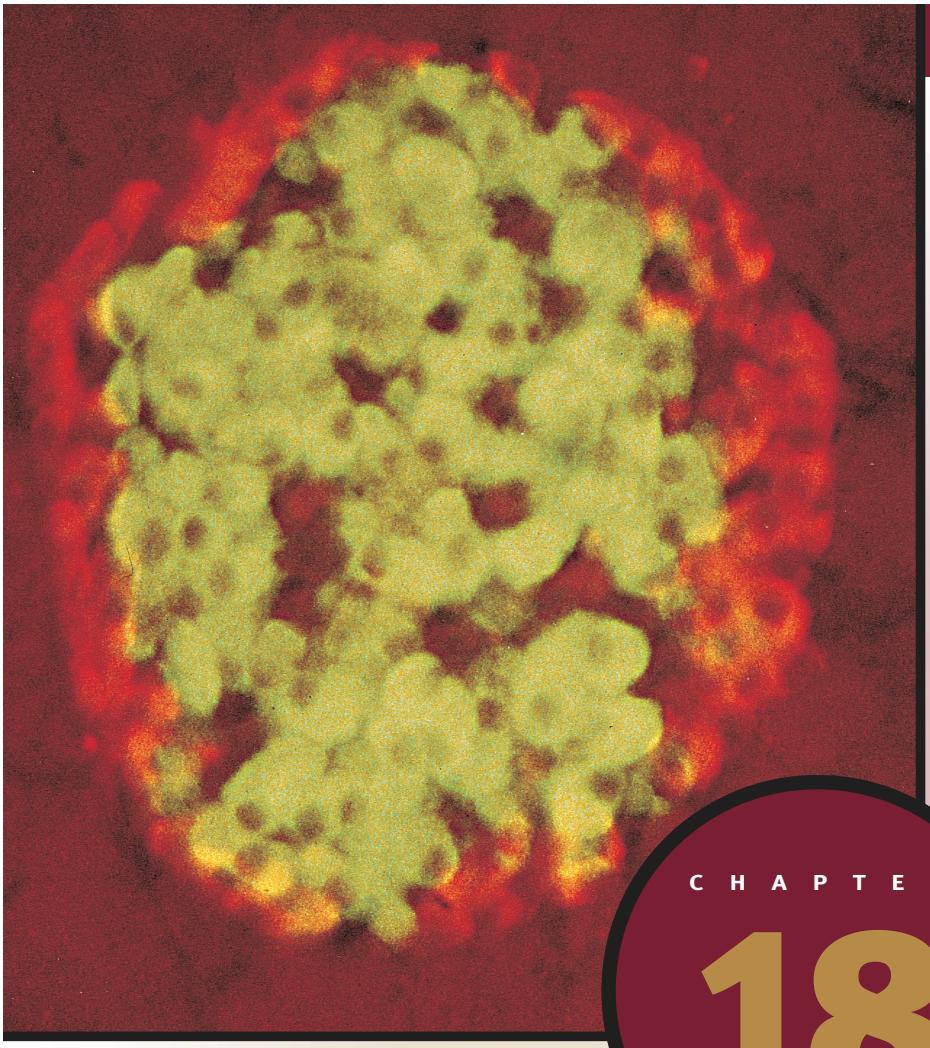


Light micrograph of a pancreatic islet showing insulin-secreting beta cells (green) and the glucagon-secreting cells (red).

CHAPTER

18

Endocrine Glands

Homeostasis depends on the precise regulation of the organs and organ systems of the body. Together the nervous and endocrine systems regulate and coordinate the activity of nearly all other body structures. When either the nervous or endocrine system fails to function properly, conditions can rapidly deviate from homeostasis. Disorders of the endocrine system can result in diseases like insulin-dependent diabetes and Addison's disease. Early in the 1900s, people who developed these diseases died. No effective treatments were available for these and other diseases of the endocrine system, such as diabetes insipidus, Cushing's syndrome, and many reproductive abnormalities. Advances have been made in understanding the endocrine system, so the outlook for people with these and other endocrine diseases has improved.

The endocrine system is small compared to its importance to healthy body functions. It consists of several small glands distributed throughout the body that could escape notice if not for the importance of the small amounts of hormones they secrete.

This chapter first explains the *functions of the endocrine system* (598) and then profiles the *pituitary gland and hypothalamus* (598), *hormones of the pituitary gland* (601), *thyroid gland* (607), *parathyroid glands* (613), *adrenal glands* (615), and *pancreas* (620). It then moves to discussions about *hormonal regulation of nutrients* (624), *hormones of the reproductive system* (627), *pineal body* (628), *thymus* (630), and *gastrointestinal tract* (630), and *hormonelike substances* (630). The chapter concludes with a look at the *effects of aging on the endocrine system* (632).

Functions of the Endocrine System

Objective

- ***Describe the main regulatory functions of the endocrine system.***

Several pieces of information are needed to understand how the endocrine system regulates body functions.

1. the anatomy of each gland and its location;
2. the hormone secreted by each gland;
3. the target tissues and the response of target tissues to each hormone;
4. the means by which the secretion of each hormone is regulated;
5. the consequences and causes, if known, of hypersecretion and hyposecretion of the hormone.

The main regulatory functions of the endocrine system include:

1. *Metabolism and tissue maturation*. The endocrine system regulates the rate of metabolism and influences the maturation of tissues such as those of the nervous system.
2. *Ion regulation*. The endocrine system helps regulate blood pH as well as Na^+, K^+, and Ca^{2+} concentrations in the blood.
3. *Water balance*. The endocrine system regulates water balance by controlling the solute concentration of the blood.
4. *Immune system regulation*. The endocrine system helps control the production of immune cells.
5. *Heart rate and blood pressure regulation*. The endocrine system helps regulate the heart rate and blood pressure and helps prepare the body for physical activity.
6. *Control of blood glucose and other nutrients*. The endocrine system regulates blood glucose levels and other nutrient levels in the blood.
7. *Control of reproductive functions.* The endocrine system controls the development and functions of the reproductive systems in males and females.
8. *Uterine contractions and milk release*. The endocrine system regulates uterine contractions during delivery and stimulates milk release from the breasts in lactating females.

1. What pieces of information are needed to understand how the endocrine system regulates body functions?
2. List 8 regulatory functions of the endocrine system.

Pituitary Gland and Hypothalamus

Objectives

- ***Describe the embryonic development, anatomy, and location of the pituitary gland as well as the structural relationship between the hypothalamus and the pituitary gland.***
- ***Describe the means by which anterior pituitary hormone secretion is regulated, and list the major releasing and inhibiting hormones released from hypothalamic neurons.***
- ***Describe the secretory cells of the posterior pituitary, including the location of their cell bodies, and the sites of hormone synthesis, transport, and secretion.***

The **pituitary** (pi-too′i-tār-rē) **gland,** or **hypophysis** (hī-pof′i-sis; an undergrowth), secretes nine major hormones that regulate numerous body functions and the secretory activity of several other endocrine glands.

The **hypothalamus** (hī′pō-thal′ă-mŭs) of the brain and the pituitary gland are major sites where the nervous and endocrine systems interact (figure 18.1). The hypothalamus regulates the secretory activity of the pituitary gland. Indeed, the posterior pituitary is an extension of the hypothalamus. Hormones, sensory information that enters the central nervous system, and emotions, in turn, influence the activity of the hypothalamus.

Structure of the Pituitary Gland

The pituitary gland is roughly 1 cm in diameter, weighs 0.5–1.0 g, and rests in the sella turcica of the sphenoid bone (see figure 18.1). It is located inferior to the hypothalamus and is connected to it by a stalk of tissue called the **infundibulum** (in-fŭn-dib′ū-lŭm).

The pituitary gland is divided functionally into two parts: the **posterior pituitary,** or **neurohypophysis** (noor′ō-hī-pof′i-sis), and the **anterior pituitary,** or **adenohypophysis** (ad′ĕ-nō-hī-pof′i-sis).

Posterior Pituitary, or Neurohypophysis

The posterior pituitary is called the neurohypophysis because it is continuous with the brain (*neuro-* refers to the nervous system). It is formed during embryonic development from an outgrowth of the inferior part of the brain in the area of the hypothalamus (see chapter 29). The outgrowth of the brain forms the infundibulum, and the distal end of the infundibulum enlarges to form the posterior pituitary (figure 18.2). Secretions of the posterior pituitary are considered **neurohormones** (noor-ōhōr′mōnz) because it is an extension of the nervous system.

Anterior Pituitary, or Adenohypophysis

The anterior pituitary, or adenohypophysis (*adeno-* means gland), arises as an outpocketing of the roof of the embryonic oral cavity called the pituitary diverticulum or Rathke's pouch, which grows

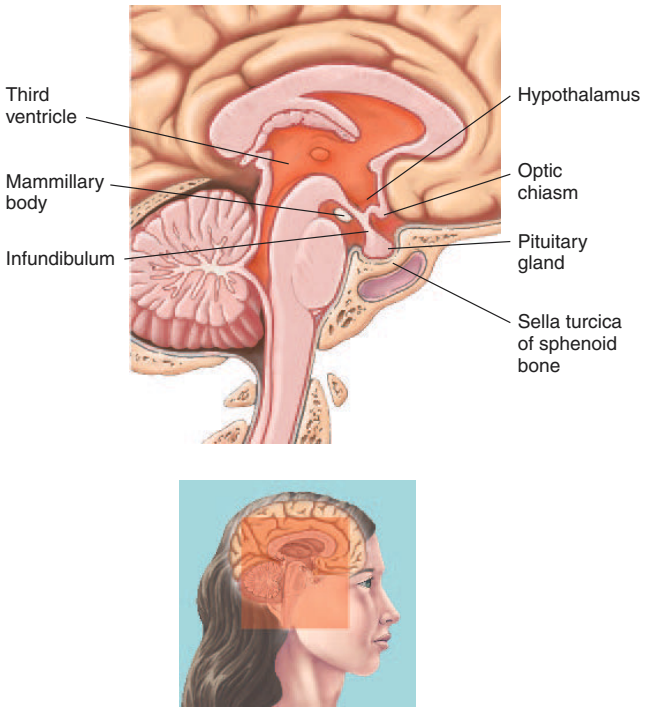


Figure 18.1 The Hypothalamus and Pituitary Gland

A midsagittal section of the head through the pituitary gland showing the location of the hypothalamus and the pituitary. The pituitary gland is in a depression called the sella turcica in the floor of the skull. It's connected to the hypothalamus of the brain by the infundibulum.

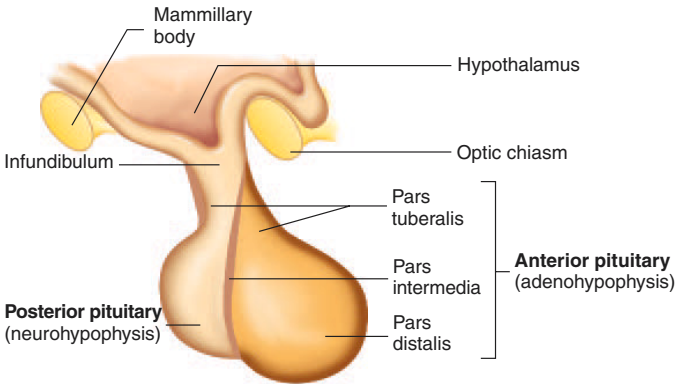


Figure 18.2 Subdivisions of the Pituitary Gland

The pituitary gland is divided into the anterior pituitary, or adenohypophysis, and the posterior pituitary, or neurohypophysis. The anterior pituitary is subdivided further into the pars distalis, pars intermedia, and pars tuberalis. The posterior pituitary consists of the enlarged distal end of the infundibulum, which connects the posterior pituitary to the hypothalamus.

toward the posterior pituitary. As it nears the posterior pituitary, the pituitary diverticulum loses its connection with the oral cavity and becomes the anterior pituitary. The anterior pituitary is subdivided into three areas with indistinct boundaries: the pars tuberalis, the pars distalis, and the pars intermedia (see figure 18.2). The hormones secreted from the anterior pituitary, in contrast to those from the posterior pituitary, are not neurohormones because the anterior pituitary is derived from epithelial tissue of the embryonic oral cavity and not from neural tissue.

Relationship of the Pituitary to the Brain

Portal vessels are blood vessels that begin and end in a capillary network. The **hypothalamohypophysial** (hī′pō-thal′ă-mō-hī′pō-fiz′ē-ăl) **portal system** extends from a part of the hypothalamus to the anterior pituitary (figure 18.3). The primary capillary network in the hypothalamus is supplied with blood from arteries that deliver blood to the hypothalamus. From the primary capillary network, the hypothalamohypophysial portal vessels carry blood to a secondary capillary network in the anterior pituitary. Veins from the secondary capillary network eventually merge with the general circulation.

Neurohormones, produced and secreted by neurons of the hypothalamus, enter the primary capillary network and are carried to the secondary capillary network. There the neurohormones leave the blood and act on cells of the anterior pituitary. They act either as **releasing hormones,** increasing the secretion of anterior pituitary hormones, or as **inhibiting hormones,** decreasing the secretion of anterior pituitary hormones. Each releasing hormone stimulates and each inhibiting hormone inhibits the production and secretion of a specific hormone by the anterior pituitary. In response to the releasing hormones, anterior pituitary cells secrete hormones that enter the secondary capillary network and are carried by the general circulation to their target tissues. Thus, the hypothalamohypophysial portal system provides a means by which the hypothalamus, using neurohormones as chemical signals, regulates the secretory activity of the anterior pituitary (see figure 18.3).

Several major releasing and inhibiting hormones are released from hypothalamic neurons. **Growth hormone-releasing hormone (GHRH)** is a small peptide that stimulates the secretion of growth hormone from the anterior pituitary gland, and **growth hormone-inhibiting hormone (GHIH),** also called **somatostatin,** is a small peptide that inhibits growth hormone secretion. **Thyroid-releasing hormone (TRH)** is a small peptide that stimulates the secretion of thyroid-stimulating hormone from the anterior pituitary gland. **Corticotropin-releasing hormone (CRH)** is a peptide that stimulates adrenocorticotropic hormone from the anterior pituitary gland. **Gonadotropin-releasing hormone (GnRH)** is a small peptide that stimulates luteinizing hormone and follicle-stimulating hormone from the anterior pituitary gland. **Prolactin-releasing hormone (PRH)** and **prolactin-inhibiting hormone (PIH)** regulate the secretion of prolactin from the

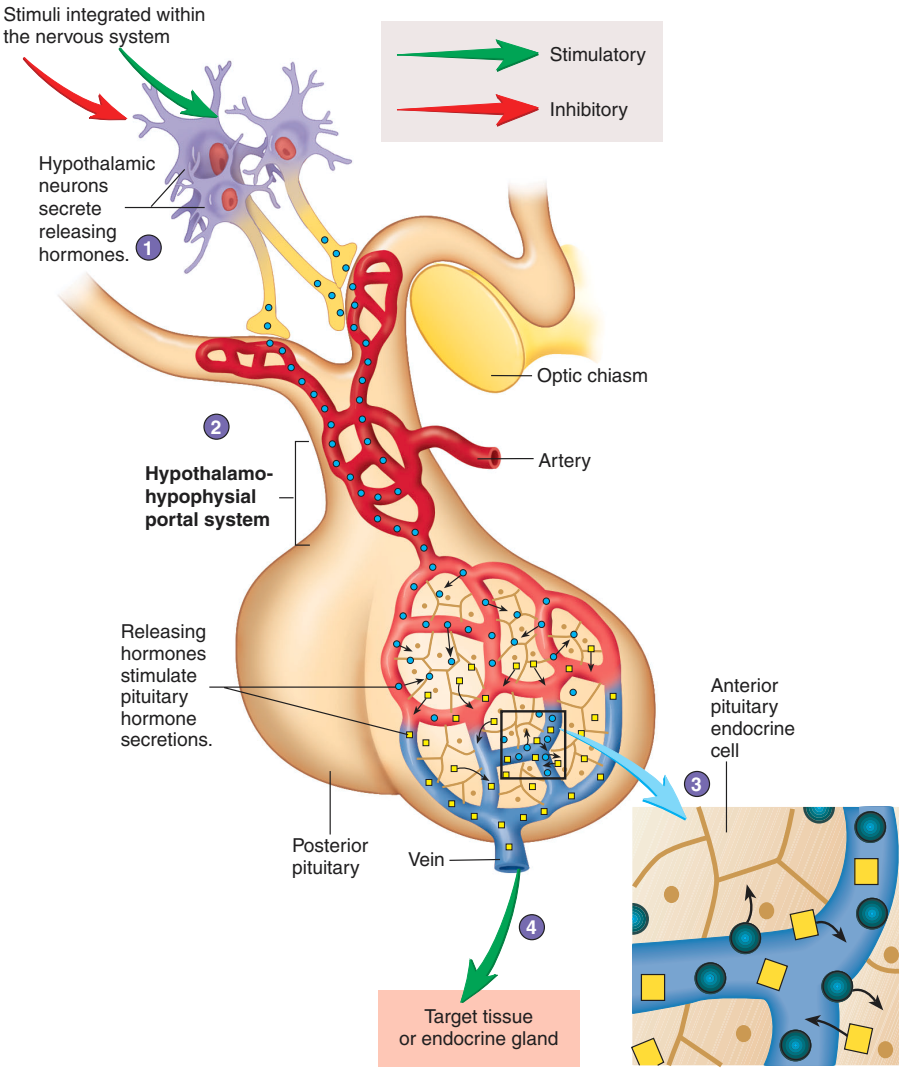


Figure 18.3 Relationship Among the Hypothalamus, Anterior Pituitary, and Target Tissues

anterior pituitary gland (table 18.1). These releasing hormones are sometimes referred to as releasing or inhibiting factors because their structure is not certain or because more than one substance from the hypothalamus is known to act as a releasing or inhibiting factor. The term hormone has been used in this text, to avoid confusion and because the *rapid* rate at which new discoveries are made. Secretions of the anterior pituitary gland are described in a following section called "Anterior Pituitary Hormones" (p 604).

There is no portal system to carry hypothalamic neurohormones to the posterior pituitary. Neurohormones released from the posterior pituitary are produced by neurosecretory cells with their cell bodies located in the hypothalamus. The axons of these cells extend from the hypothalamus through the infundibulum into the posterior pituitary and form a nerve tract called the **hypothalamohypophysial tract** (figure 18.4). Neurohormones produced in the hypothalamus pass down these axons in tiny vesicles and are stored in secretory vesicles in the enlarged ends of the axons. Action potentials originating in the neuron cell bodies in the hypothalamus are propagated along the axons to the axon terminals in the posterior pituitary. The action potentials cause the release of neurohormones from the axon terminals, and they enter the circulatory system. Secretions of the posterior pituitary gland are described in a following section called "Posterior Pituitary Hormones" (p 601).

3. *Where is the pituitary gland located? Contrast the embryonic origin of the anterior pituitary and the posterior pituitary.*
4. *Name the parts of the pituitary gland and the function of each part.*
5. *Define portal system. Describe the hypothalamohypophysial portal system. How does the hypothalamus regulate the secretion of the anterior pituitary hormones?*

Table 18.1 Hormones of the Hypothalamus

Hormones	Structure	Target Tissue	Response
Growth hormone-releasing hormone (GHRH)	Small peptide	Anterior pituitary cells that secrete growth hormone	Increased growth hormone secretion
Growth hormone-inhibiting hormone (GHIH), or somatostatin	Small peptide	Anterior pituitary cells that secrete growth hormone	Decreased growth hormone secretion
Thyroid-releasing hormone (TRH)	Small peptide	Anterior pituitary cells that secrete thyroid-stimulating hormone	Increased thyroid-stimulating hormone secretion
Corticotropin-releasing hormone (CRH	Peptide	Anterior pituitary cells that secrete adrenocorticotropic hormone	Increased adrenocorticotropic hormone secretion
Gonadotropin-releasing hormone (GnRH)	Small peptide	Anterior pituitary cells that secrete luteinizing hormone and follicle-stimulating hormone	Increased secretion of luteinizing hormone and follicle-stimulating hormone
Prolactin-inhibiting hormone (PIH)	Unknown (possibly dopamine)	Anterior pituitary cells that secrete prolactin	Decreased prolactin secretion
Prolactin-releasing hormone (PRH)	Unknown	Anterior pituitary cells that secrete prolactin	Increased prolactin secretion

6. *List the releasing and inhibiting hormones that are released from hypothalamic neurons.*
7. *Describe the hypothalamohypophysial tract, including the production of neurohormones in the hypothalamus and their secretion from the posterior pituitary.*

PREDICT 1

Surgical removal of the posterior pituitary in experimental animals results in marked symptoms, but these symptoms associated with hormone shortage are temporary. Explain these results.

Hormones of the Pituitary Gland

Objective

- ***Describe the target tissues, regulation, and responses to each of the posterior and anterior pituitary hormones.***

This section describes the hormones secreted from the pituitary gland (table 18.2), their effects on the body, and the mechanisms that regulate their secretion rate. In addition, some major consequences of abnormal hormone secretion are stressed.

Posterior Pituitary Hormones

The posterior pituitary stores and secretes two polypeptide neurohormones called antidiuretic hormone and oxytocin. A separate population of cells secretes each hormone.

Antidiuretic Hormone

Antidiuretic (an′tē-d-ī-ū-ret′ik) **hormone (ADH)** is so named because it prevents *(anti-)* the output of large amounts of urine *(diuresis)*. ADH is sometimes called **vasopressin** (vā-sō-pres′in, vas-ō-pres′in) because it constricts blood vessels and raises blood pressure when large amounts are released. ADH is synthesized by neuron cell bodies in the supraoptic nuclei of the hypothalamus and transported within the axons of the hypothalamohypophysial tract to the posterior pituitary, where it is stored in axon terminals. ADH is released from these axon terminals into the blood and carried to its primary target tissue, the kidneys, where it promotes the retention of water and reduces urine volume (see chapter 26).

The secretion rate for ADH changes in response to alterations in blood osmolality and blood volume. The osmolality of a solution increases as the concentration of solutes in the solution increases. Specialized neurons, called **osmoreceptors** (os′mō-rē-sep′terz, os′mō-rē-sep′tōrz), synapse with the ADH neurosecretory cells in the hypothalamus. When blood osmolality increases, the frequency of action potentials in the osmoreceptors increases, resulting in a greater frequency of action potentials in the neurosecretory cells. As a consequence, ADH secretion increases. Alternatively, an increase in blood osmolality can directly stimulate the ADH neurosecretory cells. Because ADH stimulates the kidneys to retain water, it functions to reduce blood osmolality and resists any further increase in the osmolality of body fluids.

As the osmolality of the blood decreases, the action potential frequency in the osmoreceptors and the neurosecretory cells decreases. Thus, less ADH is secreted from the posterior pituitary gland, and the volume of water eliminated in the form of urine increases.

Urine volume increases within minutes to a few hours in response to the consumption of a large volume of water. In contrast, urine volume decreases and urine concentration increases within hours if little water is consumed. ADH plays a major role in these changes in urine formation. The effect is to maintain the osmolality

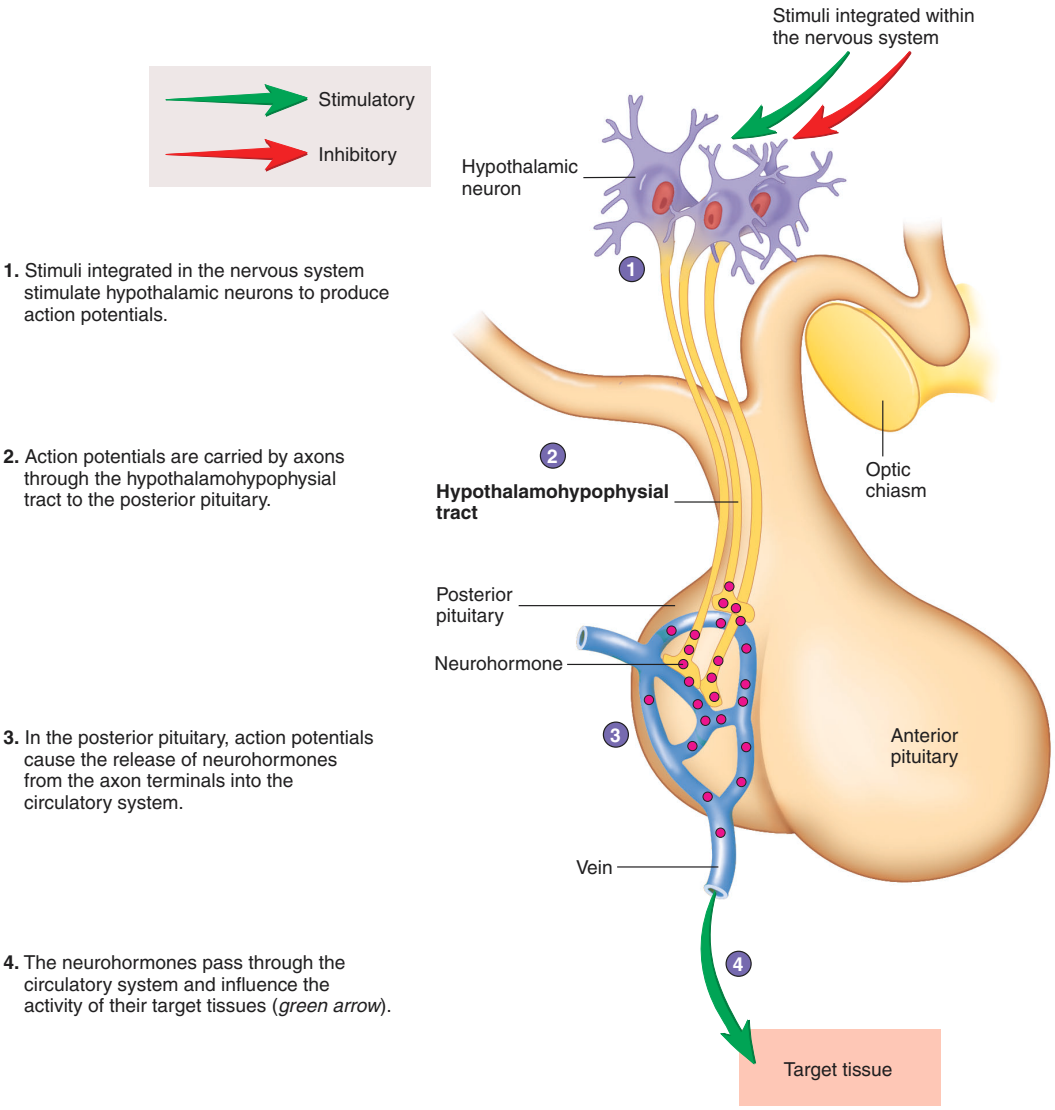


Figure 18.4 Relationship Among the Hypothalamus, Posterior Pituitary, and Target Tissues

and the volume of the extracellular fluid within a normal range of values.

Sensory receptors that detect changes in blood pressure send action potentials through sensory nerve fibers of the vagus nerve that eventually synapse with the ADH neurosecretory cells. A decrease in blood pressure, which normally accompanies a decrease in blood volume, causes an increased action potential frequency in the neurosecretory cells and increased ADH secretion, which stimulates the kidneys to retain water. Because the water in urine is derived from blood as it passes through the kidneys, ADH slows any further reduction in blood volume.

An increase in blood pressure decreases the action potential frequency in neurosecretory cells. This leads to the secretion of less ADH from the posterior pituitary. As a result, the volume of urine produced by the kidneys increases (figure 18.5). The effect of ADH on the kidney and its role in the regulation of extracellular osmolality and volume are described in greater detail in chapters 26 and 27.

Table 18.2 Hormones of the Pituitary Gland

Hormones	Structure	Target Tissue	Response
Posterior Pituitary (Neurohypophysis)			
Antidiuretic hormone (ADH)	Small peptide	Kidney	Increased water reabsorption (less water is lost in the form of urine)
Oxytocin	Small peptide	Uterus; mammary glands	Increased uterine contractions; increased milk expulsion from mammary glands; unclear function in males
Anterior Pituitary (Adenohypophysis)			
Growth hormone (GH), or somatotropin	Protein	Most tissues	Increased growth in tissues; increased amino acid uptake and protein synthesis; increased breakdown of lipids and release of fatty acids from cells; increased glycogen synthesis and increased blood glucose levels; increased somatomedin production
Thyroid-stimulating hormone (TSH)	Glycoprotein	Thyroid gland	Increased thyroid hormone secretion
Adrenocorticotropic hormone (ACTH)	Peptide	Adrenal cortex	Increased glucocorticoid hormone secretion
Lipotropins	Peptides	Fat tissues	Increased fat breakdown
β endorphins	Peptides	Brain, but not all target tissues are known	Analgesia in the brain; inhibition of gonadotropin-releasing hormone secretion
Melanocyte-stimulating hormone (MSH)	Peptide	Melanocytes in the skin	Increased melanin production in melanocytes to make the skin darker in color
Luteinizing hormone (LH)	Glycoprotein	Ovaries in females; testes in males	Ovulation and progesterone production in ovaries; testosterone synthesis and support for sperm cell production in testes
Follicle-stimulating hormone (FSH)	Glycoprotein	Follicles in ovaries in females; seminiferous tubes in males	Follicle maturation and estrogen secretion in ovaries; sperm cell production in testes
Prolactin	Protein	Ovaries and mammary glands in females	Milk production in lactating women; increased response of follicle to LH and FSH; unclear function in males

Diabetes Insipidus

A lack of ADH secretion is one cause of diabetes insipidus and leads to the production of a large amount of dilute urine, which can approach 20 L/day. The loss of many liters of water in the form of urine causes an increase in the osmolality of the body fluids, and a decrease in extracellular fluid volume, but negative-feedback mechanisms fail to stimulate ADH release. The volume of urine produced each day increases rapidly as the rate of ADH secretion becomes less than 50% of normal. Diabetes insipidus can also result from either damage to the kidneys or a genetic disorder that makes the kidneys incapable of responding to ADH. Damage to the nephrons can result from infection or other diseases that damage the nephrons and make them insensitive to ADH. In genetic disorders either the receptor for ADH is abnormal or the intracellular signal molecules fail to produce a normal response. The consequences of diabetes insipidus are not obvious until the condition becomes severe. When the condition is severe, dehydration and death can result unless the intake of water is adequate to accommodate its loss.

Oxytocin

Oxytocin (ok-sē-tō′sin) is synthesized by neuron cell bodies in the paraventricular nuclei of the hypothalamus and then is transported through axons to the posterior pituitary, where it is stored in the axon terminals.

Oxytocin stimulates smooth muscle cells of the uterus. This hormone plays an important role in the expulsion of the fetus from the uterus during delivery by stimulating uterine smooth muscle contraction. It also causes contraction of uterine smooth muscle in nonpregnant women, primarily during menses and sexual intercourse. The uterine contractions play a role in the expulsion of the uterine epithelium and small amounts of blood during menses and can participate in the movement of sperm cells through the uterus after sexual intercourse. Oxytocin is also responsible for milk ejection in lactating females by promoting contraction of smooth musclelike cells surrounding the alveoli of the mammary glands (see chapter 29). Little is known about the effect of oxytocin in males.

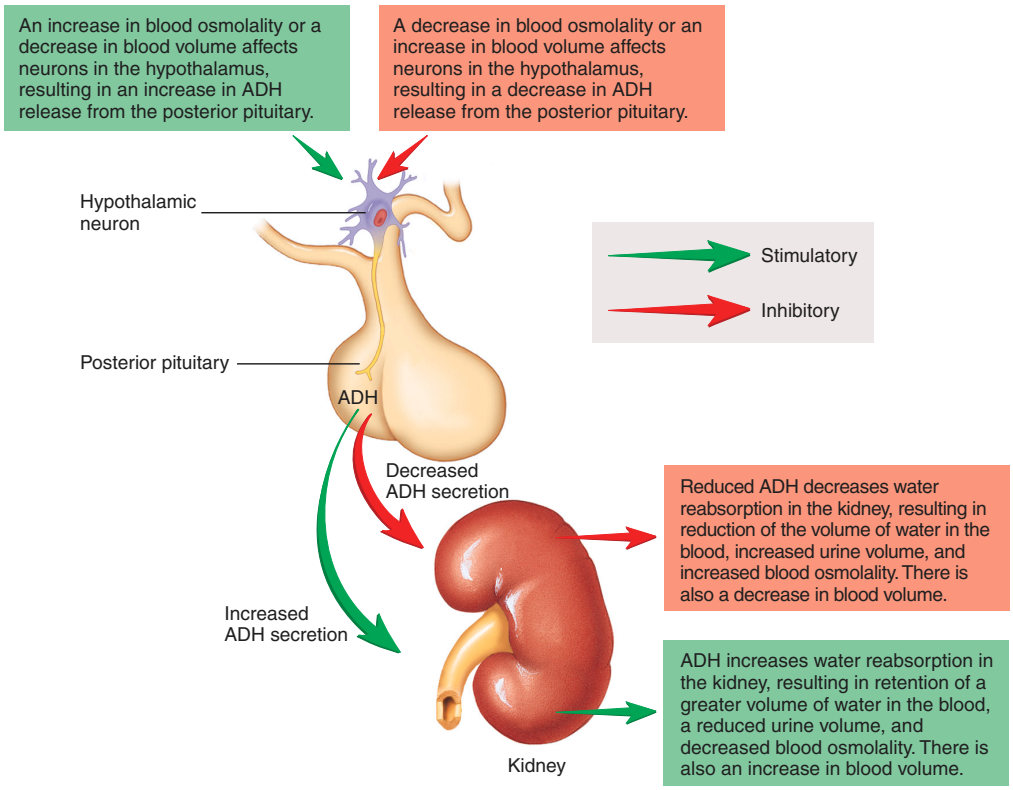


Figure 18.5 Control of Antidiuretic Hormone (ADH) Secretion

The relationship among blood osmolality, blood volume, ADH secretion, and kidney function. Small changes in blood osmolality are important in regulating ADH secretion. Larger changes in blood volume are required to influence ADH secretion.

Stretch of the uterus, mechanical stimulation of the cervix, or stimulation of the nipples of the breast when a baby nurses activate nervous reflexes that stimulate oxytocin release. Action potentials are carried by sensory neurons from the uterus and from the nipples to the spinal cord. Action potentials are then carried up the spinal cord to the hypothalamus, where they increase action potentials in the oxytocin-secreting neurons. Action potentials in the oxytocin-secreting neurons pass along the axons in the hypothalamohypophysial tract to the posterior pituitary, where they cause the axon terminals to release oxytocin. The role of oxytocin in the reproductive system is described in greater detail in chapter 29.

8. *Where is ADH produced, from where is it secreted, and what is its target tissue? When ADH levels increase, how are urine volume, blood osmolality, and blood volume affected?*
9. *The secretion rate for ADH changes in response to alterations in what two factors? Name the types of sensory cells that respond to alterations in those factors.*
10. *Where is oxytocin produced and secreted, and what effects does it have on its target tissues? What factors stimulate the secretion of oxytocin?*

Anterior Pituitary Hormones

Releasing and inhibiting hormones that pass from the hypothalamus through the hypothalamohypophysial portal system to the anterior pituitary influence anterior pituitary secretions. For some anterior pituitary hormones, the hypothalamus produces both releasing hormones and inhibiting hormones. For others regulation is primarily by releasing hormones (see table 18.1).

The hormones released from the anterior pituitary are proteins, glycoproteins, or polypeptides. They are transported in the circulatory system, have a half-life measured in minutes, and bind to membrane-bound receptor molecules on their target cells. For the most part, each hormone is secreted by a separate cell type. Adrenocorticotropic hormone and lipotropin are exceptions because these hormones are derived from the same precursor protein.

Anterior pituitary hormones are called **tropic** (trop′ik, trō′ pik) **hormones.** They are released from the anterior pituitary gland and regulate target tissues including the secretion of hormones from other endocrine glands. The tropic hormones include growth hormone, adrenocorticotropic hormone and related substances, luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone.

Growth Hormone

Growth hormone (GH), sometimes called **somatotropin** (sō′mă-tō-trō′pin), stimulates growth in most tissues, plays a major role in regulating growth, and therefore, plays an important role in determining how tall a person becomes. It is also a regulator of metabolism. GH increases the number of amino acids entering cells and favors their incorporation into proteins. It increases lipolysis, or the breakdown of lipids and the release of fatty acids from fat cells. Fatty acids then can be used as energy sources to drive chemical reactions, including anabolic reactions, by other cells. GH increases glycogen synthesis and storage in tissues, and the increased use of fats as an energy source spares glucose. GH plays an important role in regulating blood nutrient levels after a meal and during periods of fasting.

GH binds directly to membrane-bound receptors on target cells (see chapter 17), such as fat cells, to produce responses. These responses are called the direct effects of GH and include the increased breakdown of lipids and decreased use of glucose as an energy source.

GH also has indirect effects on some tissues. It increases the production of a number of polypeptides, primarily by the liver but also by skeletal muscle and other tissues. These polypeptides, called **somatomedins** (sō′mă-tō-mē′dinz), circulate in the blood and bind to receptors on target tissues. The best understood effects of the somatomedins are the stimulation of growth in cartilage and bone and the increased synthesis of protein in skeletal muscles. The best known somatomedins are two polypeptide hormones produced by the liver called **insulinlike growth factor I** and **II** because of the similarity of their structure to insulin and because the receptor molecules function through a mechanism similar to the receptors for insulin. Growth hormone and growth factors, like somatomedins, bind to membrane-bound receptors that phosphorylate intracellular proteins (see chapter 17).

Two neurohormones released from the hypothalamus regulate the secretion of GH (figure 18.6). One factor, growth hormone-releasing hormone (GHRH), stimulates the secretion of GH, and the other, growth hormone-inhibiting hormone (GHIH), or **somatostatin** (sō′mă-tō-stat′in), inhibits the secretion of GH. Stimuli that influence GH secretion act on the hypothalamus to increase or decrease the secretion of the releasing and inhibiting hormones. Low blood glucose levels and stress stimulate secretion of GH, and high blood glucose levels inhibit secretion of GH. Rising blood levels of certain amino acids also increases GH secretion.

In most people, a rhythm of GH secretion occurs. Daily peak levels of GH are correlated with deep sleep. A chronically elevated blood GH level during periods of rapid growth does not occur, although children tend to have somewhat higher blood levels of GH than adults. In addition to GH, factors like genetics, nutrition, and sex hormones influence growth.

Several pathologic conditions are associated with abnormal GH secretion. In general, the causes for hypersecretion or hyposecretion of GH are the result of tumors in the hypothalamus or pituitary, the synthesis of structurally abnormal GH, the inability of the liver to produce somatomedins, or the lack of functional receptors in target tissues. The consequences of hypersecretion and hyposecretion of growth hormone are described in the Clinical Focus on "Growth Hormone and Growth Disorders" (page 606); also see chapter 6.

P R E D I C T 2

Mr. Hoops has a son who wants to be a basketball player almost as much as Mr. Hoops wants him to be one. Mr. Hoops knows a little bit about growth hormone and asks his son's doctor if he would prescribe some for his son, so he can grow tall. What do you think the doctor tells Mr. Hoops?

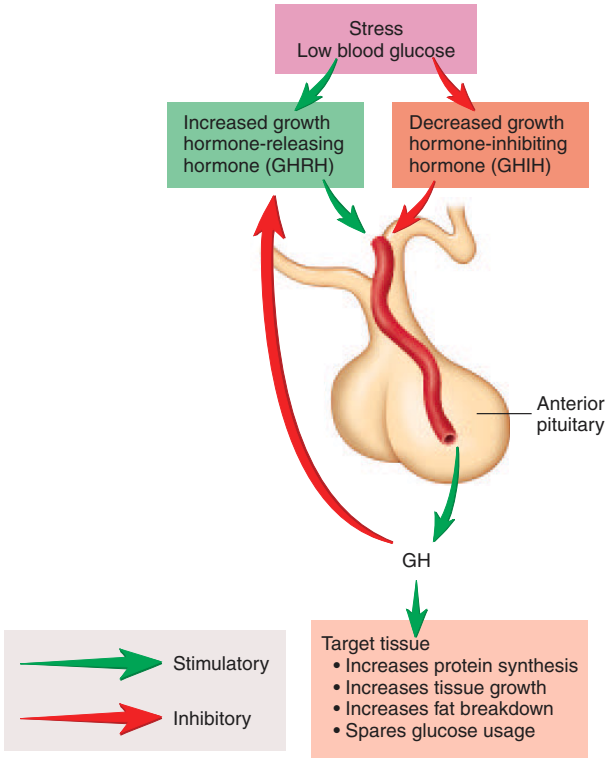


Figure 18.6 Control of Growth Hormone (GH) Secretion

Secretion of GH is controlled by two neurohormones released from the hypothalamus: growth hormone-releasing hormone (GHRH), which stimulates GH secretion, and growth hormone-inhibiting hormone (GHIH), which inhibits GH secretion. Stress increases GHRH secretion and inhibits GHIH secretion. High levels of GH have a negative-feedback effect on the production of GHRH by the hypothalamus.

Clinical Focus Growth Hormone and Growth Disorders

Chronic hyposecretion of GH in infants and children leads to **dwarfism** (dwōrf′izm), or short stature due to delayed bone growth. The bones usually have a normal shape, however. In contrast to dwarfism caused by hyposecretion of thyroid hormones, these dwarfs exhibit normal intelligence. Other symptoms resulting from the lack of GH include mild obesity and retarded development of adult reproductive functions. Two types of dwarfism result from a lack of GH secretion: (1) In approximately two-thirds of the cases, GH and other anterior pituitary hormones are secreted in reduced amounts. The decrease in other anterior pituitary hormones can result in additional disorders, such as reduced secretion of thyroid hormones and inability to reproduce; (2) in the remaining approximately one-third of cases, a reduced amount of GH is observed, and the secretion of other anterior pituitary hormones is closer to normal. Normal reproduction is possible for these individuals. No obvious pathology is associated with hyposecretion of GH in adults, although some evidence suggests that lack of GH can lead to reduced bone mineral content in adults.

The gene responsible for determining the structure of GH has been transferred successfully from human cells to bacterial cells, which produce GH that is identical to human GH. The GH produced in this fashion is available to treat patients who suffer from a lack of GH secretion.

Chronic hypersecretion of GH leads to **giantism** (jī′an-tizm) or **acromegaly** (ak-rō-meg′ă-lē), depending on whether the hypersecretion occurs before or after complete ossification of the epiphysial plates in the skeletal system. Chronic hypersecretion of GH before the epiphysial plates have ossified causes exaggerated and prolonged growth in long bones, resulting in giantism. Some individuals thus affected have grown to be 8 feet tall or more.

In adults, chronically elevated GH levels result in acromegaly. No increase in height occurs because of the ossified epiphysial plates. The condition does result in an increased diameter of fingers, toes, hands, and feet; the deposition of heavy bony ridges above the eyes; and a prominent jaw. The influence of GH on soft tissues results in a bulbous or broad nose, an enlarged tongue, thickened skin, and sparse subcutaneous adipose tissue. Nerves frequently are compressed as a result of the proliferation of connective tissue. Because GH spares glucose usage, chronic hyperglycemia results, frequently leading to diabetes mellitus and the development of severe atherosclerosis. Treatment for chronic hypersecretion of GH often involves surgical removal or irradiation of a GH-producing tumor.

Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH), also called **thyrotropin** (thī-rot′rō-pin, thī-rō-trō′pin), stimulates the synthesis and secretion of thyroid hormones from the thyroid gland. TSH is a glycoprotein consisting of α and β subunits, which bind to membrane-bound receptors of the thyroid gland. The receptors respond through a G protein mechanism that increases the intracellular chemical signal, cAMP. In higher concentrations, TSH also increases the activity of phospholipase. Phospholipase activates mechanisms that open Ca^{2+} channels and increases the Ca^{2+} concentration in cells of the thyroid gland (see chapter 17).

TSH secretion is controlled by TRH from the hypothalamus and thyroid hormones from the thyroid gland. TRH binds to membrane-bound receptors in cells of the anterior pituitary gland and activates G proteins, which results in increased TSH secretion. In contrast, thyroid hormones inhibit both TRH and TSH secretion. TSH is secreted in a pulsatile fashion and its blood levels are highest at night, but it's secreted at a rate so that blood levels of thyroid hormones are maintained within a narrow range of values (see "Thyroid Hormones" p 608).

Adrenocorticotropic Hormone and Related Substances

Adrenocorticotropic (ă-drē′nō-kōr′ti-kō-trō′pik) **hormone (ACTH)** is one of several anterior pituitary hormones derived from a precursor molecule called **proopiomelanocortin** (prō-ō′pē-ō-mel′ă-nō-kōr′tin). This large molecule gives rise to ACTH, lipotropins, β endorphin, and melanocyte-stimulating hormone.

ACTH binds to membrane-bound receptors and activates a G protein mechanism that increases cAMP, which produces a response. ACTH increases the secretion of hormones, primarily cortisol, from the adrenal cortex. ACTH and melanocyte-stimulating hormone also bind to melanocytes in the skin and increase skin pigmentation (see chapter 5). In pathologic conditions like Addison's disease, blood levels of ACTH and related hormones are chronically elevated, and the skin becomes markedly darker. Regulation of ACTH secretion and the effect of hypersecretion and hyposecretion of ACTH are described in the section on "Adrenal Glands" on page 615.

The **lipotropins** (li-pō-trō′pinz) secreted from the anterior pituitary bind to membrane-bound receptor molecules on adipose

tissue cells. They cause fat breakdown and the release of fatty acids into the circulatory system.

The **β endorphins** (en′dōr-finz) have the same effects as opiate drugs like morphine, and they can play a role in analgesia in response to stress and exercise. Other functions have been proposed for the β endorphins, including regulation of body temperature, food intake, and water balance. Both ACTH and β-endorphin secretions increase in response to stress and exercise.

Melanocyte-stimulating hormone (MSH) binds to membrane-bound receptors on skin melanocytes and stimulates increased melanin deposition in the skin. The regulation of MSH secretion and its function in humans is not well understood, although it's an important regulator of skin pigmentation in some other vertebrates.

Luteinizing Hormone, Follicle-Stimulating Hormone, and Prolactin

Gonadotropins (gō′nad-ō-trō′pinz) are hormones capable of promoting growth and function of the **gonads,** which include the ovaries and testes. The two major gonadotropins secreted from the anterior pituitary are **luteinizing** (loo′tē-ĭ-nīz-ing) **hormone (LH)** and **follicle-stimulating hormone (FSH).** LH, FSH, and another anterior pituitary hormone called **prolactin** (prō-lak′tin) play important roles in regulating reproduction.

LH and FSH secreted into the blood bind to membrane-bound receptors, increase the intracellular synthesis of cAMP through G protein mechanisms, and stimulate the production of **gametes** (gam′ēts)—sperm cells in the testes and oocytes in ovaries. LH and FSH also control the production of reproductive hormones—estrogens and progesterone in the ovaries and testosterone in the testes.

LH and FSH are released from anterior pituitary cells under the influence of the hypothalamic-releasing hormone, **gonadotropin-releasing hormone (GnRH).** GnRH is also called **luteinizing hormone-releasing hormone (LHRH).**

Prolactin plays an important role in milk production in the mammary glands of lactating females. It binds to a membrane-bound receptor that phosphorylates intracellular proteins. The phosphorylated proteins produce the response in the cell. Prolactin can also increase the number of receptor molecules for FSH and LH in the ovaries (up regulation), and it therefore has a permissive effect for FSH and LH on the ovary. Prolactin also can enhance progesterone secretion of the ovary after ovulation. No role for this hormone has been clearly established in males. Several hypothalamic neurohormones can be involved in the complex regulation of prolactin secretion. One neurohormone is prolactin-releasing hormone (PRH), and another is prolactin-inhibiting hormone (PIH). The regulation of gonadotropin and prolactin secretion and their specific effects are explained more fully in chapter 28.

11. *Structurally, what kind of hormones are released from the posterior pituitary and the anterior pituitary? Do these hormones bind to plasma proteins, how long is their half-life, and how do they activate their target tissues?*
12. *For each of the following hormones secreted by the anterior pituitary—GH, TSH, ACTH, LH, FSH, and prolactin—name its target tissue and the effect of the hormone on its target tissue.*
13. *What effects do stress, amino acid levels in the blood, and glucose levels in the blood have on GH secretion?*
14. *What stimulates somatomedin production, where is it produced, and what are its effects?*
15. *How are ACTH, MSH, lipotropins, and β endorphins related? What are the functions of these hormones?*
16. *Define gonadotropins, and name two gonadotropins produced by the anterior pituitary.*

Thyroid Gland

Objectives

- *Describe the histology and location of the thyroid gland and describe the synthesis and transport of thyroid hormones.*
- *Explain the response of target tissues to thyroid hormones, and outline the regulation of thyroid hormone secretion.*
- *Explain the regulation of calcitonin secretion, and describe its function.*

The **thyroid gland** is composed of two lobes connected by a narrow band of thyroid tissue called the **isthmus.** The lobes are lateral to the upper portion of the trachea just inferior to the larynx, and the isthmus extends across the anterior aspect of the trachea (figure 18.7*a*). The thyroid gland is one of the largest endocrine glands, with a weight of approximately 20 g. It is highly vascular and appears more red than its surrounding tissues.

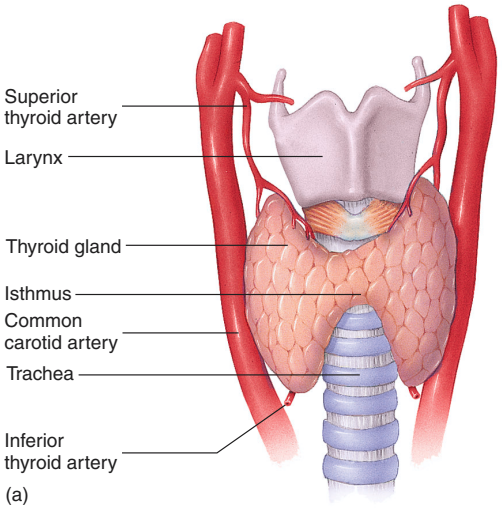
Histology

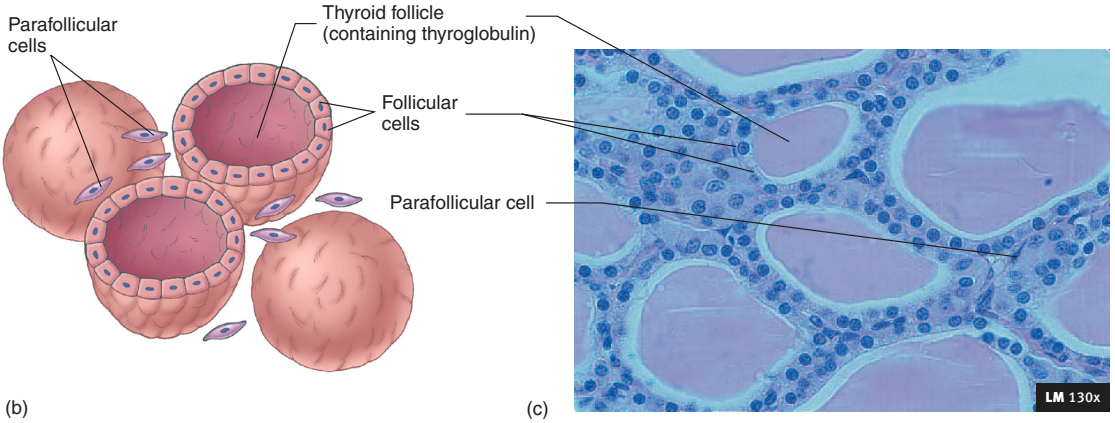
The thyroid gland contains numerous **follicles,** which are small spheres whose walls are composed of a single layer of cuboidal epithelial cells (figure 18.7*b* and *c*). The center, or lumen, of each thyroid follicle is filled with a protein called **thyroglobulin** (thī-rō-glob′ū-lin) to which thyroid hormones are bound. Because of thyroglobulin the follicles store large amounts of the thyroid hormones.

Between the follicles, a delicate network of loose connective tissue contains numerous capillaries. Scattered **parafollicular** (par-ă-fo-lik′ū-lăr) **cells** are found between the follicles and among the cells that make up the walls of the follicle. **Calcitonin** (kal-si-tō′nin) is secreted from the parafollicular cells and plays a role in reducing the concentration of calcium in the body fluids when calcium levels become elevated.

Figure 18.7 Anatomy and Histology of the Thyroid Gland

(*a*) Frontal view of the thyroid gland. (*b*) Histology of the thyroid gland. The gland is made up of many spheric thyroid follicles containing thyroglobulin. Parafollicular cells are in the tissue between the thyroid follicles. (*c*) Low-power photomicrograph of thyroid follicles.





Thyroid Hormones

The thyroid hormones include both **triiodothyronine** (trī-ī′ō-dō-thī′rō-nēn; **T_3**) and **tetraiodothyronine** (tet′ră-ī′ō-dō-thī′rō-nēn; **T_4**). T_4 is also called **thyroxine** (thī-rok′sēn, thī-rok′sin). These substances constitute the major secretory products of the thyroid gland, consisting of 10% T_3 and 90% T_4 (table 18.3).

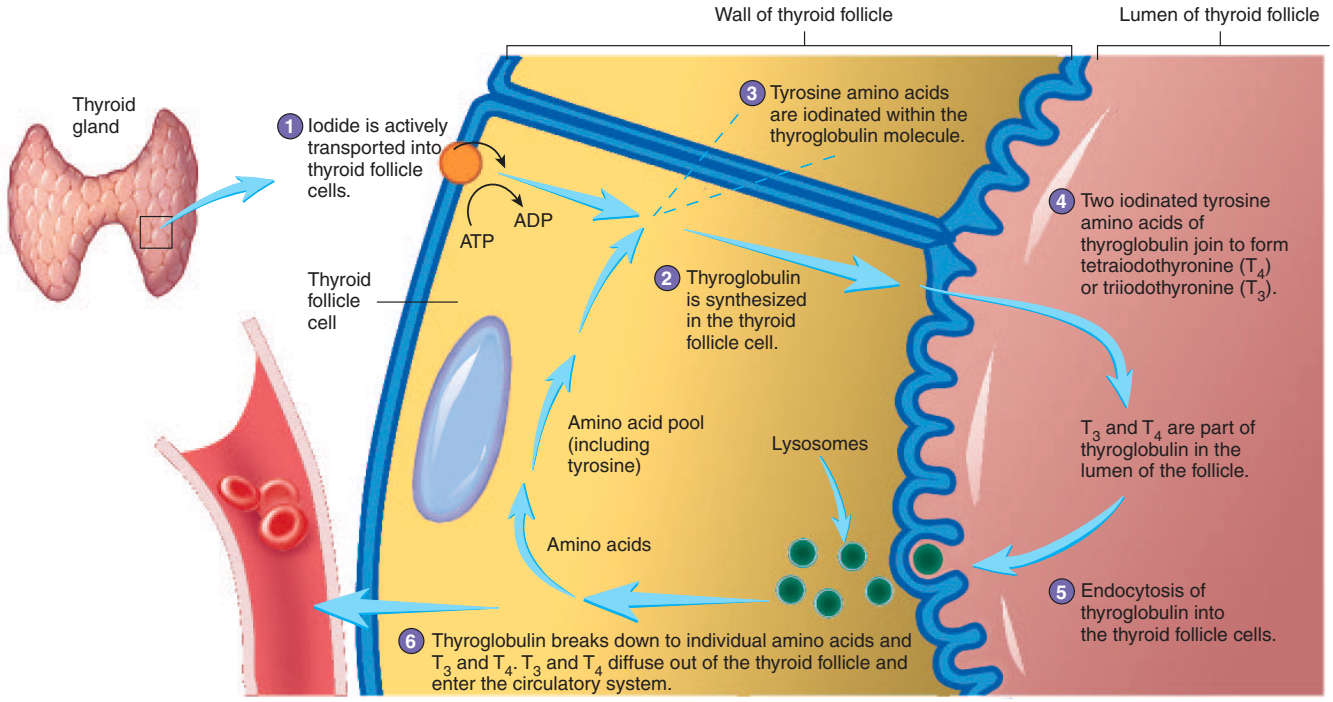
Thyroid Hormone Synthesis

Thyroid-stimulating hormone (TSH) from the anterior pituitary must be present to maintain thyroid hormone synthesis and secretion. TSH causes an increase in synthesis of thyroid hormones, which are then stored inside of the thyroid follicles attached to thyroglobulin. Also, some of the thyroid hormones are released from thyroglobulin and enter the circulatory system. An adequate amount of iodine in the diet also is required for thyroid hormone synthesis. The following events in the thyroid follicles result in thyroid hormone synthesis and secretion (figure 18.8):

1. Iodide ions (I^-) are taken up by thyroid follicle cells by active transport. The active transport of the I^- is against a concentration gradient of approximately 30-fold in healthy individuals.
2. Thyroglobulins, which contain numerous tyrosine amino acid molecules, are synthesized within the cells of the follicle.
3. Nearly simultaneously, the I^- are oxidized to form iodine (I) and either one or two iodine atoms are bound to each of the tyrosine molecules of thyroglobulin. This occurs close to the time the thyroglobulin molecules are secreted by the process of exocytosis into the lumen of the follicle. As a result, the secreted thyroglobulin contains many iodinated tyrosines.
4. In the lumen of the follicle, two diiodotyrosine molecules of thyroglobulin combine to form tetraiodothyronine (T_4), or one monoiodotyrosine and one diiodotyrosine molecule combine to form triiodothyronine (T_3). Large amounts of T_3 and T_4 are stored within the thyroid follicles as part of thyroglobulin. A reserve sufficient to supply thyroid hormones for approximately 2 weeks is stored in this form.

Table 18.3 Hormones of the Thyroid and Parathyroid Glands

Hormones	Structure	Target Tissue	Response
Thyroid Gland			
Thyroid Follicles			
Thyroid hormones (triiodothyronine and tetraiodothyronine)	Amino acid derivative	Most cells of the body	Increased metabolic rate; essential for normal process of growth and maturation
Parafollicular Cells			
Calcitonin	Polypeptide	Bone	Decreased rate of breakdown of bone by osteoclasts; prevention of a large increase in blood calcium levels
Parathyroid			
Parathyroid hormone	Peptide	Bone; kidney; small intestine	Increased rate of breakdown of bone by osteoclasts; increased reabsorption of calcium in kidneys; increased absorption of calcium from the small intestine; increased vitamin D synthesis; increased blood calcium levels



Process Figure 18.8 Biosynthesis of Thyroid Hormones

The numbered steps describe the synthesis and the secretion of thyroid hormones from the thyroid gland. See text for details of each numbered step.

5. Thyroglobulin is taken into the thyroid follicle cells by endocytosis where lysosomes fuse with the endocytotic vesicles.
6. Proteolytic enzymes break down thyroglobulin to release T_3 and T_4, which then diffuse from the follicular cells into the interstitial spaces and finally into the capillaries of the thyroid gland. The remaining amino acids of thyroglobulin are used again to synthesize more thyroglobulin.

Transport in the Blood

Thyroid hormones are transported in combination with plasma proteins in the circulatory system. Approximately 70%–75% of the circulating T_3 and T_4 are bound to **thyroxine-binding globulin (TBG),** which is synthesized by the liver and 20% to 30% are bound to other plasma proteins, including albumen. T_3 and T_4, bound to these plasma proteins, form a large reservoir of circulating thyroid hormones, and the half-life of these hormones is increased greatly because of this binding. After thyroid gland removal in experimental animals, it takes approximately 1 week for T_3 and T_4 levels in the blood to decrease by 50%. As free T_3 and T_4 levels decrease in the interstitial spaces, additional T_3 and T_4 dissociate from the plasma proteins to maintain the levels in the tissue spaces. When sudden secretion of T_3 and T_4 occurs, the excess binds to the plasma proteins. As a consequence, the concentration of thyroid hormones in the tissue spaces fluctuates very little.

Approximately 33%–40% of the T_4 is converted to T_3 in the body tissues. This conversion can be important in the action of thyroid hormones on their target tissues because T_3 is the major hormone that interacts with target cells. In addition, T_3 is several times more potent than T_4.

Much of the circulating T_4 is eliminated from the body by being converted to tetraiodothyroacetic acid and then excreted in the urine or bile. In addition, a large amount is converted to an inactive form of T_3 and rapidly metabolized and excreted.

Mechanism of Action of Thyroid Hormones

Thyroid hormones interact with their target tissues in a fashion similar to that of the steroid hormones. They readily diffuse through plasma membranes into the cytoplasm of cells. Within cells, they bind to receptor molecules in the nuclei. Thyroid hormones combined with their receptor molecules interact with DNA in the nucleus to influence regulatory genes and initiate new protein synthesis. The newly synthesized proteins within the target cells mediate the response of the cells to thyroid hormones. It takes up to a week after the administration of thyroid hormones for a maximal response to develop, and new protein synthesis occupies much of that time.

Effects of Thyroid Hormones

Thyroid hormones affect nearly every tissue in the body, but not all tissues respond identically. Metabolism is primarily affected in some tissues, and growth and maturation are influenced in others.

The normal rate of metabolism for an individual depends on an adequate supply of thyroid hormone, which increases the rate at which glucose, fat, and protein are metabolized. Blood levels of cholesterol decline. Thyroid hormones increase the activity of Na^+–K^+exchange pump, which contributes to an increase in body temperature. Thyroid hormones can alter the number and activity of mitochondria, resulting in greater ATP and heat production. The metabolic rate can increase from 60%–100% when blood thyroid hormones are elevated. Low levels of thyroid hormones lead to the opposite effect. Normal body temperature depends on an adequate amount of thyroid hormone.

Normal growth and maturation of organs also depend on thyroid hormones. For example, bone, hair, teeth, connective tissue, and nervous tissue require thyroid hormone for normal growth and development. Both normal growth and normal maturation of the brain require thyroid hormones. Also, thyroid hormones play a permissive role for GH, and GH does not have its normal effect on target tissues if thyroid hormones are not present.

The specific effects of hyposecretion and hypersecretion of thyroid hormones are outlined in table 18.4. Hypersecretion of thyroid hormones increases the rate of metabolism. High body temperature, weight loss, increased appetite, rapid heart rate, and an enlarged thyroid gland are major symptoms.

Hyposecretion of thyroid hormone decreases the rate of metabolism. Low body temperature, weight gain, reduced appetite, reduced heart rate, reduced blood pressure, weak skeletal muscles, and apathy are major symptoms. If hyposecretion of thyroid hormones occurs during development there is a decreased rate of metabolism, abnormal nervous system development, abnormal growth, and abnormal maturation of tissues. The consequence is a mentally retarded person of short stature and distinctive form called a **cretin** (krē′tin).

Regulation of Thyroid Hormone Secretion

Thyroid-releasing hormone (TRH) from the hypothalamus and TSH from the anterior pituitary function together to increase T_3 and T_4 secretion from the thyroid gland. Exposure to cold and stress cause increased TRH secretion and prolonged fasting decreases TRH secretion. TRH stimulates the secretion of TSH from the anterior pituitary. When TRH release increases, TSH secretion from the anterior pituitary gland also increases. When TRH release decreases, TSH secretion decreases. Small fluctuations in blood levels of TSH occur on a daily basis, with a small nocturnal increase. TSH stimulates T_3 and T_4 secretion from the thyroid gland. TSH also increases the synthesis of T_3 and T_4 as well as causing hypertrophy (increased cell size) and hyperplasia (increased cell number) of the thyroid gland. Decreased blood levels of TSH lead to decreased T_3 and T_4 secretion and thyroid gland atrophy. Figure 18.9 illustrates the regulation of T_3 and T_4 secretion. The thyroid hormones have a negative-feedback effect on the hypothalamus and anterior pituitary gland. As T_3 and T_4 levels increase in the circulatory system, they inhibit TRH and TSH secretion. Also, if the thyroid gland is removed or if T_3 and T_4 secretion declines, TSH levels in the blood increase dramatically.

Abnormal thyroid conditions are outlined in table 18.5. Hypothyroidism, or reduced secretion of thyroid hormones, can result from iodine deficiency, taking certain drugs, and exposure to other chemicals that inhibit thyroid hormone synthesis. It can also be due to inadequate secretion of TSH, an autoimmune disease that depresses thyroid hormone function, or surgical removal of the thyroid gland. Hypersecretion of thyroid hormones can result from the synthesis of an immune globulin that can bind to TSH receptors and acts like TSH, and from TSH-secreting tumors of the pituitary gland.

Table 18.4 Effects of Hyposecretion and Hypersecretion of Thyroid Hormones

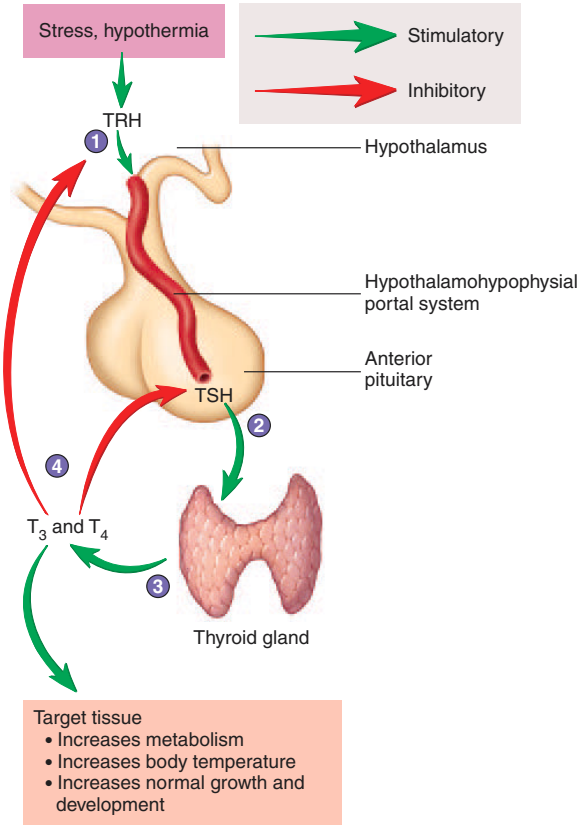
Hypothyroidism	Hyperthyroidism
Decreased metabolic rate, low body temperature, cold intolerance	Increased metabolic rate, high body temperature, heat intolerance
Weight gain, reduced appetite	Weight loss, increased appetite
Reduced activity of sweat and sebaceous glands, dry and cold skin	Copious sweating, warm and flushed skin
Reduced heart rate, reduced blood pressure, dilated and enlarged heart	Rapid heart rate, elevated blood pressure, abnormal electrocardiogram
Weak, flabby skeletal muscles, sluggish movements	Weak skeletal muscles that exhibit tremors, quick movements with exaggerated reflexes
Constipation	Bouts of diarrhea
Myxedema (swelling of the face and body) as a result of mucoprotein deposits	Exophthalmos (protruding of the eyes) as a result of mucoprotein and other deposits behind the eye
Apathetic, somnolent	Hyperactivity, insomnia, restlessness, irritability, short attention span
Coarse hair, rough and dry skin	Soft, smooth hair and skin
Decreased iodide uptake	Increased iodide uptake
Possible goiter (enlargement of the thyroid gland)	Almost always develops goiter

1. Thyroid-releasing hormone (TRH) is released from neurons within the hypothalamus into the blood. It passes through the hypothalamohypophysial portal system to the anterior pituitary.

2. TRH causes cells of the anterior pituitary to secrete thyroid-stimulating hormone (TSH).

3. TSH passes through the general circulation to the thyroid gland, where it causes both increased synthesis and secretion of thyroid hormones (T_3 and T_4).

4. T_3 and T_4 have an inhibitory effect on the secretion of TRH from the hypothalamus and TSH from the anterior pituitary.



Process Figure 18.9 Regulation of Thyroid Hormone (T_3 and T_4) Secretion

Table 18.5 Abnormal Thyroid Conditions

Cause	Description
Hypothyroidism	
Iodine deficiency	Causes inadequate thyroid hormone synthesis, which results in elevated thyroid-stimulating hormone (TSH) secretion; thyroid gland enlarges (goiter) as a result of TSH stimulation; thyroid hormones frequently remain in the low to normal range
Goiterogenic substances	Found in certain drugs and in small amounts in certain plants such as cabbage; inhibit thyroid hormone synthesis
Cretinism	Caused by maternal iodine deficiency or congenital errors in thyroid hormone synthesis; results in mental retardation and a short, grotesque appearance
Lack of thyroid gland	Removed surgically or destroyed as a treatment for Graves' disease (hyperthyroidism)
Pituitary insufficiency	Results from lack of TSH secretion; often associated with inadequate secretion of other adenohypophyseal hormones
Hashimoto's disease	Autoimmune disease in which thyroid function is normal or depressed
Hyperthyroidism (Toxic goiter)	
Graves' disease	Characterized by goiter and exophthalmos; apparently an autoimmune disease; most patients have long-acting thyroid stimulator, a TSH-like immune globulin, in their plasma
Tumors—benign adenoma or cancer	Result in either normal secretion or hypersecretion of thyroid hormones (rarely hyposecretion)
Thyroiditis—a viral infection	Produces painful swelling of the thyroid gland with normal or slightly increased thyroid hormone production
Elevated TSH levels	Result from a pituitary tumor
Thyroid storm	Sudden release of large amounts of thyroid hormones; caused by surgery, stress, infections, and unknown reasons

Goiter and Exophthalmos

An abnormal enlargement of the thyroid gland is called a **goiter.** Goiters can result from conditions that cause hypothyroidism as well as conditions that cause hyperthyroidism. An **iodine deficiency goiter** results when dietary iodine intake is very low and there is too little iodine to synthesize T_3 and T_4 (see table 18.5). As a result, blood levels of T_3 and T_4 decrease and the person may exhibit symptoms of hypothyroidism. The reduced negative feedback of T_3 and T_4 on the anterior pituitary and hypothalamus result in elevated TSH secretion. TSH causes hypertrophy and hyperplasia of the thyroid gland and increased thyroglobulin synthesis even though there is not enough iodine to synthesize T_3 and T_4 . Consequently, the thyroid gland enlarges. **Toxic goiter** secretes excess T_3 and T_4, and it can result from elevated TSH secretion or elevated TSH-like immune globulin molecules (see Graves' disease in table 18.5). Toxic goiter results in elevated T_3 and T_4 secretion and symptoms of hyperthyroidism. **Exophthalmos** often accompanies hyperthyroidism and is caused by the deposition of excess connective tissue proteins behind the eyes. The excess tissue makes the eyes move anteriorly, and consequently they appear to be larger than normal.

Graves disease is the most common cause of hyperthyroidism. Elevated T_3 and T_4 resulting from this condition suppresses TSH and TRH, but the T_3 and T_4 levels remain elevated. Exophthalmos is common. Treatment often involves removal of the thyroid gland followed by the oral administration of the appropriate amount of T_3 and T_4. Unfortunately removal of the thyroid gland normally does not reverse exophthalmos.

P R E D I C T 3

Predict the effect of surgical removal of the thyroid gland on blood levels of TRH, TSH, T_3 and T_4. Predict the effect of oral administration of T_3 and T_4 on TRH and TSH.

Calcitonin

The parafollicular cells of the thyroid gland, which secrete calcitonin, are dispersed between the thyroid follicles throughout the thyroid gland. The major stimulus for increased calcitonin secretion is an increase in calcium levels in the body fluids.

The primary target tissue for calcitonin is bone (see chapter 6). Calcitonin binds to membrane-bound receptors, decreases osteoclast activity, and lengthens the life span of osteoblasts. The result is a decrease in blood calcium and phosphate levels caused by increased bone deposition.

The importance of calcitonin in the regulation of blood calcium levels is unclear. Its rate of secretion increases in response to elevated blood calcium levels, and it may function to prevent large increases in blood calcium levels following a meal. Blood levels of calcitonin decrease with age to a greater extent in females than males. Osteoporosis increases with age and occurs to a greater degree in females than males. Complete thyroidectomy does not result in high blood calcium levels, however. It's possible that the regulation of blood calcium levels by other hormones, such as parathyroid hormone, and vitamin D compensates for the loss of calcitonin in individuals who have undergone a thyroidectomy. No pathologic condition is associated directly with a lack of calcitonin secretion.

17. *Where is the thyroid gland located? Describe the follicles and the parafollicular cells within the thyroid. What hormones do they produce?*
18. *Starting with the uptake of iodide by the follicles, describe the production and secretion of thyroid hormones.*
19. *How are the thyroid hormones transported in the blood? What effect does this transportation have on their half-life?*

20. *What are the target tissues of thyroid hormone? By what mechanism do thyroid hormones alter the activities of their target tissues? What effects are produced?*
21. *Starting in the hypothalamus, explain how chronic exposure to cold, food deprivation, or stress can affect thyroid hormone production.*
22. *Diagram two negative-feedback mechanisms involving hormones that function to regulate production of thyroid hormones.*
23. *What effect does calcitonin have on osteoclasts, osteoblasts, and blood calcium levels? What stimulus can cause an increase in calcitonin secretion?*

Parathyroid Glands

Objectives

- *Explain the activity of parathyroid hormone, and describe the means by which its secretion is regulated.*
- *Explain the relationship between parathyroid hormone and vitamin D.*

The **parathyroid** (par-ă-thī′royd) **glands** are usually embedded in the posterior part of each lobe of the thyroid gland. Usually four parathyroid glands are present, with their cells organized in densely packed masses or cords rather than in follicles (figure 18.10).

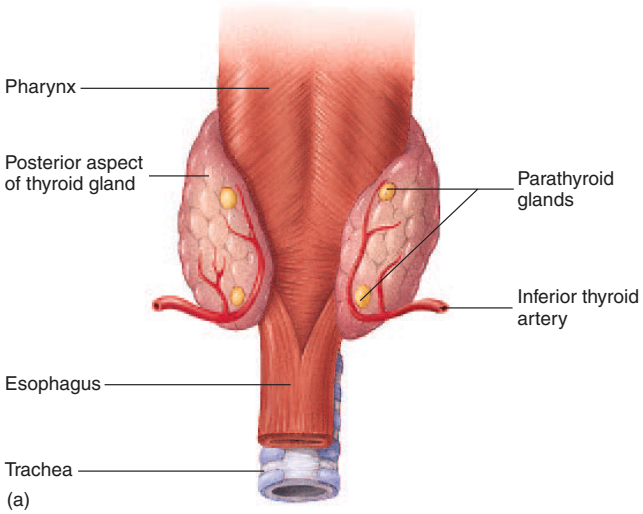
The parathyroid glands secrete **parathyroid hormone (PTH),** a polypeptide hormone that is important in the regulation of calcium levels in body fluids (see table 18.3). Bone, the kidneys, and the intestine are its major target tissues. Parathyroid hormone binds to membrane-bound receptors and activates a G protein mechanism that increases intracellular cAMP levels in target tissues. Without functional parathyroid glands, the ability to adequately regulate blood calcium levels is lost.

PTH stimulates osteoclast activity in bone and can cause the number of osteoclasts to increase. The increased osteoclast activity results in bone resorption and the release of calcium and phosphate, causing an increase in blood calcium levels. PTH receptors are not present on osteoclasts but are present on osteoblasts and on red bone marrow stromal (stem) cells. PTH binds to receptors on osteoblasts which then promote an increase in osteoclast activity (see chapter 6).

PTH induces calcium reabsorption within the kidneys so that less calcium leaves the body in urine. It also increases the enzymatic formation of active vitamin D in the kidneys. Calcium is actively absorbed by the epithelial cells of the small intestine, and the synthesis of transport proteins in the intestinal cells requires active vitamin D. PTH increases the rate of active vitamin D synthesis, which in turn increases the rate of calcium and phosphate absorption in the intestine, thereby elevating blood levels of calcium.

Although PTH increases the release of phosphate ions (PO_4^{3-}) from bone and increases PO_4^{3-} absorption in the gut, it increases PO_4^{3-} excretion in the kidney. The overall effect of PTH is to decrease blood phosphate levels. A simultaneous increase in both Ca^{2+} and PO_4^{3-} results in the precipitation of calcium phosphate in soft tissues of the body, where they cause irritation and inflammation.

The regulation of PTH secretion is outlined in figure 18.11. The primary stimulus for the secretion of PTH is a decrease in blood Ca^{2+} levels, whereas elevated blood Ca^{2+} levels inhibit PTH secretion. This regulation keeps blood Ca^{2+} levels fluctuating within a normal range of values. Both hypersecretion and hyposecretion of PTH cause serious symptoms (table 18.6). The regulation of blood Ca^{2+} levels is discussed more thoroughly in chapter 27.



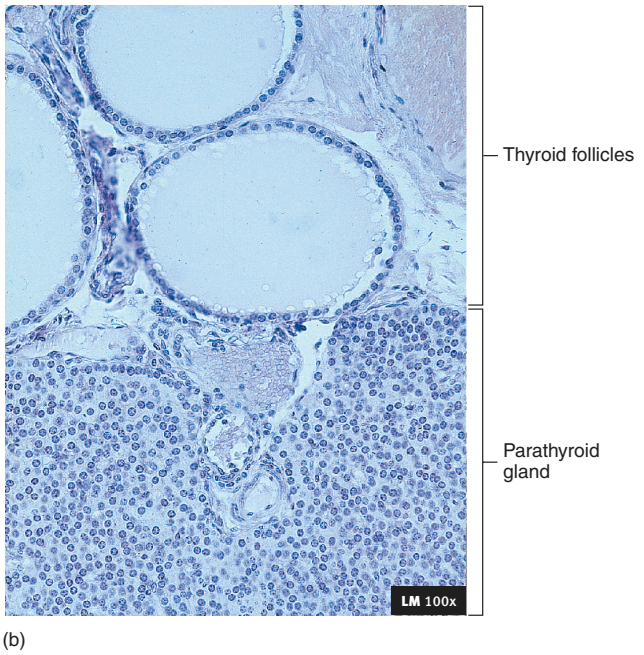
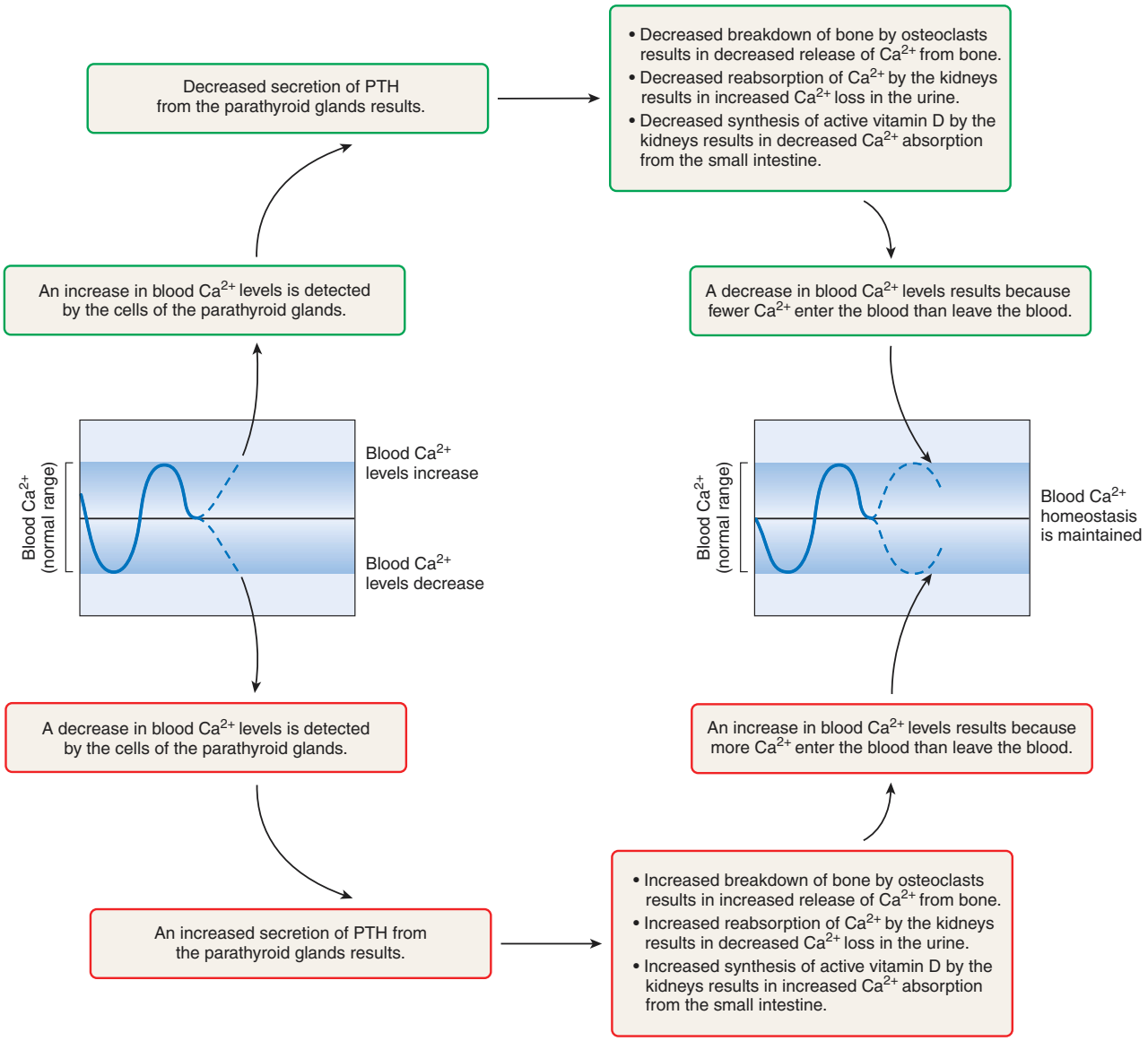


Figure 18.10 **Anatomy and Histology of the Parathyroid Glands**

(*a*) The parathyroid glands are embedded in the posterior part of the thyroid gland. (*b*) The parathyroid glands are composed of densely packed cords of cells.



Homeostasis Figure 18.11 Regulation of Parathyroid Hormone (PTH) Secretion

P R E D I C T 4

Predict the effect of an inadequate dietary intake of calcium on PTH secretion and on target tissues for PTH.

Inactive parathyroid glands result in hypocalcemia. Reduced extracellular calcium levels cause voltage-gated Na^+ channels in plasma membranes to open, which increases the permeability of plasma membranes to Na^+. As a consequence, Na^+ diffuse into cells and cause depolarization (see chapter 11). Symptoms of hypocalcemia are nervousness, muscle spasms, cardiac arrhythmias, and convulsions. In extreme cases, tetany of skeletal muscles results and tetany of the respiratory muscles can cause death.

24. *Where are the parathyroid glands located, and what hormone do they produce?*
25. *What effect does PTH have on osteoclasts, osteoblasts, the kidneys, the small intestine, and blood calcium and blood phosphate levels? What stimulus can cause an increase in PTH secretion?*

P R E D I C T 5

A patient with a malignant tumor had his thyroid gland removed. What effect would this removal have on blood levels of Ca^{2+}? If the parathyroid glands are inadvertently removed along with the thyroid gland during surgery, death can result because muscles of respiration undergo sustained contractions. Explain.

Table 18.6 Causes and Symptoms of Hypersecretion and Hyposecretion of Parathyroid Hormone

Hypoparathyroidism	Hyperparathyroidism
Causes	
Accidental removal during thyroidectomy	Primary hyperparathyroidism: a result of abnormal parathyroid function—adenomas of the parathyroid gland (90%), hyperplasia of parathyroid idiopathic (unknown cause) cells (9%), and carcinomas (1%) Secondary hyperparathyroidism: caused by conditions that reduce blood Ca^{2+} levels, such as inadequate Ca^{2+} in the diet, inadequate levels of vitamin D, pregnancy, or lactation
Symptoms	
Hypocalcemia	Hypercalcemia or normal blood Ca^{2+} levels; calcium carbonate salts may be deposited throughout the body, especially in the renal tubules (kidney stones), lungs, blood vessels, and gastric mucosa
Normal bone structure	Bones weaken and are eaten away as a result of resorption; some cases are first diagnosed when a radiograph is taken of a broken bone
Increased neuromuscular excitability; tetany, laryngospasm, and death from asphyxiation can result	Neuromuscular system less excitable; muscular weakness may be present
Flaccid heart muscle; cardiac arrhythmia may develop	Increased force of contraction of cardiac muscle; at very high blood Ca^{2+} levels, cardiac arrest during contraction is possible
Diarrhea	Constipation

Adrenal Glands

Objectives

- ***Describe the structure and embryologic development of the adrenal glands, and describe the response of the target tissues to each of the adrenal hormones.***
- ***Describe the means by which secretions of the adrenal glands are regulated.***

The **adrenal** (ă-drē′năl) **glands,** also called the **suprarenal** (soo′pră-rē′năl) **glands,** are near the superior poles of the kidneys. Like the kidneys, they are retroperitoneal, and they are surrounded by abundant adipose tissue. The adrenal glands are enclosed by a connective tissue capsule and have a well-developed blood supply (figure 18.12*a*).

The adrenal glands are composed of an inner **medulla** and an outer **cortex,** which are derived from two separate embryonic tissues. The adrenal medulla arises from neural crest cells, which also give rise to postganglionic neurons of the sympathetic division of the autonomic nervous system (see chapters 16 and 29). Unlike most glands of the body, which develop from invaginations of epithelial tissue, the adrenal cortex is derived from mesoderm.

Histology

Trabeculae of the connective tissue capsule penetrate into the adrenal gland in several locations, and numerous small blood vessels course with them to supply the gland. The medulla consists of closely packed polyhedral cells centrally located in the gland (figure 18.12*b*). The cortex is composed of smaller cells and forms three indistinct layers: the **zona glomerulosa** (glō-mār′ū-lōs-ă), the **zona fasciculata** (fa-sik′ū-lă-tă), and the **zona reticularis** (re-tik′ū-lăr′is). These three layers are functionally and structurally specialized. The zona glomerulosa is immediately beneath the capsule and is composed of small clusters of cells. Beneath the zona glomerulosa is the thickest part of the adrenal cortex, the zona fasciculata. In this layer, the cells form long columns, or fascicles, of cells that extend from the surface toward the medulla of the gland. The deepest layer of the adrenal cortex is the zona reticularis, which is a thin layer of irregularly arranged cords of cells.

Hormones of the Adrenal Medulla

The adrenal medulla secretes two major hormones: **epinephrine** (**adrenaline;** ă-dren′ă-lin), 80%, and **norepinephrine** (**noradrenaline;** nor-ă-dren′ă-lin), 20% (table 18.7). Epinephrine and norepinephrine are closely related to each other. In fact, norepinephrine is a precursor to the formation of epinephrine. Because the adrenal medulla consists of cells derived from the same cells that give rise to postganglionic sympathetic neurons, its secretory products are neurohormones.

Epinephrine and norepinephrine combine with adrenergic receptors, which are membrane-bound receptors in target cells. They are classified as either α-adrenergic or β-adrenergic receptors, and each of these categories has subcategories. All of the adrenergic receptors function through G protein mechanisms. The α-adrenergic receptors cause Ca^{2+} channels to open, cause the release of Ca^{2+} from endoplasmic reticulum by activating phospholipase enzymes, open K^+ channels, decrease cAMP synthesis, or stimulate the synthesis of eicosanoid molecules such as prostaglandins. The β-adrenergic receptors all increase cAMP synthesis. The effects of epinephrine and norepinephrine released from the adrenal medulla are described when the systems these hormones affect are discussed (see chapters 16, 20, 21, 24, and 26).

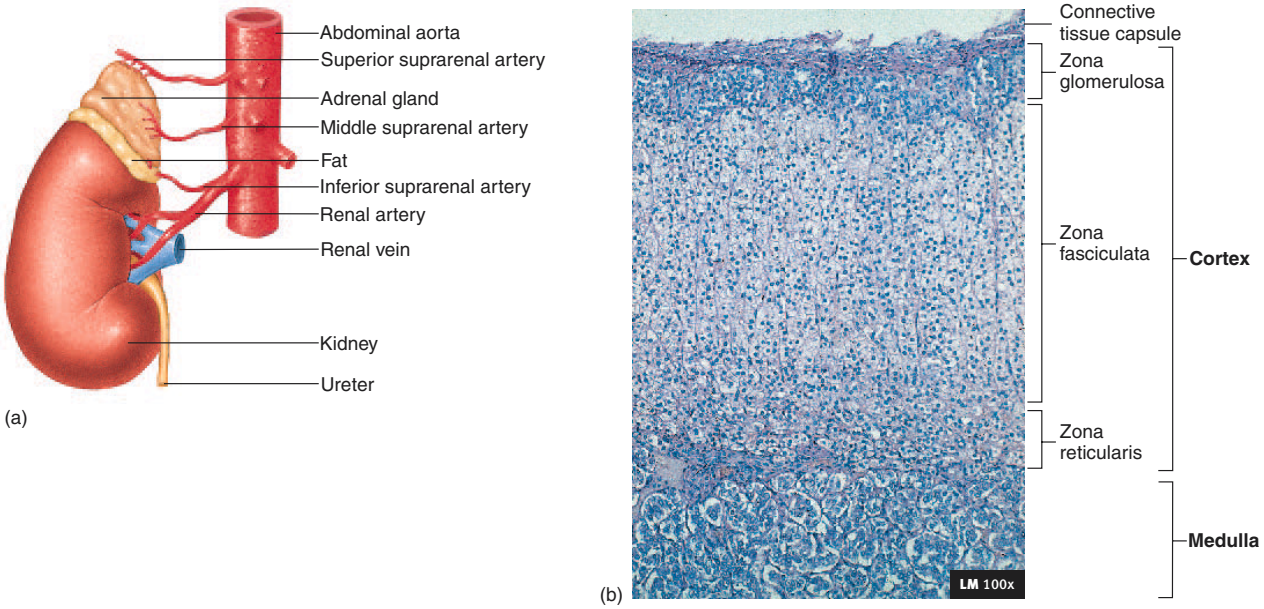


Figure 18.12 Anatomy and Histology of the Adrenal Gland

(*a*) An adrenal gland is at the superior pole of each kidney. (*b*) The adrenal glands have an outer cortex and an inner medulla. The cortex is surrounded by a connective tissue capsule and consists of three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis.

Epinephrine increases blood levels of glucose. It combines with membrane-bound receptors in the liver cells and activates cAMP synthesis within the cells. Cyclic AMP, in turn, activates enzymes that catalyze the breakdown of glycogen to glucose, thereby causing its release into the blood. Epinephrine also increases glycogen breakdown, the intracellular metabolism of glucose in skeletal muscle cells, and the breakdown of fats in adipose tissue. Epinephrine and norepinephrine increase the heart's rate and force of contraction and cause blood vessels to constrict in the skin, kidneys, gastrointestinal tract, and other viscera. Also, epinephrine causes dilation of blood vessels in skeletal muscles and cardiac muscle.

Secretion of adrenal medullary hormones prepares the individual for physical activity and is a major component of the fight-or-flight response (see chapter 16). The response results in reduced activity in organs not essential for physical activity and in increased blood flow and metabolic activity in organs that participate in physical activity. In addition, it mobilizes nutrients that can be used to sustain physical exercise.

The effects of epinephrine and norepinephrine are short-lived because they are rapidly metabolized, excreted, or taken up by tissues. Their half-life in the circulatory system is measured in minutes.

The release of adrenal medullary hormones primarily occurs in response to stimulation by sympathetic neurons because the adrenal medulla is a specialized part of the autonomic nervous system. Several conditions, including emotional excitement, injury, stress, exercise, and low blood glucose levels, lead to the release of adrenal medullary neurohormones (figure 18.13).

Table 18.7 Hormones of the Adrenal Gland

Hormones	Structure	Target Tissue	Response
Adrenal Medulla			
Epinephrine primarily; norepinephrine	Amino acid derivatives	Heart, blood vessels, liver, fat cells	Increased cardiac output; increased blood flow to skeletal muscles and increased blood flow to the heart (see chapter 20); increased release of glucose and fatty acids into blood; in general, preparation for physical activity
Adrenal Cortex			
Cortisol	Steroid	Most tissues	Increased protein and fat breakdown; increased glucose production; inhibition of immune response
Aldosterone	Steroid	Kidney	Increased Na^+ reabsorption and K^+ and H^+ excretion
Sex steroids (primarily androgens)	Steroids	Many tissues	Minor importance in males; in females, development of some secondary sexual characteristics, such as axillary and pubic hair

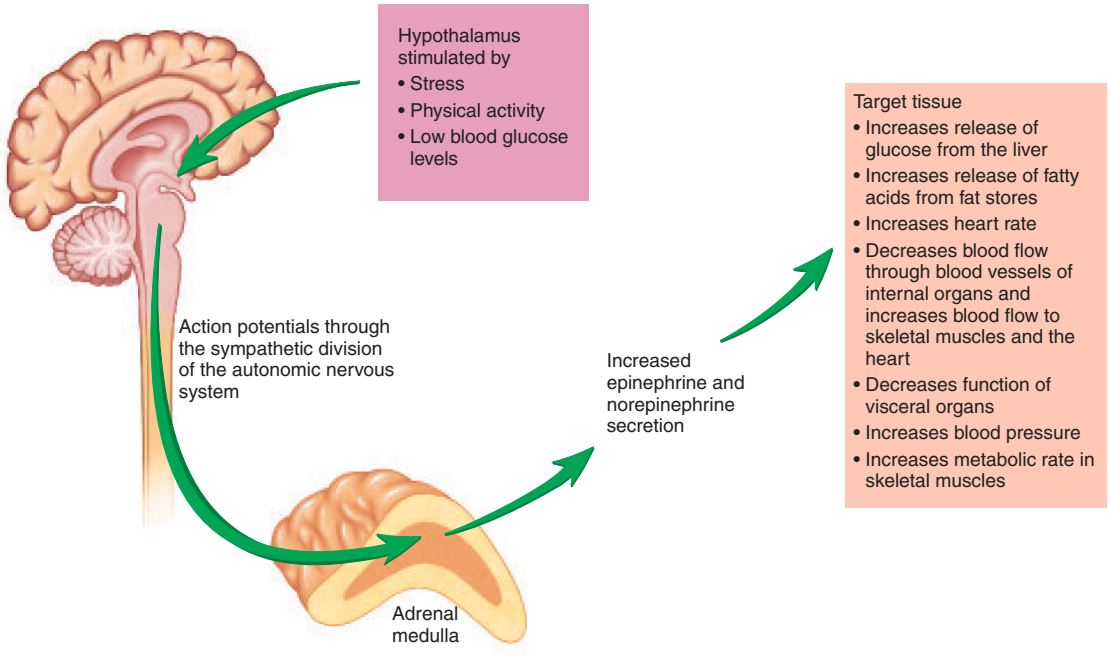


Figure 18.13 Regulation of Adrenal Medullary Secretions

Stress, physical exercise, and low blood glucose levels cause increased activity of the sympathetic nervous system, which increases epinephrine and norepinephrine secretion from the adrenal medulla.

Pheochromocytoma and Neuroblastoma

The two major disorders of the adrenal medulla are both tumors: pheochromocytoma (fē′ō-krō′mō-sī-tō′mă), a benign tumor, and neuroblastoma (noor′ō-blas-tō′mă), a malignant tumor. Symptoms result from the release of large amounts of epinephrine and norepinephrine and include hypertension (high blood pressure), sweating, nervousness, pallor, and tachycardia (rapid heart rate). The high blood pressure results from the effect of these hormones on the heart and blood vessels and is correlated with an increased chance of heart disease and stroke.

Hormones of the Adrenal Cortex

The adrenal cortex secretes three hormone types: **mineralocorticoids** (min′er-al-ō-kōr′ti-koydz), **glucocorticoids** (gloo-kō-kōr′ti-koydz), and **androgens** (an′drō-jenz) (see table 18.7). All are similar in structure in that they are steroids, highly specialized lipids that are derived from cholesterol. Because they are lipid-soluble, they are not stored in the adrenal gland cells but diffuse from the cells as they are synthesized. Adrenal cortical hormones are transported in the blood in combination with specific plasma proteins; they are metabolized in the liver and excreted in the bile and urine. The hormones of the adrenal cortex bind to intracellular receptors and stimulate the synthesis of specific proteins that are responsible for producing the cell's responses.

Mineralocorticoids

The major secretory products of the zona glomerulosa are the mineralocorticoids. **Aldosterone** (al-dos′ter-ōn) is produced in the greatest amounts, although other closely related mineralocorticoids are also secreted. Aldosterone increases the rate of sodium reabsorption by the kidneys, thereby increasing blood levels of sodium. Sodium reabsorption can result in increased water reabsorption by the kidneys and an increase in blood volume providing ADH is also secreted. Aldosterone increases K^+ excretion into the urine by the kidneys, thereby decreasing blood levels of K^+. It also increases the rate of H^+ excretion into the urine. When aldosterone is secreted in high concentrations, it can result in reduced blood levels of K^+ and alkalosis (elevated pH of body fluids). The details of the effects of aldosterone and the mechanisms controlling aldosterone secretion are discussed along with kidney functions in chapters 26 and 27 and with the cardiovascular system in chapter 21.

PREDICT 6

Alterations in blood levels of sodium and potassium have profound effects on the electrical properties of cells. Because high blood levels of aldosterone cause retention of sodium and excretion of potassium, predict and explain the effects of high aldosterone levels on nerve and muscle function. Conversely, because low blood levels of aldosterone cause low blood levels of sodium and elevated blood levels of potassium, predict the effects of low aldosterone levels on nerve and muscle function.

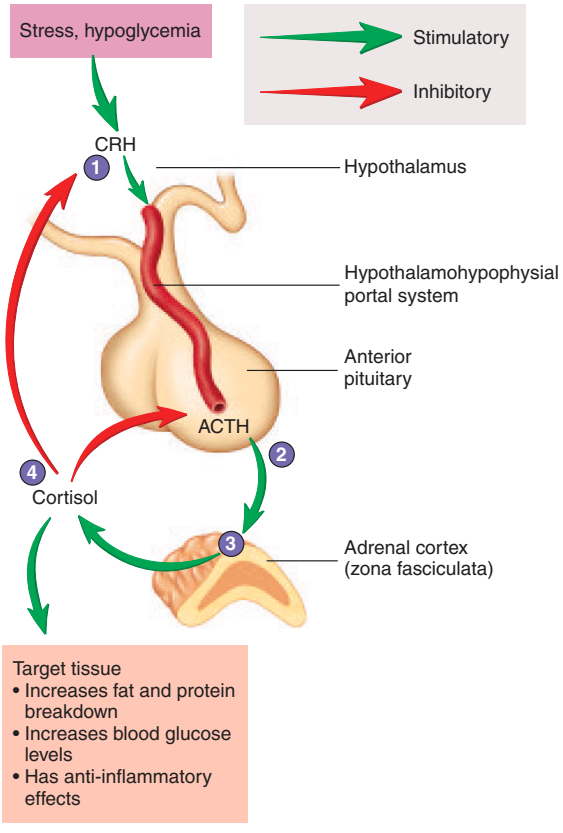
Glucocorticoids

The zona fasciculata of the adrenal cortex primarily secretes **glucocorticoid hormones,** the major one of which is **cortisol** (kōr′ti-sol). The target tissues and responses to the glucocorticoids are numerous (table 18.8). The responses are classified as metabolic, developmental, or anti-inflammatory. Glucocorticoids increase fat catabolism, decrease glucose and amino acid uptake in skeletal muscle, increase **gluconeogenesis** (gloo′kō-nē-ō-jen′ĕ-sis; the synthesis of glucose from precursor molecules like amino acids in the liver), and increase protein degradation. Thus, some major effects of glucocorticoids are an increase in fat and protein metabolism, blood glucose levels, and glycogen deposits in cells. As a result, a reservoir of molecules that can be metabolized rapidly is available to cells. Glucocorticoids are also required for the maturation of tissues like fetal lungs and for the development of receptor molecules in target tissues for epinephrine and norepinephrine. Glucocorticoids decrease the intensity of the inflammatory response by decreasing both the number of white blood cells and the secretion of inflammatory chemicals from tissues. This anti-inflammatory effect is most important under conditions of stress, when the rate of glucocorticoid secretion is relatively high.

Table 18.8 Target Tissues and Their Responses to Glucocorticoid Hormones

Target Tissues	Responses
Peripheral tissues, such as skeletal muscle, liver, and adipose tissue	Inhibits glucose use; stimulates formation of glucose from amino acids and, to some degree, from fats (gluconeogenesis) in the liver, which results in elevated blood glucose levels; stimulates glycogen synthesis in cells; mobilizes fats by increasing lipolysis, which results in the release of fatty acids into the blood and an increased rate of fatty acid metabolism; increases protein breakdown and decreases protein synthesis
Immune tissues	Anti-inflammatory—depresses antibody production, white blood cell production, and the release of inflammatory components in response to injury
Target cells for epinephrine	Receptor molecules for epinephrine and norepinephrine decrease without adequate amounts of glucocorticoid hormone

1. Cortiocotropin-releasing hormone (CRH) is released from hypothalamic neurons in response to stress or hypoglycemia and passes, by way of the hypothalamohypophysial portal system, to the anterior pituitary.
2. In the anterior pituitary CRH binds to and stimulates cells that secrete adrenocorticotropic hormone (ACTH).
3. ACTH binds to membrane-bound receptors on cells of the adrenal cortex and stimulates the secretion of glucocorticoids, primarily cortisol.
4. Cortisol inhibits CRH and ACTH secretion.



Process Figure 18.14 Regulation of Cortisol Secretion

ACTH is necessary to maintain the secretory activity of the adrenal cortex, which rapidly atrophies without this hormone. Corticotropin-releasing hormone (CRH) is released from the hypothalamus and stimulates the anterior pituitary to secrete ACTH. ACTH acts on the zona glomerulosa to enhance aldosterone secretion and on the zona fasciculata to increase cortisol secretion. The regulation of ACTH and cortisol secretion is outlined in figure 18.14. Both ACTH and cortisol inhibit CRH secretion from the hypothalamus and thus constitute a negative-feedback influence on CRH secretion. In addition, high concentrations of cortisol in the blood inhibit ACTH secretion from the anterior pituitary, and low concentrations stimulate it. This negative-feedback loop is important in maintaining blood cortisol levels within a narrow range of concentrations. In response to stress or hypoglycemia, blood levels of cortisol increase rapidly because these stimuli trigger a large increase in CRH release from the hypothalamus. Table 18.9 outlines several abnormalities associated with hypersecretion and hyposecretion of adrenal hormones.

P R E D I C T 7

Cortisone, a drug similar to cortisol, is sometimes given to people who have severe allergies or extensive inflammation or who suffer from autoimmune diseases. Taking this substance chronically can damage the adrenal cortex. Explain how this damage can occur.

Adrenal Androgens

Some adrenal steroids, including **androstenedione** (an-drō-stēn′dī-ōn), are weak androgens. They are secreted by the zona reticularis and converted by peripheral tissues to the more potent androgen, testosterone. Adrenal androgens stimulate pubic and axillary hair growth and sexual drive in females. Their effects in males are negligible in comparison to testosterone secreted by the testes. Chapter 28 presents additional information about androgens.

26. *Where are the adrenal glands located? Describe the embryonic origin of the adrenal medulla and adrenal cortex.*
27. *Name two hormones secreted by the adrenal medulla, and list the effects of these hormones.*
28. *List several conditions that can stimulate the production of adrenal medullary hormones. What role does the nervous system play in the release of adrenal medullary hormones? How does this role relate to the embryonic origin of the adrenal medulla?*
29. *Describe the three layers of the adrenal cortex, and name the hormones produced by each layer.*
30. *Name the target tissue of aldosterone, and list the effects of an increase in aldosterone secretion on the concentration of ions in the blood.*

Table 18.9 Symptoms of Hyposecretion and Hypersecretion of Adrenal Cortex Hormones

Hyposecretion	Hypersecretion
Aldosterone	
Hyponatremia (low blood levels of sodium)	Slight hypernatremia (high blood levels of sodium)
Hyperkalemia (high blood levels of potassium)	Hypokalemia (low blood levels of potassium)
Acidosis	Alkalosis
Low blood pressure	High blood pressure
Tremors and tetany of skeletal muscles	Weakness of skeletal muscles
Polyuria	Acidic urine
Cortisol	
Hypoglycemia (low blood glucose levels)	Hyperglycemia (high blood glucose levels; adrenal diabetes)—leads to diabetes mellitus
Depressed immune system	Depressed immune system
Protein and fats from diet are unused, resulting in weight loss	Destruction of tissue proteins, causing muscle atrophy and weakness, osteoporosis, weak capillaries (easy bruising), thin skin, and impaired wound healing; mobilization and redistribution of fats, causing depletion of fat from limbs and deposition in face (moon face), neck (buffalo hump), and abdomen
Loss of appetite, nausea, and vomiting	Emotional effects, including euphoria and depression
Increased skin pigmentation (caused by elevated ACTH)	
Androgens	
In women reduction of pubic and axillary hair	In women hirsuitism (excessive facial and body hair), acne, increased sex drive, regression of breast tissue, and loss of regular menses

Clinical Focus Hormone Pathologies of the Adrenal Cortex

Several pathologies are associated with abnormal secretion of adrenal cortex hormones.

Addison's disease results from abnormally low levels of aldosterone and cortisol. The cause of many cases of Addison's disease is unknown, but it is a suspected autoimmune disease in which the body's defense mechanisms inappropriately destroy the adrenal cortex. Bacteria like tuberculosis bacteria, acquired immunodeficiency syndrome (AIDS), fungal infections, adrenal hemorrhage, and cancer can also damage the adrenal cortex, thus causing some cases of Addison's disease. Prolonged treatment with glucocorticoids, which suppresses pituitary gland function, can cause Addison's disease, as can tumors that damage the hypothalamus. Symptoms of Addison's disease include weakness, fatigue, weight loss, anorexia, and in many cases increased pigmentation of the skin. Reduced blood pressure results from the loss of Na^+ and water through the kidney. Reduced blood pressure is the most critical manifestation and requires immediate treatment. Low blood levels of Na^+, high blood levels of K^+, and reduced blood pH are consistent with the condition.

Aldosteronism (al-dos′ter-on-izm) is caused by excess production of aldosterone. Primary aldosteronism results from an adrenal cortex tumor, and secondary aldosteronism occurs when some extraneous factor like overproduction of renin, a substance produced by the kidney, increases aldosterone secretion. Major symptoms of aldosteronism include reduced blood levels of K^+, increased blood pH, and elevated blood pressure. Elevated blood pressure is a result of the retention of water and Na^+ by the kidneys.

Cushing's syndrome (figure A) is a disorder characterized by hypersecretion of cortisol and androgens and possibly by excess aldosterone production. The majority of cases are caused by excess ACTH production by nonpituitary tumors, which usually result from a type of lung cancer. Some cases of increased ACTH secretion do result from pituitary tumors. Sometimes adrenal tumors or unidentified causes can be responsible for hypersecretion of the adrenal cortex without increases in ACTH secretion. Elevated secretion of glucocorticoids results in muscle wasting, the accumulation of adipose tissue in the face and trunk of the body, and increased blood glucose levels.

Hypersecretion of androgens from the adrenal cortex causes a condition called **adrenogenital** (ă-drē′nō-jen′i-tăl) **syndrome,** in which secondary sexual characteristics develop early in male children, and female children are masculinized. If the condition develops before birth in females, the external genitalia can be masculinized to the extent that the infant's reproductive structures are neither clearly female nor male. Hypersecretion of adrenal androgens in male children before puberty results in rapid and early development of the reproductive system. If not treated, early sexual development and short stature result. The short stature results from the effect of androgens on skeletal growth (see chapter 6). In adult females partial development of male secondary sexual characteristics, such as facial hair and a masculine voice, occurs.

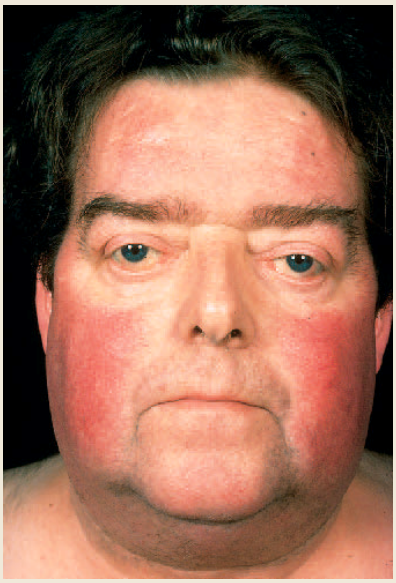


Figure A Male Patient with Cushing's Syndrome

31. *Describe the effects produced by an increase in cortisol secretion. Starting in the hypothalamus, describe how stress or low blood sugar levels can stimulate cortisol release.*
32. *What effects do adrenal androgens have on males and females?*

Pancreas

Objectives

- *Describe the position and structure of the pancreas, and list the substances secreted by the pancreas and their functions.*
- *Explain the regulation of insulin and glucagon secretion.*

The **pancreas** (pan′krē-us) lies behind the peritoneum between the greater curvature of the stomach and the duodenum. It is an elongated structure approximately 15 cm long weighing approximately 85–100 g. The head of the pancreas lies near the duodenum, and its body and tail extend toward the spleen.

Histology

The pancreas is both an exocrine gland and an endocrine gland. The exocrine portion consists of **acini** (as′i-nī), which produce pancreatic juice, and a duct system, which carries the pancreatic juice to the small intestine (see chapter 24). The endocrine part, consisting of **pancreatic islets** (islets of Langerhans), which (figure 18.15) produce hormones that enter the circulatory system.

Between 500,000 and 1 million pancreatic islets are dispersed among the ducts and acini of the pancreas. Each islet is composed of **alpha (α) cells** (20%), which secrete **glucagon,** a small polypeptide hormone; **beta (β) cells** (75%), which secrete **insulin,** a small protein hormone consisting of two polypeptide chains bound together;

Clinical Focus Stress

The adrenal cortex and the adrenal medulla play major roles in response to stress.

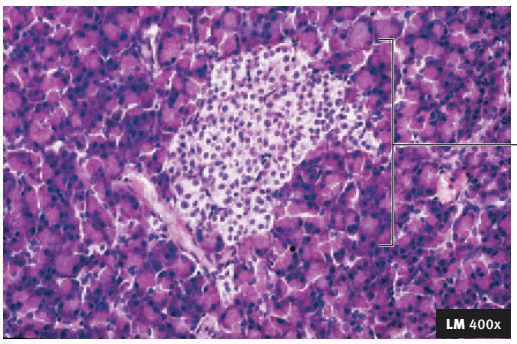
In general, stress activates nervous and endocrine responses that prepare the body for physical activity, even when physical activity is not the most appropriate response to the stressful conditions, such as during an examination or other mentally stressful situations. The endocrine response to stress involves increased CRH release from the hypothalamus and increased sympathetic stimulation of the adrenal medulla. CRH stimulates ACTH secretion from the anterior pituitary, which in turn stimulates cortisol from the adrenal cortex. Increased sympathetic stimulation of the adrenal medulla increases epinephrine and norepinephrine secretion.

Together, epinephrine and cortisol increase blood glucose levels and the release of fatty acids from adipose tissue and the liver. Sympathetic innervation of the pancreas decreases insulin secretion. Consequently, most tissues do not readily take up and use glucose. Thus, glucose is available primarily to the nervous system, and fatty acids are used by skeletal muscle, cardiac muscle, and other tissues.

Epinephrine and sympathetic stimulation also increase cardiac output, increase blood pressure, and act on the central nervous system to increase alertness and aggressiveness. Cortisol also decreases the initial inflammatory response.

Responses to stress illustrate the close relationship between the nervous and endocrine systems and provide an example of their integrated functions. Our ability to respond to stressful conditions depends on the nervous and endocrine responses to stress.

Although responses to stress are adaptive under many circumstances, they can become harmful. For example, if stress is chronic, the elevated secretion of cortisol and epinephrine produces harmful effects.



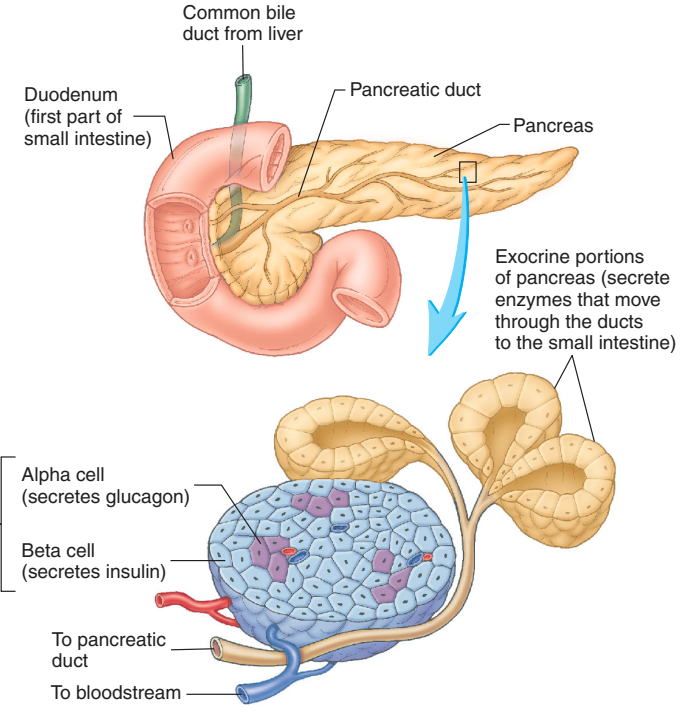


Figure 18.15 Histology of the Pancreatic Islets

A pancreatic islet consists of clusters of specialized cells among the acini of the exocrine portion of the pancreas. The stain used for this slide does not distinguish between alpha and beta cells.

and other cell types (5%). The remaining cells are either immature cells of questionable function or **delta (δ) cells,** which secrete somatostatin, a small polypeptide hormone. Nerves from both divisions of the autonomic nervous system innervate the pancreatic islets, and a well-developed capillary network surrounds each islet.

Effect of Insulin and Glucagon on Their Target Tissues

The pancreatic hormones play an important role in regulating the concentration of critical nutrients in the circulatory system, especially glucose, or blood sugar, and amino acids (table 18.10). The major target tissues of insulin are the liver, adipose tissue, muscles, and the satiety center within the hypothalamus of the brain. The **satiety** (sa′-tī-ĕ-tē) **center** is a collection of neurons in the hypothalamus that controls appetite, but insulin doesn't directly affect most areas of the nervous system. The specific effects of insulin on these target tissues are listed in table 18.11.

Insulin molecules bind to membrane-bound receptors on target cells. Once insulin molecules bind their receptors, the receptors cause specific proteins in the membrane to become phosphorylated. Part of the cells' response to insulin is to increase the number of active-transport proteins in the membrane of cells for glucose and amino acids. Finally, insulin and receptor molecules are taken by endocytosis into the cell. The insulin molecules are released from the insulin receptors and broken down within the cell, and the insulin receptor can once again become associated with the plasma membrane.

In general, the target tissue response to insulin is an increase in its ability to take up and use glucose and amino acids. Glucose molecules that are not needed immediately as an energy source to maintain cell metabolism are stored as glycogen in skeletal muscle, the liver, and other tissues and are converted to fat in adipose tissue. Amino acids can be broken down and used as an energy source or to synthesize glucose, or they can be converted to protein. Without insulin, the ability of these tissues to take up glucose and amino acids and use them is minimal.

The normal regulation of blood glucose levels requires insulin. Blood glucose levels can increase dramatically when too little insulin is secreted or when insulin receptors do not respond to it (see Clinical Focus on "Diabetes Mellitus" p 623). In the absence of insulin, the movement of glucose and amino acids into cells de-

Table 18.10 Pancreatic Hormones

Cells In Islets	Hormone	Structure	Target Tissue	Response
Beta (β)	Insulin	Protein	Especially liver, skeletal muscle, fat tissue	Increased uptake and use of glucose and amino acids
Alpha (α)	Glucagon	Polypeptide	Liver primarily	Increased breakdown of glycogen; release of glucose into the circulatory system
Delta (δ)	Somatostatin	Peptide	Alpha and beta cells (some somatostatin is produced in the hypothalamus)	Inhibition of insulin and glucagon secretion

Table 18.11 Effect of Insulin and Glucagon on Target Tissues

Target Tissue	Response to Insulin	Response to Glucagon
Skeletal muscle, cardiac muscle, cartilage, bone, fibroblasts, leukocytes, and mammary glands	Increased glucose uptake and glycogen synthesis; increased uptake of certain amino acids	Little effect
Liver	Increased glycogen synthesis; increased use of glucose for energy (glycolysis)	Causes rapid increase in the breakdown of glycogen to glucose (glycogenolysis) and release of glucose into the blood Increased formation of glucose (gluconeogenesis) from amino acids and, to some degree, from fats Increased metabolism of fatty acids, resulting in increased ketones in the blood
Adipose cells	Increased glucose uptake, glycogen synthesis, fat synthesis, and fatty acid uptake; increased glycolysis	High concentrations cause breakdown of fats (lipolysis); probably unimportant under most conditions
Nervous system	Little effect except to increase glucose uptake in the satiety center	No effect

Clinical Focus Diabetes Mellitus

Diabetes mellitus results primarily from inadequate secretion of insulin or the inability of tissues to respond to insulin. **Insulin-dependent diabetes mellitus (IDDM),** also called **type I diabetes mellitus,** affects approximately 3% of people with diabetes mellitus and results from diminished insulin secretion. It develops as a result of autoimmune destruction of the pancreatic islets, and symptoms appear after approximately 90% of the islets are destroyed. IDDM most commonly develops in young people. Heredity may play some role in the condition, although initiation of pancreatic islet destruction may involve a viral infection of the pancreas (see the Systems Pathology essay p 631).

Noninsulin-dependent diabetes mellitus (NIDDM), also called **type II diabetes mellitus,** results from the inability of tissues to respond to insulin. NIDDM usually develops in people older than 40–45 years of age, although the age of onset varies considerably. A strong genetic component exists in the disease, but its actual cause is unknown. A peptide hormone called leptin (see chapter 25) produced by fat cells has been shown to decrease the response of target tissues to insulin. It is possible that over production of substances like this could be responsible for NIDDM. In some cases, abnormal receptors for insulin or antibodies may bind to and damage insulin receptors, or, in other cases, abnormalities may occur in the mechanisms that the insulin receptors activate.

NIDDM is more common than IDDM. Approximately 97% of people who have diabetes mellitus have NIDDM. The reduced number of functional receptors for insulin make the uptake of glucose by cells very slow, which results in elevated blood glucose levels after a meal. Obesity is common, although not universal, in patients with NIDDM. Elevated blood glucose levels cause fat cells to convert glucose to fat, even though the rate at which adipose cells take up glucose is impaired. Increased blood glucose and increased urine production lead to hyperosmolality of blood and dehydration of cells. The poor use of nutrients and dehydration of cells leads to lethargy, fatigue, and periods of irritability. The elevated blood glucose levels lead to recurrent infections and prolonged wound healing.

Patients with NIDDM don't suffer sudden, large increases in blood glucose and severe tissue wasting because a slow rate of glucose uptake does occur, even though the insulin receptors are defective. In some people with NIDDM, insulin production eventually decreases because pancreatic islet cells atrophy and IDDM develops. Approximately 25%–30% of patients with NIDDM take insulin, 50% take oral medication to increase insulin secretion and increase the efficiency of glucose utilization, and the remainder control blood glucose levels with exercise and diet.

Glucose tolerance tests are used to diagnose diabetes mellitus. In general, the test involves feeding the patient a large amount of glucose after a period of fasting. Blood samples are collected for a few hours, and a sustained increase in blood glucose levels strongly indicates that the person is suffering from diabetes mellitus.

Too much insulin relative to the amount of glucose ingested leads to insulin shock. The high levels of insulin cause target tissues to take up glucose at a very high rate. As a result, blood glucose levels rapidly fall to a low level. Because the nervous system depends on glucose as its major source of energy, neurons malfunction because of a lack of metabolic energy. The result is a series of nervous system responses that include disorientation, confusion, and convulsions. Taking too much insulin, too little food intake after an injection of insulin, or increased metabolism of glucose due to excess exercise by a diabetic patient can cause insulin shock.

It appears that damage to blood vessels and reduced nerve function can be reduced in diabetic patients suffering from either IDDM or NIDDM by keeping blood glucose well within normal levels at all times. Doing so, however, requires increased attention to diet, frequent blood glucose testing, and increased chance of suffering from low blood glucose levels, which leads to symptoms of insulin shock. A strict diet and routine exercise are often effective components of a treatment strategy for diabetes mellitus, and in many cases diet and exercise are adequate to control NIDDM.

clines dramatically, even though blood levels of these molecules may increase to very high levels. The satiety center requires insulin to take up glucose. In the absence of insulin, the satiety center cannot detect the presence of glucose in the extracellular fluid even when high levels are present. The result is an intense sensation of hunger in spite of high blood glucose levels.

Blood glucose levels can fall to very low levels when too much insulin is secreted. When too much insulin is present, target tissues rapidly take up glucose from the blood, causing blood levels of glucose to decline to very low levels. Although the nervous system, except for cells of the satiety center, is not a target tissue for insulin, the nervous system depends primarily on blood glucose for a nutrient source. Consequently, low blood glucose levels cause the central nervous system to malfunction.

Glucagon primarily influences the liver, although it has some effect on skeletal muscle and adipose tissue (see table 18.11). Glucagon binds to membrane-bound receptors, activates G proteins, and increases cAMP synthesis. In general, glucagon causes the breakdown of glycogen and increased glucose synthesis in the liver. It also increases the breakdown of fats. The amount of glucose released from the liver into the blood increases dramatically after glucagon secretion increases. Because glucagon is secreted into the hepatic portal circulation, which carries blood from the intestine and pancreas to the liver, it is delivered in a relatively high concentration to

the liver, where it has its major effect. The liver also rapidly metabolizes it. Thus, glucagon has less of an effect on skeletal muscles and adipose tissue than on the liver.

Regulation of Pancreatic Hormone Secretion

Blood levels of nutrients, neural stimulation, and hormones control the secretion of insulin. Hyperglycemia, or elevated blood levels of glucose, directly affects the beta cells and stimulates insulin secretion. Hypoglycemia, or low blood levels of glucose, directly inhibits insulin secretion. Thus, blood glucose levels play a major role in the regulation of insulin secretion. Certain amino acids also stimulate insulin secretion by acting directly on the beta cells. After a meal, when glucose and amino acid levels increase in the circulatory system, insulin secretion increases. During periods of fasting, when blood glucose levels are low, the rate of insulin secretion declines (figure 18.16).

The autonomic nervous system also controls insulin secretion. Parasympathetic stimulation is associated with food intake, and its stimulation acts with the elevated blood glucose levels to increase insulin secretion. Sympathetic innervation inhibits insulin secretion and helps prevent a rapid fall in blood glucose levels. Because most tissues, except nervous tissue, require insulin to take up glucose, sympathetic stimulation maintains blood glucose levels in a normal range during periods of physical activity or excitement. This response is important for maintaining normal functioning of the nervous system.

Gastrointestinal hormones involved with the regulation of digestion, such as gastrin, secretin, and cholecystokinin (see chapter 24), increase insulin secretion. Somatostatin inhibits insulin and glucagon secretion, but the factors that regulate somatostatin secretion are not clear. It can be released in response to food intake, in which case somatostatin may prevent oversecretion of insulin.

PREDICT 8

Explain why the increase in insulin secretion in response to parasympathetic stimulation and gastrointestinal hormones is consistent with the maintenance of blood glucose levels in the circulatory system.

Low blood glucose levels stimulate glucagon secretion, and high blood glucose levels inhibit it. Certain amino acids and sympathetic stimulation also increase glucagon secretion. After a high-protein meal, amino acids increase both insulin and glucagon secretion. Insulin causes target tissues to accept the amino acids for protein synthesis, and glucagon increases the process of glucose synthesis from amino acids in the liver (gluconeogenesis). Both protein synthesis and the use of amino acids to maintain blood glucose levels result from the low, but simultaneous, secretion of insulin and glucagon induced by meals high in protein content.

33. *Where is the pancreas located? Describe the exocrine and endocrine parts of this gland and the secretions produced by each portion.*
34. *Name the target tissues for insulin and glucagon, and list the effects they have on their target tissues.*
35. *How does insulin affect the nervous system in general and the satiety center in the hypothalamus in particular?*
36. *What effect do blood glucose levels, blood amino acid levels, the autonomic nervous system, and somatostatin have on insulin and glucagon secretion?*

PREDICT 9

Compare the regulation of glucagon and insulin secretion after a meal high in carbohydrates, after a meal low in carbohydrates but high in proteins, and during physical exercise.

Hormonal Regulation of Nutrients

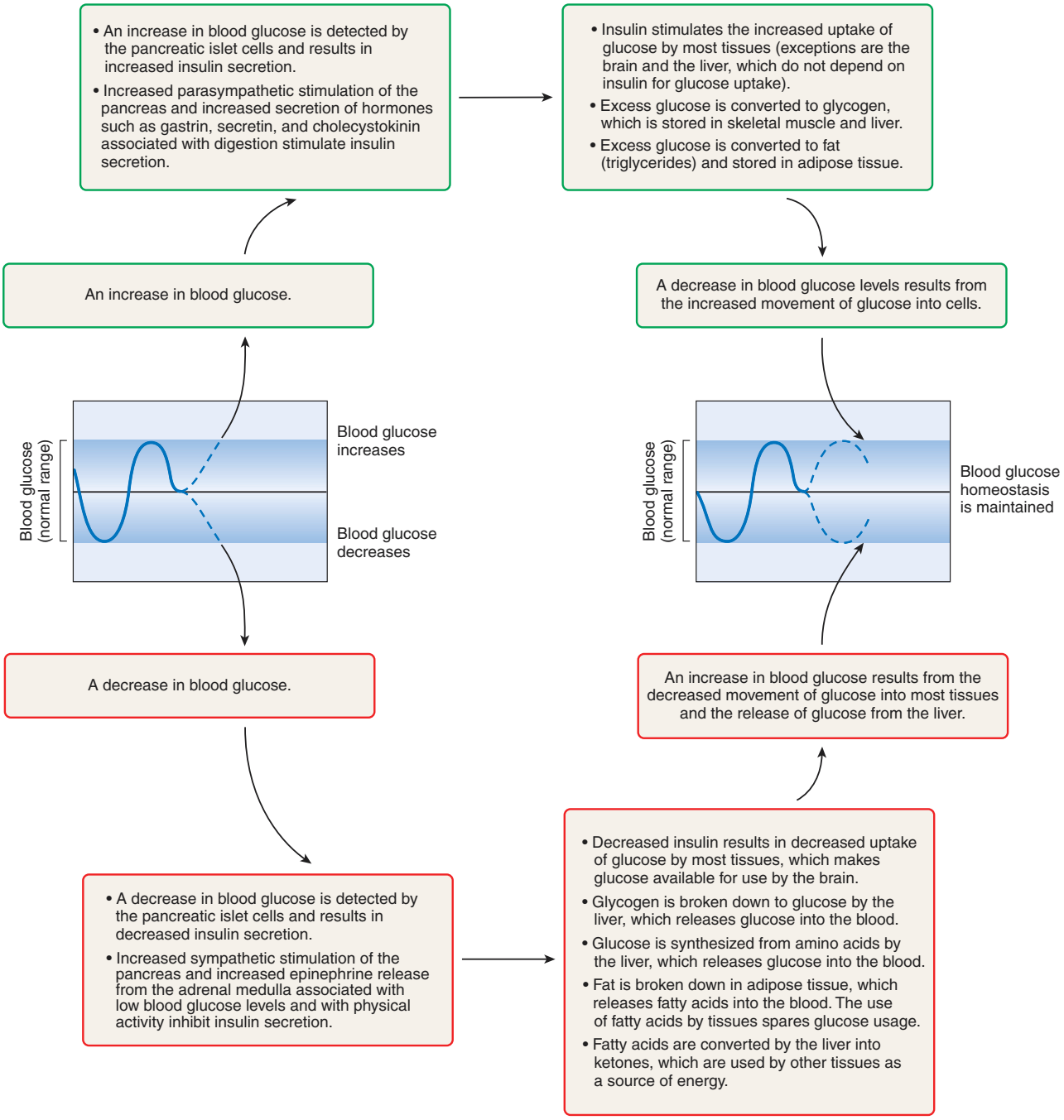
Objective

- ***Describe how blood nutrient levels are regulated by hormones after a meal and during exercise.***

Two different situations—after a meal and during exercise—can illustrate how several hormones function together to regulate blood nutrient levels.

After a meal and under resting conditions, secretion of glucagon, cortisol, GH, and epinephrine is reduced (figure 18.17*a*). Both increasing blood glucose levels and parasympathetic stimulation elevate insulin secretion to increase the uptake of glucose, amino acids, and fats by target tissues. Substances not immediately used for cell metabolism are stored. Glucose is converted to glycogen in skeletal muscle and the liver, and is used for fat synthesis in adipose tissue and the liver. The rapid uptake and storage of glucose prevent too large an increase in blood glucose levels. Amino acids are incorporated into proteins and fats that were ingested as part of the meal are stored in adipose tissue and the liver. If the meal is high in protein, a small amount of glucagon is secreted, thereby increasing the rate at which the liver uses amino acids to form glucose.

Within 1–2 hours after the meal, absorption of digested materials from the gastrointestinal tract declines, and blood glucose levels decline (figure 18.17*b*). As a result, secretion of glucagon, cortisol, GH, and epinephrine increases, thereby stimulating the release of glucose from tissues. As blood glucose decreases, insulin secretion decreases, and the rate of glucose entry into the target tissues for insulin decreases. Glycogen is converted back to glucose and is used as an energy source. Glucose is released into the blood by the liver. The decreased uptake of glucose by most tissues, combined with its release from the liver, helps maintain blood glucose at levels necessary for normal brain function. Cells that use less glucose start using more fats and proteins. Adipose tissue releases fatty acids, and the liver releases triglycerides (in lipoproteins) and ketones into the blood. Tissues take up these substances from the



Homeostasis Figure 18.16 Regulation of Insulin Secretion

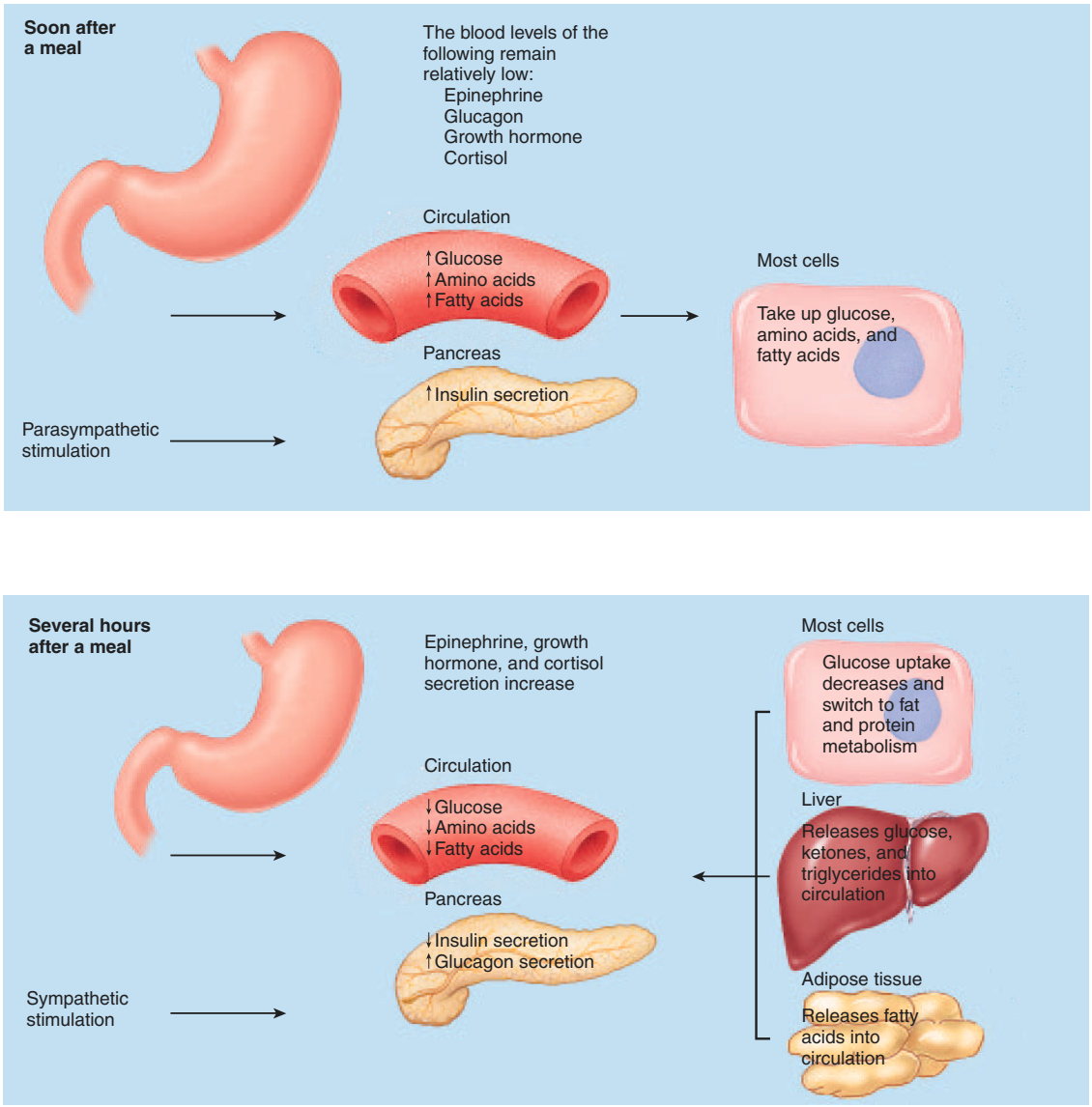


Figure 18.17 **Regulation of Blood Nutrient Levels After a Meal**

(*a*) Soon after a meal, glucose, amino acids, and fatty acids enter the bloodstream from the intestinal tract. Glucose and amino acids stimulate insulin secretion. In addition, parasympathetic stimulation increases insulin secretion. Cells take up the glucose and amino acids and use them in their metabolism. (*b*) Several hours after a meal, absorption from the intestinal tract decreases, and blood levels of glucose, amino acids, and fatty acids decrease. As a result, insulin secretion decreases, and glucagon, epinephrine, and GH secretion increase. Cell uptake of glucose decreases, and usage of fats and proteins increases.

blood and use them for energy. Fat molecules are a major source of energy for most tissues when blood glucose levels are low.

The interactions of insulin, GH, glucagon, epinephrine, and cortisol are excellent examples of negative-feedback mechanisms. When blood glucose levels are high, these hormones cause rapid uptake and storage of glucose, amino acids, and fats. When blood glucose levels are low, they cause release of glucose and a switch to fat and protein metabolism as a source of energy for most tissues.

During exercise, skeletal muscles require energy to support the contraction process (see chapter 9). Although metabolism of intracellular nutrients can sustain muscle contraction for a short time, additional energy sources are required during prolonged activity. Sympathetic nervous system activity, which increases during exercise, stimulates the release of epinephrine from the adrenal medulla and of glucagon from the pancreas (figure 18.18). These hormones induce the conversion of glycogen to glucose in the liver

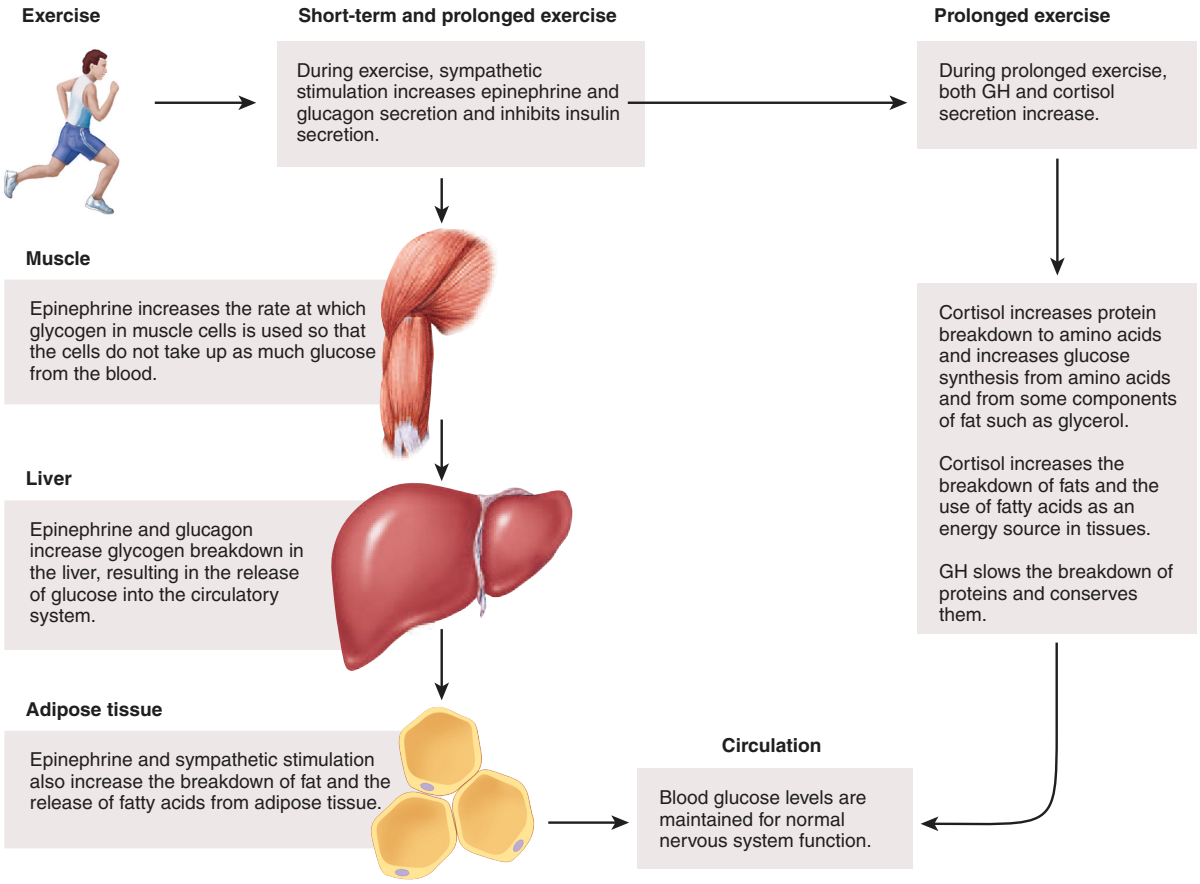


Figure 18.18 Regulation of Blood Nutrient Levels During Exercise

and the release of glucose into the blood, thus providing skeletal muscles with a source of energy. Because epinephrine and glucagon have short half-lives, they can rapidly adjust blood glucose levels for varying conditions of activity.

During sustained activity, glucose released from the liver and other tissues is not adequate to support muscle activity, and a danger exists that blood glucose levels will become too low to support brain function. A decrease in insulin prevents uptake of glucose by most tissues, thus conserving glucose for the brain. Epinephrine, glucagon, cortisol, and GH cause an increase of fatty acids, triglycerides, and ketones in the blood. GH also inhibits the breakdown of proteins, thereby preventing muscles from using themselves as an energy source. Consequently, glucose metabolism decreases, and fat metabolism in skeletal muscles increases. At the end of a long race, for example, muscles rely to a large extent on fat metabolism for energy.

37. *Describe the hormonal effects after a meal that result in the movement of nutrients into cells and their storage. Describe the hormonal effects that later cause the release of stored materials for use as energy.*

38. *During exercise, how does sympathetic nervous system activity regulate blood glucose levels? Name five hormones that interact to ensure that both the brain and muscles have adequate energy sources.*

P R E D I C T 10

Explain why long-distance runners may not have much of a "kick" left when they try to sprint to the finish line.

Hormones of the Reproductive System

Objective

- *List the hormones secreted by the testes and ovaries, describe their functions, and explain how they are regulated.*

Reproductive hormones are secreted primarily from the ovaries, testes, placenta, and pituitary gland (table 18.12). These hormones are discussed in chapter 28. The main endocrine glands of the male reproductive system are the testes. The functions of the

Table 18.12 Hormones of the Reproductive Organs

Hormones	Structure	Target Tissue	Response
Testis			
Testosterone	Steroid	Most cells	Aids in spermatogenesis; maintenance of functional reproductive organs; secondary sex characteristics; sexual behavior
Inhibin	Polypeptide	Anterior pituitary gland	Inhibits FSH secretion
Ovary			
Estrogens	Steroids	Most cells	Uterine and mammary gland development and function; external genitalia structure; secondary sex characteristics; sexual behavior and menstrual cycle
Progesterone	Steroid	Most cells	Uterine and mammary gland development and function; external genitalia structure; secondary sex characteristics; menstrual cycle
Inhibin	Polypeptide	Anterior pituitary gland	Inhibits FSH secretion
Relaxin	Polypeptide	Connective tissue cells	Increases flexibility of connective tissue in the pelvic area, especially the symphysis pubis

testes depend on the secretion of FSH and LH from the anterior pituitary gland. The main hormone secreted by the testes is testosterone, an androgen. **Testosterone** regulates the production of sperm cells by the testes and the development and maintenance of male reproductive organs and secondary sex characteristics. The testes secrete another hormone called **inhibin,** which inhibits the secretion of FSH from the anterior pituitary.

The main endocrine glands of the female reproductive system are the ovaries. Like the testes, the functions of the ovaries depend on the secretion of FSH and LH from the anterior pituitary gland. The main hormones secreted by the ovaries are estrogen and progesterone. These hormones, along with FSH and LH, control the female reproductive cycle, prepare the mammary glands for lactation, and maintain pregnancy. Estrogen and progesterone are also responsible for the development of the female reproductive organs and female secondary sex characteristics. The ovaries also secrete inhibin, which inhibits FSH secretion.

During pregnancy the ovaries and the placenta secrete estrogen and progesterone, which are essential to maintain pregnancy. In addition they secrete **relaxin,** which increases the flexibility of connective tissue of the symphysis pubis and helps dilate the cervix of the uterus. This facilitates delivery by making the birth canal larger.

39. List the hormones secreted by the testes, and give their functions. What hormones regulate the testes?

40. List the hormones secreted by the ovaries, and give their functions. During pregnancy, what other organ, in addition to the ovaries, secretes hormones? Upon what hormones does ovarian function depend?

Hormones of the Pineal Body

Objective

- ***Describe the structure and location of the pineal body, the products it secretes, and the functions of these products.***

The **pineal** (pin′ē-ăl) **body** in the epithalamus of the brain secretes hormones that act on the hypothalamus or the gonads to inhibit reproductive functions. Two substances have been proposed as secretory products: **melatonin** (mel-ă-tōn′in) and **arginine vasotocin** (ar′ji-nēn vā-sō-tō′sin, vas-ō-tos′in) (table 18.13). Melatonin can decrease GnRH secretion from the hypothalamus and may inhibit reproductive functions through this mechanism. It may also help regulate sleep cycles by increasing the tendency to sleep.

The **photoperiod** is the amount of daylight and darkness that occurs each day and changes with the seasons of the year. In some animals, the photoperiod regulates pineal secretions (figure 18.19). For example, increased daylight initiates action potentials in the retina of the eye that are propagated to the brain and cause a decrease in the action potentials sent first to the spinal cord and then through sympathetic neurons to the pineal body. Decreased pineal secretion results. In the dark, action potentials delivered by sympathetic neurons to the pineal body increase, thereby stimulating the secretion of pineal hormones. Humans secrete larger amounts of melatonin at night than in the daylight. In animals that breed in the spring, the increased length of a day decreases pineal secretions. Because pineal secretions inhibit reproductive functions in these species, the increased length of a day results in hypertrophy of the reproductive structures.

Table 18.13 Other Hormones and Hormonelike Substances

Chemical Signal	Structure	Target Tissue	Response
Pineal Body			
Melatonin	Amino acid derivative	At least the hypothalamus	Inhibition of gonadotropin-releasing hormone secretion, thereby inhibiting reproduction; significance is not clear in humans; may help regulate sleep–wake cycles
Arginine vasotocin	Amino acid derivative	Possibly the hypothalamus	Possible inhibition of gonadotropin-releasing hormone secretion
Thymus Gland			
Thymosin	Peptide	Immune tissues	Development and function of the immune system
Several Tissues (autocrine and paracrine regulatory substances)			
Eicosanoids			
Prostaglandins	Modified fatty acid	Most tissues	Mediation of the inflammatory response increased uterine contractions; ovulation, possible inhibition of progesterone synthesis; blood coagulation; and other functions
Prostacyclins	Modified fatty acid	Most tissues	Mediation of the inflammatory response and other functions
Thromboxanes	Modified fatty acid	Most tissues	Mediation of the inflammatory response and other functions
Leukotrienes	Modified fatty acid	Most tissues	Mediation of the inflammatory response and other functions
Enkephalins and endorphins	Peptides	Nervous system	Reduction of pain sensation and other functions
Epidermal growth factor	Protein	Many tissues	Stimulates division in many cell types and plays a role in embryonic development
Fibroblast growth factor	Protein	Many tissues	Stimulates cell division in many cell types and plays a role in embryonic development
Interleukin-2	Protein	Certain immune competent cells	Stimulates cell division of T lymphocytes

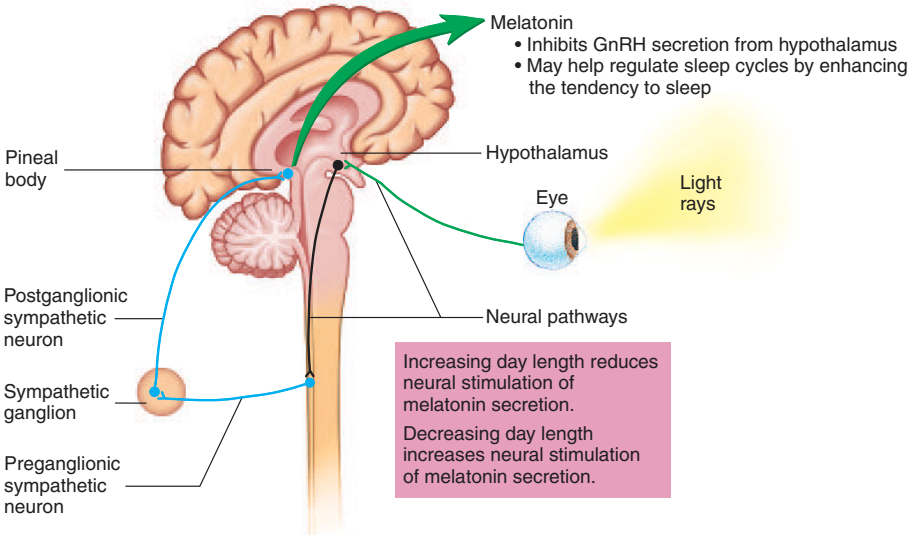


Figure 18.19 Regulation of Melatonin Secretion from the Pineal Body

Light entering the eye inhibits and dark stimulates the release of melatonin from the pineal body.

The function of melatonin in the regulation of reproductive functions in humans is not clear, but it is recommended by some to enhance sleep. Because melatonin causes atrophy of reproductive structures in some species there's a possibility of undesirable side effects on the reproductive system.

The function of the pineal body in humans is not clear, but tumors that destroy the pineal body correlate with early sexual development, and tumors that result in pineal hormone secretion correlate with retarded development of the reproductive system. It's not clear, however, if the pineal body controls the onset of puberty.

Arginine vasotocin works with melatonin to regulate the function of the reproductive system in some animals. Evidence for the role of melatonin is more extensive, however.

41. *Where is the pineal body located? Name the hormones it produces and their possible effects.*

Hormones of the Thymus

The **thymus** (thī′mŭs) is in the neck and superior to the heart in the thorax, and it secretes a hormone called **thymosin** (thī′mō-sin) (see table 18.13). Both the thymus and thymosin play an important role in the development of the immune system and are discussed in chapter 22.

Hormones of the Gastrointestinal Tract

Several hormones are released from the gastrointestinal tract. They regulate digestive functions by influencing the activity of the stomach, intestines, liver, and pancreas. They are discussed in chapter 24.

Hormonelike Substances

Objective

- *Define and give examples of autocrine and paracrine chemical signals in the body.*

Autocrine chemical signals are released from cells that influence the same cell type from which they are released. **Paracrine chemical signals** are released from one cell type, diffuse short distances, and influence the activity of another cell type, which is its target tissue. Autocrine and paracrine chemical signals differ from hormones in that they are not secreted from discrete endocrine glands, they have local effects rather than systemic effects, or they have functions that are not understood adequately to explain their role in the body. Examples of autocrine chemical signals include chemical mediators of inflammation derived from the fatty acid **arachidonic** (ă-rak-i-don′ik) **acid,** such as eicosanoids and modified phospholipids. The **eicosanoids** include **prostaglandins** (pros′stă-glandinz), **thromboxanes** (throm′bok-zānz), **prostacyclins** (pros-tă-sī′klinz), and **leukotrienes** (loo′kō-trī′ēnz). Modified phospholipids include platelet activating factor (see chapter 19). Paracrine chemical signals include substances that play a role in modulating the sensation of pain, such as **endorphins** (en′dōr-finz) and **enkephalins** (enkef′ă-linz), and several peptide growth factors, such as **epidermal growth factor, fibroblast growth factor,** and **interleukin-2** (inter-loo′kin) (see table 18.13).

Prostaglandins, thromboxanes, prostacyclins, and leukotrienes are released from injured cells and are responsible for initiating some of the symptoms of inflammation (see chapter 22), in addition to being released from certain healthy cells. For example, prostaglandins are involved in the regulation of uterine contractions during menstruation and childbirth, the process of ovulation, the inhibition of progesterone synthesis by the corpus luteum, the regulation of coagulation, kidney function, and modification of the effect of other hormones on their target tissues. Pain receptors are stimulated directly by prostaglandins and other inflammatory compounds, or prostaglandins cause vasodilation of blood vessels, which is associated with headaches. Anti-inflammatory drugs like aspirin inhibit prostaglandin synthesis and, as a result, reduce inflammation and pain. These examples are paracrine regulatory substances because they are synthesized and secreted by the cells near their target cells. Once prostaglandins enter the circulatory system, they are metabolized rapidly.

Three classes of peptide molecules, which are endogenously produced on analgesics, bind to the same receptor molecules as morphine. They include enkephalins, endorphins, and **dynorphins** (dī′nōr-finz). They are produced in several sites in the body, such as parts of the brain, pituitary, spinal cord, and gut. They act as neurotransmitters in some neurons of both the central and peripheral nervous systems and as hormones or paracrine regulatory substances. In general, they moderate the sensation of pain (see chapter 14). Decreased sensitivity to painful stimuli during exercise and stress may result from the increased secretion of these substances.

Several proteins can be classified as growth factors. They generally function as paracrine chemical signals because they are secreted near their target tissues. Epidermal growth factor stimulates cell divisions in a number of tissues and plays an important role in embryonic development. Interleukin-2 stimulates the proliferation of T lymphocytes and plays a very important role in immune responses (see chapter 22). The number of hormonelike substances in the body is large, and only a few of them have been mentioned here. Chemical communication among cells in the body is complex, well developed, and necessary for maintenance of homeostasis. Investigations into chemical regulation increase our knowledge of body functions—knowledge that can be used in the development of techniques for the treatment of pathologic conditions.

42. *Define autocrine chemical signals. List eicosanoids and modified phospholipids that function as autocrine chemical signals, and explain their function.*
43. *Define paracrine chemical signals. List examples of substances that play a role in modulating pain or are peptide growth factors. How can prostaglandins function as both autocrine and paracrine chemical signals?*

Systems Pathology

Insulin-Dependent Diabetes Mellitus

Billy, a 10-year-old boy, was diagnosed as having insulin-dependent diabetes mellitus (IDDM). Billy's mother took him to a physician after noticing that he was constantly hungry and was losing weight rapidly in spite of his unusually large food intake. More careful observation made it clear that Billy was constantly thirsty and that he urinated frequently. In addition, he felt weak and lethargic, and his breath occasionally had a distinctive sweet, or acetone, odor. Diagnostic tests confirmed that he had IDDM.

Background Information

IDDM is caused by diminished insulin secretion. In patients with IDDM, nutrients are absorbed from the intestine after a meal, but skeletal muscle, adipose tissue, and other target tissues don't readily take glucose into their cells, and liver cells cannot convert glucose to glycogen. Consequently, blood levels of glucose increase dramatically. Glucagon and glucocorticoid secretion increase because the glucose in the blood cannot enter the cells that produce these hormones, so their rate of secretion is similar to when blood glucose levels are low. Epinephrine secretion also increases. In response to these hormones, glycogen, fats, and proteins are broken down and metabolized to produce the ATP required by cells.

When blood glucose levels are very high, glucose is excreted in the urine, which results in an increase in urine volume. The rapid loss of water in the urine increases the osmotic concentration of blood, which increases the sensation of thirst. The increased osmolality of blood and the ionic imbalances caused by the loss of Ca^{2+} and K^{+} in the large amount of urine produced cause neurons to malfunction and result in diabetic coma in severe cases. When insulin levels in the blood are low and cells of the nervous system that control appetite appear to be unable to take up glucose even when blood glucose levels are high, the result is an increased appetite. **Polyuria** (pol-ē-ū′rē-ă; increased urine volume), **polydipsia** (pol-ē-dip′sē-ă; increased thirst), and **polyphagia** (pol-ē-fā′jē-ă; increased appetite) are major symptoms of IDDM. Acidosis is caused by rapid fat catabolism, which results in increased levels of **acetoacetic** (as′e-tō-a-sē′tik) **acid,** which is converted to **acetone** (as′e-tōn) and **β-hydroxybutyric** (bā′tă hī-drok′sē-bū-tir′ik) **acid.** These three substances collectively are referred to as **ketone** (kē′tōn) **bodies.** The presence of excreted ketone bodies in the urine and in expired air ("acetone breath") suggests that the person has diabetes mellitus.

Billy's physician explained that prior to the late 1920s people with his condition always died in a relatively short time. They suffered from massive weight loss and appeared to starve to death in spite of eating a large amount of food. The physician explained that because of the discovery of insulin, many people with his type of diabetes mellitus are able to live nearly normal lives. Taking insulin injections (figure B), monitoring blood glucose levels, and following a strict diet to keep blood glucose levels within a normal range of values are the major treatments for IDDM.

Figure B A 10-Year-Old Boy Giving Himself Insulin

P R E D I C T 11

After Billy was diagnosed with diabetes mellitus, he followed a strict diet and took insulin for a few months. He began to feel much better than before. In fact, he felt so well that he began to sneak candy and soft drinks when his parents were not around. Predict the consequences of his actions on his health.

System Interactions Effect of IDDM on Other Systems

System	Interaction
Muscular	Untreated diabetes mellitus, especially IDDM, results in severe muscle atrophy because glycogen, stored fat, and proteins of muscles are broken down and used as energy sources. Ionic imbalances can also lead to muscular weakness.
Nervous	Untreated IDDM can have dramatic effects on the nervous system. When the blood glucose reaches very high levels, the osmolality of the extracellular fluid is increased. Thus, water diffuses from the neurons of the brain. In addition, acidosis develops because of the rapid metabolism of fats. As a result, the nervous system cannot function normally, and diabetic coma can result. A long-term effect is the degeneration of the myelin sheaths of neurons, resulting in abnormal nerve functions.
Cardiovascular	Atherosclerosis develops more rapidly in diabetics than in the healthy population. Changes in the capillary structure and high blood glucose levels increase the probability of reduced circulation and gangrene.
Lymphatic and immune	The tendency to develop infections increases, and the rate of healing is slower. In some cases, an allergic reaction to the injected insulin occurs.
Respiratory	Acidosis causes hyperventilation, which increases blood pH back toward normal levels by decreasing blood CO_2 levels.
Urinary	High blood glucose levels cause polyuria, the urine contains glucose and has a high osmolality, and people with diabetes are more likely to develop urinary tract infections.
Reproductive	Pregnant women with diabetes mellitus may have babies with a larger-than-normal birth weight because the blood glucose levels may be high in the mother and fetus, and the fetus's pancreas produces insulin. Glucose is therefore taken up by cells of the fetus, where it is converted to fat.

Effects of Aging on the Endocrine System

Objective

- ***Describe the effects of aging on the endocrine system.***

Age-related changes in the endocrine system are not the same for all of the endocrine glands. There's a gradual decrease in the secretory activity of some endocrine glands, but not in all of them. In addition, some decreases in secretory activity of endocrine glands appear to be secondary to a decrease in physical activity as people age.

There is a decrease in the secretion of GH as people age. The decrease is greater in people who do not exercise, and it may not occur in people who exercise regularly. Decreasing GH secretion may explain the gradual decrease in lean body mass. For example, bone mass and muscle mass decrease as GH levels decline. At the same time adipose tissue increases.

Melatonin secretion decreases in aging people. The decrease may influence age-related changes in sleep patterns and the secretory patterns of other hormones such as GH and testosterone.

The secretion of thyroid hormones decreases slightly with increasing age, and there's a decrease in the T_3/T_4 ratio. This may be less of a decrease in the secretory activity of the thyroid gland than it is compensating for the decrease in the lean body mass in aging people. Age-related damage to the thyroid gland by the immune system can occur. This change occurs in women more than in men. The result is that approximately 10% of elderly women have thyroid glands that don't produce enough T_3 and T_4.

Parathyroid hormone secretion doesn't appear to decrease with age. Blood levels of Ca^{2+} may decrease slightly because of reduced dietary calcium intake and vitamin D levels. The greatest risk is a loss of bone matrix as parathyroid hormone increases to maintain blood levels of Ca^{2+} within their normal range.

The kidneys of the elderly secrete less renin. Consequently, there's a reduced ability to respond to decreases in blood pressure by activating the renin-angiotensin-aldosterone mechanism (see chapter 26).

Reproductive hormone secretion gradually declines in elderly men, and women experience menopause. These age-related changes are described in chapter 28.

There are no age-related decreases in the ability to regulate blood glucose levels. However, there's an age-related tendency to develop type II diabetes for those who have a familial tendency to do so, and it is correlated with age-related increases in body weight.

Thymosin from the thymus decreases with age. Fewer immature lymphocytes are able to mature and become functional, and the immune system becomes less effective in protecting the body. There's an increased susceptibility to infection and to cancer.

44. ***Describe age-related changes in the secretion and the consequences of these changes in the following: GH, melatonin, thyroid hormones, renin, and reproductive hormones. Name one hormone that doesn't appear to decrease with age.***

S U M M A R Y

Functions of the Endocrine System (p. 598)

Main regulatory functions include water balance, uterine contractions and milk release, metabolism and tissue maturation, ion regulation, heart rate and blood pressure regulation, control of blood glucose and other nutrients, immune system regulation, and control of reproductive functions.

Pituitary Gland and Hypothalamus (p. 598)

1. The pituitary gland secretes at least nine hormones that regulate numerous body functions and other endocrine glands.
2. The hypothalamus regulates pituitary gland activity through neurohormones and action potentials.

Structure of the Pituitary Gland

1. The posterior pituitary develops from the floor of the brain and consists of the infundibulum and pars nervosa.
2. The anterior pituitary develops from the roof of the mouth and consists of the pars distalis, pars intermedia, and pars tuberalis.

Relationship of the Pituitary to the Brain

1. The hypothalamohypophysial portal system connects the hypothalamus and the anterior pituitary.
   - Neurohormones are produced in hypothalamic neurons.
   - Through the portal system, the neurohormones inhibit or stimulate hormone production in the anterior pituitary.
2. The hypothalamohypophysial tract connects the hypothalamus and the posterior pituitary.
   - Neurohormones are produced in hypothalamic neurons.
   - The neurohormones move down the axons of the nerve tract and are secreted from the posterior pituitary.

Hormones of the Pituitary Gland (p. 601)

Posterior Pituitary Hormones

1. ADH promotes water retention by the kidneys.
2. Oxytocin promotes uterine contractions during delivery and causes milk ejection in lactating women.

Anterior Pituitary Hormones

1. GH, or somatotropin
   - GH stimulates the uptake of amino acids and their conversion into proteins and stimulates the breakdown of fats and glycogen.
   - GH stimulates the production of somatomedins; together they promote bone and cartilage growth.
   - GH secretion increases in response to an increase in blood amino acids, low blood glucose, or stress.
   - GH is regulated by GHRH and GHIH, or somatostatin.
2. TSH, or thyrotropin, causes the release of thyroid hormones.
3. ACTH is derived from proopiomelanocortin; it stimulates cortisol secretion from the adrenal cortex and increases skin pigmentation.
4. Several hormones in addition to ACTH are derived from proopiomelanocortin.
   - Lipotropins cause fat breakdown.
   - β endorphins play a role in analgesia.
   - MSH increases skin pigmentation.
5. LH and FSH
   - Both hormones regulate the production of gametes and reproductive hormones (testosterone in males; estrogen and progesterone in females).
   - GnRH from the hypothalamus stimulates LH and FSH secretion.
6. Prolactin stimulates milk production in lactating females. Prolactin-releasing hormone and prolactin-inhibiting hormone from the hypothalamus affect prolactin secretion.

Thyroid Gland (p. 607)

The thyroid gland is just inferior to the larynx.

Histology

1. The thyroid gland is composed of small, hollow balls of cells called follicles, which contain thyroglobulin.
2. Parafollicular cells are scattered throughout the thyroid gland.

Thyroid Hormones

1. Thyroid hormone synthesis
   - Iodide ions are taken into the follicles by active transport, are oxidized, and are bound to tyrosine molecules in thyroglobulin.
   - Thyroglobulin is secreted into the follicle lumen. Tyrosine molecules with iodine combine to form T_3 and T_4, thyroid hormones.
   - Thyroglobulin is taken into the follicular cells and is broken down; T_3 and T_4 diffuse from the follicles to the blood.
2. Thyroid hormone transport in the blood
   - T_3 and T_4 bind to thyroxine-binding globulin and other plasma proteins.
   - The plasma proteins prolong the half-life of T_3 and T_4 and regulate the levels of T_3 and T_4 in the blood.
   - Approximately one-third of the T_4 is converted into functional T_3.
3. Mechanism of action of thyroid hormones
   - Thyroid hormones bind with intracellular receptor molecules and initiate new protein synthesis.
4. Effects of thyroid hormones
   - Thyroid hormones increase the rate of glucose, fat, and protein metabolism in many tissues, thus increasing body temperature.
   - Normal growth of many tissues is dependent on thyroid hormones.
5. Regulation of thyroid hormone secretion
   - Increased TSH from the anterior pituitary increases thyroid hormone secretion.
   - TRH from the hypothalamus increases TSH secretion. TRH increases as a result of chronic exposure to cold, food deprivation, and stress.
   - T_3 and T_4 inhibit TSH and TRH secretion.

Calcitonin

1. The parafollicular cells secrete calcitonin.
2. An increase in blood calcium levels stimulates calcitonin secretion.
3. Calcitonin decreases blood calcium and phosphate levels by inhibiting osteoclasts.

Parathyroid Glands (p. 613)

1. The parathyroid glands are embedded in the thyroid glands.
2. PTH increases blood calcium levels.
   - PTH stimulates osteoclasts.
   - PTH promotes calcium reabsorption by the kidneys and the formation of active vitamin D by the kidneys.
   - Active vitamin D increases calcium absorption by the intestine.
3. A decrease in blood calcium levels stimulates PTH secretion.

Adrenal Glands (p. 615)

1. The adrenal glands are near the superior poles of the kidneys.
2. The adrenal medulla arises from neural crest cells and functions as part of the sympathetic nervous system. The adrenal cortex is derived from mesoderm.

3. Histology
   - The medulla is composed of closely packed cells.
   - The cortex is divided into three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis.
4. Hormones of the adrenal medulla
   - Epinephrine accounts for 80% and norepinephrine for 20% of the adrenal medulla hormones.
     - Epinephrine increases blood glucose levels, use of glycogen and glucose by skeletal muscle, and heart rate and force of contraction, and it causes vasoconstriction in the skin and viscera and vasodilation in skeletal and cardiac muscle.
     - Norepinephrine stimulates cardiac muscle and causes constriction of most peripheral blood vessels.
   - The adrenal medulla hormones prepare the body for physical activity.
   - Release of adrenal medulla hormones is mediated by the sympathetic nervous system in response to emotions, injury, stress, exercise, and low blood glucose levels.
5. Hormones of the adrenal cortex
   - The zona glomerulosa secretes the mineralocorticoids, especially aldosterone. Aldosterone acts on the kidneys to increase sodium and to decrease potassium and hydrogen levels in the blood.
   - The zona fasciculata secretes glucocorticoids, especially cortisol.
     - Cortisol increases fat and protein breakdown, increases glucose synthesis from amino acids, decreases the inflammatory response, and is necessary for the development of some tissues.
     - ACTH from the anterior pituitary stimulates cortisol secretion. CRH from the hypothalamus stimulates ACTH release. Low blood glucose levels or stress stimulate CRH secretion.
   - The zona reticularis secretes androgens. In females, androgens stimulate axillary and pubic hair growth and sexual drive.

Pancreas (p. 620)

1. The pancreas is located along the small intestine and the stomach. It is both an exocrine and an endocrine gland.
2. Histology
   - The exocrine portion of the pancreas consists of a complex duct system that ends in small sacs called acini that produce pancreatic digestive juices.
   - The endocrine portion consists of the pancreatic islets. Each islet is composed of alpha cells, which secrete glucagon, beta cells, which secrete insulin, and delta cells, which secrete somatostatin.
3. Effect of insulin on its target tissues
   - Insulin's target tissues are the liver, adipose tissue, muscle, and the satiety center in the hypothalamus. The nervous system is not a target tissue, but it does rely on blood glucose levels maintained by insulin.
   - Insulin increases the uptake of glucose and amino acids by cells. Glucose is used for energy or is stored as glycogen. Amino acids are used for energy or are converted to glucose or proteins.
4. Effect of glucagon on its target tissue
   - Glucagon's target tissue is mainly the liver.
   - Glucagon causes the breakdown of glycogen and fats for use as an energy source.
5. Regulation of pancreatic hormone secretion
   - Insulin secretion increases because of elevated blood glucose levels, an increase in some amino acids, parasympathetic stimulation, and gastrointestinal hormones. Sympathetic stimulation decreases insulin secretion.
   - Glucagon secretion is stimulated by low blood glucose levels, certain amino acids, and sympathetic stimulation.
   - Somatostatin inhibits insulin and glucagon secretion.

Hormonal Regulation of Nutrients (p. 624)

1. After a meal, the following events take place:
   - High glucose levels inhibit glucagon, cortisol, GH, and epinephrine, which reduces the release of glucose from tissues.
   - Insulin secretion increases as a result of the high blood glucose levels, thereby increasing the uptake of glucose, amino acids, and fats, which are used for energy or are stored.
   - Sometime after the meal, blood glucose levels drop. Glucagon, cortisol, GH, and epinephrine levels increase, insulin levels decrease, and glucose is released from tissues.
   - Adipose tissue releases fatty acids, triacylglycerols, and ketones, which most tissues use for energy.
2. During exercise the following events occur:
   - Sympathetic activity increases epinephrine and glucagon secretion, causing a release of glucose into the blood.
   - Low blood sugar levels, caused by uptake of glucose by skeletal muscles, stimulate epinephrine, glucagon, GH, and cortisol secretion, causing an increase in fatty acids, triacylglycerols, and ketones in the blood, all of which are used for energy.

Hormones of the Reproductive System (p. 627)

The ovaries, testes, placenta, and pituitary gland secrete reproductive hormones.

Hormones of the Pineal Body (p. 628)

The pineal body produces melatonin and arginine vasotocin, which can inhibit reproductive maturation and may regulate sleep–wake cycles.

Hormones of the Thymus (p. 630)

The thymus gland produces thymosin, which is involved in the development of the immune system.

Hormones of the Gastrointestinal Tract (p. 630)

The gastrointestinal tract produces several hormones that regulate digestive functions.

Hormonelike Substances (p. 630)

1. Autocrine and paracrine chemical signals are produced by many cells of the body and usually have a local effect. They affect many body functions.
2. Eicosanoids such as prostaglandins, prostacyclins, thromboxanes, and leukotrienes are derived from fatty acids and mediate inflammation and other functions. Endorphins, enkephalins, and dynorphins are analgesic substances. Growth factors influence cell division and growth in many tissues, and interleukin-2 influences cell division in T cells of the immune system.

Effects of Aging on the Endocrine System (p. 632)

There is a gradual decrease in the secretion rate of most, but not all, hormones. Some decreases are secondary to gradual decreases in physical activity.

REVIEW AND COMPREHENSION

1. The pituitary gland
   a. develops from the floor of the brain.
   b. develops from the roof of the mouth.
   c. is stimulated by neurohormones produced in the midbrain.
   d. secretes only three major hormones.
   e. both a and b.
2. The hypothalamohypophysial portal system
   a. contains one capillary bed.
   b. carries hormones from the anterior pituitary to the body.
   c. carries hormones from the posterior pituitary to the body.
   d. carries hormones from the hypothalamus to the anterior pituitary.
   e. carries hormones from the hypothalamus to the posterior pituitary.
3. Which of these hormones is *not* a hormone that is secreted into the hypothalamohypophysial portal system?
   a. GHRH
   b. TRH
   c. PIH
   d. GnRH
   e. ACTH
4. Hormones secreted from the posterior pituitary
   a. are produced in the anterior pituitary.
   b. are transported to the posterior pituitary within axons.
   c. include GH and TSH.
   d. are steroids.
   e. all of the above.
5. Which of these stimulates the secretion of ADH?
   a. elevated blood osmolality
   b. decreased blood osmolality
   c. releasing hormones from the hypothalamus
   d. ACTH
   e. increased blood pressure
6. Oxytocin is responsible for
   a. preventing milk release from the mammary glands.
   b. preventing goiter.
   c. causing contraction of the uterus.
   d. maintaining normal calcium levels.
   e. increasing metabolic rate.
7. Growth hormone
   a. increases the usage of glucose.
   b. increases the breakdown of lipids.
   c. decreases the synthesis of proteins.
   d. decreases the synthesis of glycogen.
   e. all of the above.
8. Which of these hormones stimulates somatomedin secretion?
   a. FSH
   b. GH
   c. LH
   d. Prolactin
   e. TSH
9. Hypersecretion of growth hormone
   a. results in giantism if it occurs in children.
   b. causes acromegaly in adults.
   c. increases the probability that one will develop diabetes.
   d. can lead to severe atherosclerosis.
   e. all of the above.
10. LH and FSH
    a. are produced in the hypothalamus.
    b. production is increased by TSH.
    c. promote the production of gametes and reproductive hormones.
    d. inhibit the production of prolactin.
    e. all of the above.
11. Thyroid hormones
    a. require iodine for their production.
    b. are made from the amino acid tyrosine.
    c. are transported in the blood bound to thyroxine-binding globulin.
    d. all of the above.
12. Which of these symptoms is associated with hyposecretion of the thyroid gland?
    a. hypertension
    b. nervousness
    c. diarrhea
    d. weight loss with a normal or increased food intake
    e. decreased metabolic rate
13. Which of these conditions most likely occurs if a healthy person receives an injection of thyroid hormone?
    a. The secretion rate of TSH declines.
    b. The person develops symptoms of hypothyroidism.
    c. The person develops hypercalcemia.
    d. The person secretes more TRH.
14. Which of these occurs as a response to a thyroidectomy (removal of the thyroid gland)?
    a. increased calcitonin secretion
    b. increased T_3 and T_4 secretion
    c. decreased TRH secretion
    d. increased TSH secretion
15. Choose the statement that most accurately predicts the long-term effect of a substance that prevents active transport of iodide by the thyroid gland.
    a. Large amounts of thyroid hormone accumulate within the thyroid follicles, but little is released.
    b. The person exhibits hypothyroidism.
    c. The anterior pituitary secretes smaller amounts of TSH.
    d. The circulating levels of T_3 and T_4 increase.
16. Calcitonin
    a. is secreted by the parathyroid glands.
    b. levels increase when blood calcium levels decrease.
    c. causes blood calcium levels to decrease.
    d. insufficiency results in weak bones and tetany.
17. Parathyroid hormone secretion increases in response to
    a. a decrease in blood calcium levels.
    b. increased production of parathyroid-stimulating hormone from the anterior pituitary.
    c. increased secretion of parathyroid-releasing hormone from the hypothalamus.
    d. increased secretion of calcitonin.
    e. a decrease in secretion of ACTH.
18. If parathyroid hormone levels increase, which of these conditions is expected?
    a. Osteoclast activity is increased.
    b. Calcium absorption from the small intestine is inhibited.
    c. Calcium reabsorption from the urine is inhibited.
    d. Less active vitamin D is formed in the kidneys.
    e. All of the above.
19. The adrenal medulla
    a. produces steroids.
    b. has cortisol as its major secretory product.
    c. decreases its secretions during exercise.
    d. is formed from a modified portion of the sympathetic division of the ANS.
    e. all of the above.

20. Pheochromocytoma is a condition in which a benign tumor results in hypersecretion of the adrenal medulla. The symptoms that one would expect include
    a. hypotension.
    b. bradycardia.
    c. pallor (decreased blood flow to the skin).
    d. lethargy.
    e. hypoglycemia.
21. Which of these is *not* a hormone secreted by the adrenal cortex?
    a. aldosterone
    b. androgens
    c. cortisol
    d. epinephrine
22. If aldosterone secretions increase
    a. blood potassium levels increase.
    b. blood hydrogen levels increase.
    c. acidosis results.
    d. blood sodium levels decrease.
    e. blood volume increases.
23. Glucocorticoids (cortisol)
    a. increase the breakdown of fats.
    b. increase the breakdown of proteins.
    c. increase blood glucose levels.
    d. decrease inflammation.
    e. all of the above.
24. The release of cortisol from the adrenal cortex is regulated by other hormones. Which of these hormones is correctly matched with its origin and function?
    a. CRH—secreted by the hypothalamus; stimulates the adrenal cortex to secrete cortisol
    b. CRH—secreted by the anterior pituitary; stimulates the adrenal cortex to secrete cortisol
    c. ACTH—secreted by the hypothalamus; stimulates the adrenal cortex to secrete cortisol
    d. ACTH—secreted by the anterior pituitary; stimulates the adrenal cortex to produce cortisol
25. Which of these would be expected in Cushing's syndrome?
    a. loss of hair in women
    b. deposition of fat in the face, neck, and abdomen
    c. low blood glucose
    d. low blood pressure
    e. all of the above
26. Within the pancreas, the pancreatic islets produce
    a. insulin.
    b. glucagon.
    c. digestive enzymes.
    d. both a and b.
    e. all of the above.
27. Insulin increases
    a. the uptake of glucose by its target tissues.
    b. the breakdown of protein.
    c. the breakdown of fats.
    d. glycogen breakdown in the liver.
    e. all of the above.
28. Which of these tissues is least affected by insulin?
    a. adipose tissue
    b. heart
    c. skeletal muscle
    d. brain
    e. liver
29. Glucagon
    a. primarily affects the liver.
    b. causes glycogen to be stored.
    c. causes blood glucose levels to decrease.
    d. decreases fat metabolism.
    e. all of the above.
30. When blood glucose levels increase, the secretion of which of these hormones increases?
    a. glucagon
    b. insulin
    c. GH
    d. cortisol
    e. epinephrine
31. If a person who has diabetes mellitus forgot to take an insulin injection, symptoms that may soon appear include
    a. acidosis.
    b. hyperglycemia.
    c. increased urine production.
    d. lethargy and fatigue.
    e. all of the above.
32. Which of these is *not* a hormone produced by the ovaries?
    a. estrogen
    b. progesterone
    c. prolactin
    d. inhibin
    e. relaxin
33. Melatonin
    a. is produced by the posterior pituitary.
    b. production increases as day length increases.
    c. inhibits the development of the reproductive system.
    d. increases GnRH secretion from the hypothalamus.
    e. decreases the tendency to sleep.
34. Which of these substances, produced by many tissues of the body, can promote inflammation, pain, and vasodilation of blood vessels?
    a. endorphin
    b. enkephalin
    c. thymosin
    d. epidermal growth factor
    e. prostaglandin
35. Which of the changes listed does *not* decrease with aging of the endocrine system?
    a. GH secretion
    b. melatonin secretion
    c. thyroid hormone secretion
    d. parathyroid hormone secretion
    e. renin secretion by the kidneys

Answers in Appendix F

C R I T I C A L T H I N K I N G

1. The hypothalamohypophysial portal system connects the hypothalamus with the anterior pituitary. Why is such a special circulatory system advantageous?
2. The secretion of ADH can be affected by exposure to hot or cold environmental temperatures. Predict the effect of a hot environment on ADH secretion, and explain why it is advantageous. Propose a mechanism by which temperature produces a change in ADH secretion.

3. A patient exhibits polydipsia (thirst), polyuria (excess urine production), and urine with a low specific gravity (contains few ions and no glucose). If you want to reverse the symptoms, would you administer insulin, glucagon, ADH, or aldosterone? Explain.
4. A patient complains of headaches and visual disturbances. A casual glance reveals that the patient's finger bones are enlarged in diameter, a heavy deposition of bone exists over the eyes, and the patient has a prominent jaw. The doctor tells you that the headaches and visual disturbances result from increased pressure within the skull and that the patient is suffering from a pituitary tumor that is affecting hormone secretion. Name the hormone that is causing the problem, and explain why an increase in pressure exists within the skull.
5. Most laboratories have the ability to determine blood levels of TSH, T_3, and T_4. Given that ability, design a method of determining whether hyperthyroidism in a patient results from a pituitary abnormality or from the production of a nonpituitary thyroid stimulatory substance.
6. An anatomy and physiology instructor asks two students to predict a patient's response to chronic vitamin D deficiency. One student claims that the person would suffer from hypocalcemia and the symptoms associated with that condition. The other student claims that calcium levels would remain within their normal range, although at the low end of the range, and that bone resorption would occur to the point that advanced osteomalacia might be seen. With whom do you agree, and why?
7. Given the ability to measure blood glucose levels, design an experiment that distinguishes between a person with diabetes, a healthy person, and a person who has a pancreatic tumor that secretes large amounts of insulin.
8. A patient arrives in an unconscious condition. A medical emergency bracelet reveals that he has diabetes. The patient can be in diabetic coma or insulin shock. How could you tell which, and what treatment would you recommend for each condition?
9. Diabetes mellitus can result from a lack of insulin, which results in hyperglycemia. Adrenal diabetes and pituitary diabetes also produce hyperglycemia. What hormones produce the last two conditions?
10. Predict some of the consequences of exposure to intense and prolonged stress.

Answers in Appendix G

ANSWERS TO PREDICT QUESTIONS

1. The cell bodies of the neurosecretory cells that produce ADH are in the hypothalamus, and their axons extend into the posterior pituitary, where ADH is stored and secreted. Removing the posterior pituitary severs the axons, resulting in a temporary reduction in secretion. The cell bodies still produce ADH, however, and as the ADH accumulates at the ends of severed axons, ADH secretion resumes.
2. If GH is administered to young people before growth of their long bones is complete, it causes their long bones to grow and they will grow taller. To accomplish this, however, GH would have to be administered over a considerable length of time. It's likely that some symptoms of acromegaly would develop. In addition to undesirable changes in the skeleton, nerves frequently are compressed as a result of the proliferation of connective tissue. Because GH spares glucose usage, chronic hyperglycemia results, frequently leading to diabetes mellitus and the development of severe atherosclerosis. Mr. Hoops's doctor would therefore not prescribe GH.
3. Surgical removal of the thyroid gland cause T_3 and T_4 levels to decline in the blood. TRH and TSH levels in the blood increase because, as T_3 and T_4 levels in the blood decrease, the negative feedback effect of T_3 and T_4 on TRH and TSH are removed. Oral administration of T_3 and T_4 cause blood levels of T_3 and T_4 to increase and, because of negative feedback, TRH and TSH levels decline.
4. In response to a reduced dietary intake of calcium, the blood levels of calcium begin to decline. In response to the decline in blood levels of calcium, an increase of PTH secretion from the parathyroid glands occurs. The PTH functions to increase calcium resorption from bone. Consequently, blood levels of calcium are maintained within the normal range but, at the same time, bones are being decalcified. Severe dietary calcium deficiency results in bones that become soft and eaten away because of the decrease in calcium content.
5. Removal of the thyroid gland means that the tissue responsible for thyroid hormone (T_3 and T_4) secretion from thyroid follicles, and calcitonin from parafollicular cells, would no longer occur. However, blood Ca^{2+} would remain within its normal range. Calcitonin is not essential for the maintenance of normal blood Ca^{2+} levels. Removal of the parathyroid gland would eliminate PTH secretion. Without PTH, blood levels of calcium fall. When the blood levels of calcium fall below normal, the permeability of nerve and muscle cells to Na^+ increases. As a consequence, spontaneous action potentials are produced that cause tetanus of muscles. Death can result from tetany of respiratory muscles.
6. High aldosterone levels in the blood lead to elevated Na^+ levels in the circulatory system and low blood levels of K^+. The effect of low blood levels of K^+ is hyperpolarization of muscle and neurons. The hyperpolarization results from the lower levels of K^+ in the extracellular fluid and a greater tendency for K^+ to diffuse from the cell. As a result, a greater-than-normal stimulus is required to cause the cells to depolarize to threshold and generate an action potential. Symptoms of low serum K^+ levels therefore include lethargy and muscle weakness. Elevated Na^+ concentrations result in a greater-than-normal amount of water retention in the circulatory system, which can result in elevated blood pressure. The major effect of a low rate of aldosterone secretion is elevated blood K^+ levels. As a result, nerve and muscle cells partially depolarize. Because of their partial depolarization, they produce action potentials spontaneously or in response to very small stimuli. The result is muscle spasms, or tetanus.
7. Large doses of cortisone can damage the adrenal cortex because cortisone inhibits ACTH secretion from the anterior pituitary. ACTH is required to keep the adrenal cortex from undergoing atrophy. Prolonged use of large doses of cortisone can cause the adrenal gland to atrophy to the point at which it cannot recover if ACTH secretion does increase again.

8. An increase in insulin secretion in response to parasympathetic stimulation and gastrointestinal hormones is consistent with the maintenance of homeostasis because parasympathetic stimulation and increased gastrointestinal hormones result from conditions such as eating a meal. Insulin levels therefore increase just before large amounts of glucose and amino acids enter the circulatory system. The elevated insulin levels prevent a large increase in blood glucose and the loss of glucose in the urine.
9. In response to a meal high in carbohydrates, insulin secretion is increased, and glucagon secretion is reduced. The stimulus for the insulin secretion comes from parasympathetic stimulation and, more importantly, from elevated blood levels of glucose. Target tissues take up glucose and blood glucose levels remain within a normal range. In response to a meal high in protein but low in carbohydrates, insulin secretion is increased slightly, and glucagon secretion is also increased. The lower insulin secretion causes some increase. Insulin secretion is stimulated by the parasympathetic system and an increase in blood amino acid levels. Glucagon is stimulated by low blood glucose levels and by some amino acids. In the rate of glucose uptake and amino acid uptake, but the rate of uptake is not great enough to cause blood glucose levels to fall below normal values. Glucagon also causes glucose to be released from the liver. During periods of exercise, sympathetic stimulation inhibits insulin secretion. As blood glucose levels decline, an increase of glucagon secretion occurs. The lower rate of insulin secretion decreases the rate at which tissues such as skeletal muscle take up glucose. Muscle depends on intracellular glycogen and fatty acids for energy. Blood glucose levels are maintained within its normal range of values. Glucagon prevents glucose levels from decreasing too much.
10. Sympathetic stimulation during exercise inhibits insulin secretion. Blood glucose levels are not high because skeletal muscle tissue continues to take up some glucose and metabolizes it. Muscle contraction depends on glucose stored in the form of glycogen in muscles and fatty acid metabolism. During a long run, glycogen levels are depleted. The "kick" at the end of the race results from increased energy production through anaerobic respiration, which uses glucose or glycogen as an energy source. Because blood glucose levels and glycogen levels are low, the source of energy is insufficient for greatly increased muscle activity.
11. Increased sugar intake will result in elevated blood glucose levels. The elevated blood glucose levels can lead to polyuria and to increased osmolality of the body fluids. That results in dehydration of neurons. As a result some of the neural symptoms of untreated diabetes, such as irritability and a general sensation of not feeling well, occur. Billy may also experience a sudden increase in weight gain because of increased sugar intake and insulin administration. In addition, he may have an increased chance of infections, such as urinary tract infections. Many of the long-term consequences of diabetes, such as nephropathies, neuropathies, atherosclerosis, and others, develop much more rapidly.