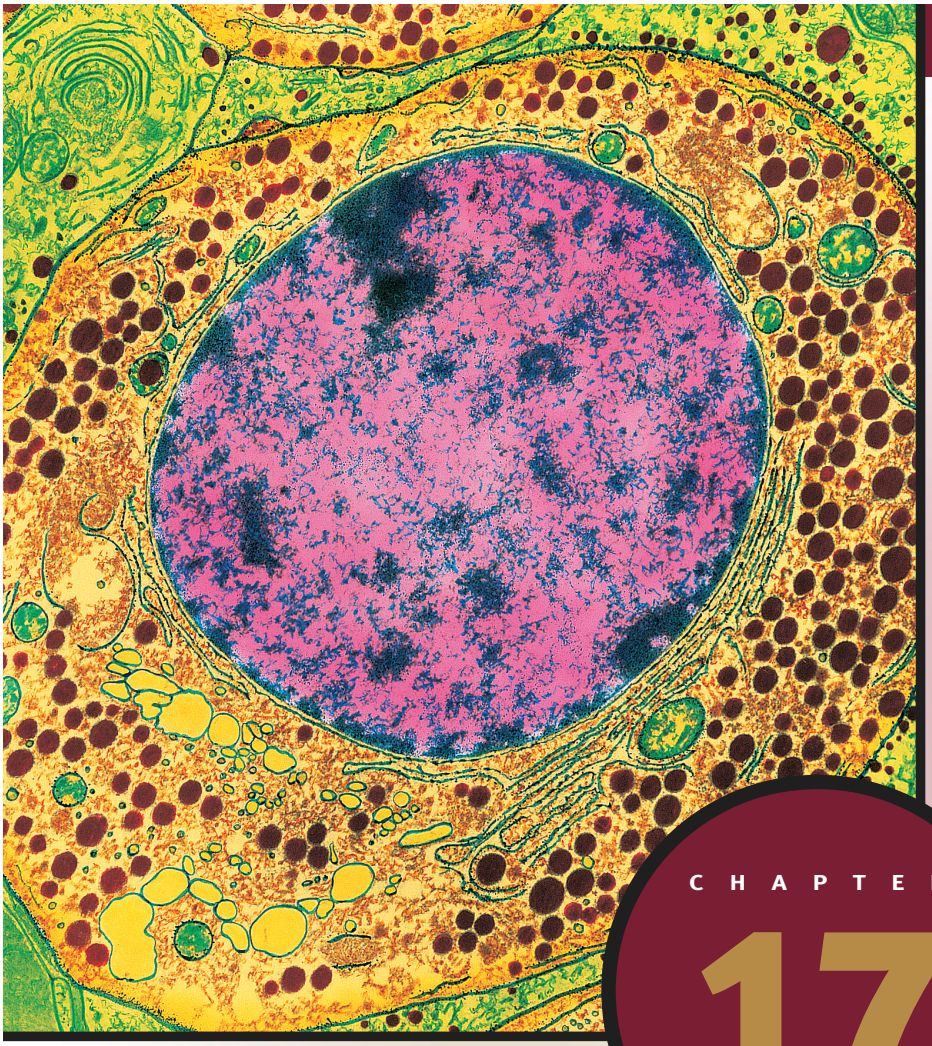


Colorized TEM of a growth hormone-secreting cell from the anterior pituitary gland. The secretory vesicles (brown) contain growth hormone.

CHAPTER 17

Functional Organization of the Endocrine System

The nervous and endocrine systems are the two major regulatory systems of the body, and together they regulate and coordinate the activity of essentially all other body structures. The nervous system functions something like telephone messages sent along telephone wires to their destination. It transmits information in the form of action potentials along the axons of nerve cells. Chemical signals in the form of neurotransmitters are released at synapses between neurons and the cells they control. The endocrine system is more like radio signals broadcast widely that everyone with radios tuned to the proper channel can receive. It sends information to the cells it controls in the form of chemical signals released from endocrine glands. The chemical signals are carried to all parts of the body by the circulatory system. Cells that are able to recognize the chemical signals respond to them and other cells do not.

This chapter introduces the general characteristics of the endocrine system. It compares some of the functions of the nervous and endocrine systems, emphasizes the role of the endocrine system in the maintenance of homeostasis, and illustrates the means by which the endocrine system regulates the functions of cells. This chapter explains the *general characteristics of the endocrine system* (572), the *chemical structure of hormones* (573), the *control of secretion rate* (573), *transport and distribution in the body* (578), *metabolism and excretion* (580), *interaction of hormones with their target tissues* (581), and *classes of hormone receptors* (583). The structure and function of the endocrine glands, the chemicals they secrete, and the means by which activities are regulated are described in chapter 18.

General Characteristics of the Endocrine System

Objectives

- *Define the terms endocrine gland, endocrine system, and hormone.*
- *Describe the functional relationship between the nervous system and endocrine system.*
- *Define and give examples of extracellular or intercellular chemical signals.*

The term **endocrine** (en′dō-krin) is derived from the Greek words *endo,* meaning within, and *crino,* to separate. The term implies that cells of endocrine glands secrete chemical signals that influence tissues that are separated from the endocrine glands by some distance. The **endocrine system** is composed of glands that secrete chemical signals into the circulatory system (figure 17.1). In contrast, exocrine glands have ducts that carry their secretions to surfaces (see chapter 4). The secretory products of endocrine glands are called **hormones** (hōr′mōnz), a term derived from the Greek word *hormon,* meaning to set into motion. Traditionally, a hormone is defined as a chemical signal, or **ligand,** that (1) is produced in minute amounts by a collection of cells; (2) is secreted into the interstitial spaces; (3) enters the circulatory system, where it is transported some distance; and (4) acts on specific tissues called **target tissues** at another site in the body to influence the activity of those tissues in a specific fashion. All hormones exhibit most components of this definition, but some components don't apply to every hormone.

Both the endocrine system and the nervous system regulate the activities of structures in the body, but they do so in different ways. For example, hormones secreted by most endocrine glands can be described as **amplitude-modulated signals** (am′pli-tood mod-ū-lāt′ed), which consist mainly of increases or decreases in the concentration of hormones in the body fluids (figure 17.2*a*). The effects produced by the hormones either increase or decrease responses as a function of the hormone concentration. On the other hand, the all-or-none action potentials carried along axons can be described as **frequency-modulated signals** (figure 17.2*b*), which vary in frequency but not in amplitude. A low frequency of action potentials is a weak stimulus, whereas a high frequency of action potentials is a strong stimulus (see chapter 11). The responses of the endocrine system are usually slower and of longer duration, and its effects are usually more generally distributed than those of the nervous system.

Although the stated differences between the endocrine and nervous systems are generally true, exceptions exist. For example, some endocrine responses are more rapid than some neural responses, and some endocrine responses have a shorter duration than some neural responses. In addition, some hormones act as both amplitude- and frequency-modulated signals, in which the concentrations of the hormones and the frequencies at which the increases in hormone concentrations occur are important.

At one time, the endocrine system was believed to be relatively independent and different from the nervous system. An intimate relationship between these systems is now recognized, however, and the two systems cannot be completely separated either anatomically or functionally. Some neurons secrete chemical signals called **neurohormones** (noor-ō-hōr′mōnz) into the circulatory system, which function like hormones. Also, some neurons directly innervate endocrine glands and influence their secretory

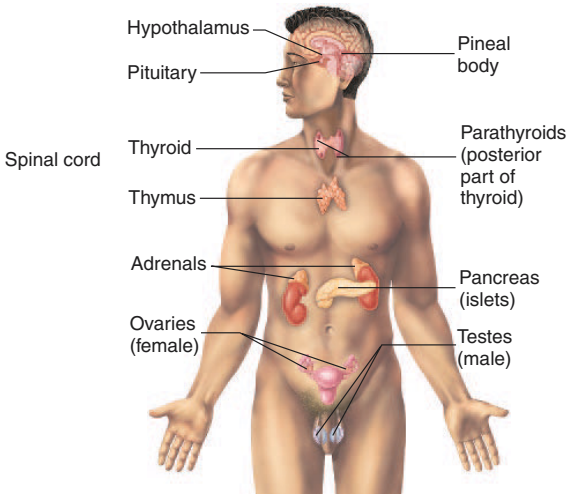


Figure 17.1 Endocrine Glands

The location of major endocrine glands in the human body.

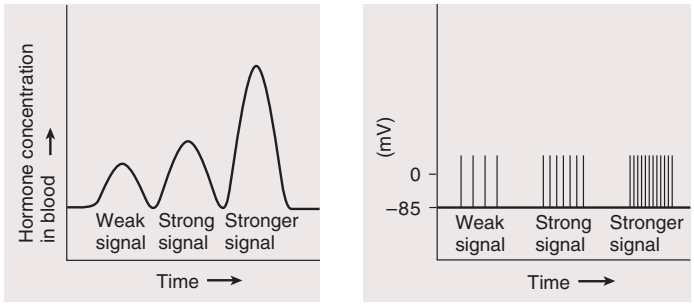


Figure 17.2 Regulatory Systems

(*a*) **Amplitude-modulated system.** The concentration of the hormone determines the strength of the signal and the magnitude of the response. For most hormones, a small concentration of a hormone is a weak signal and produces a small response, whereas a larger concentration is a stronger signal and results in a greater response. (*b*) **Frequency-modulated system.** The strength of the signal depends on the frequency, not the size, of the action potentials. All action potentials are the same size in a given tissue. A low frequency of action potentials is a weak stimulus, and a higher frequency is a stronger stimulus.

activity. Neurons release chemical signals at synapses in the form of neurotransmitters and neuromodulators, and the membrane potentials of some endocrine glands undergo depolarization or hyperpolarization, which results in either an increase or a decrease in the rate of hormone secretion. Conversely, some hormones secreted by endocrine glands affect the nervous system and markedly influence its activity.

Intercellular chemical signals allow one cell to communicate with other cells. These signals coordinate and regulate the activities of most cells. Neurotransmitters and neuromodulators are intercellular chemical signals that play important roles in the function of the nervous system (see chapter 11). Hormones are intercellular chemical signals secreted by endocrine glands.

Autocrine (aw′tō-krin) **chemical signals** are released by cells and have a local effect on the same cell type from which the chemical signals are released. Examples include prostaglandin-like chemicals released from smooth muscle cells and platelets in response to inflammation. These chemicals cause the relaxation of blood vessel smooth muscle cells and the aggregation of platelets. As a result, the blood vessels dilate and blood clots.

Paracrine (par′ă-krin) **chemical signals** are released by cells and affect other cell types locally without being transported in the blood. For example, a peptide called somatostatin is released by cells in the pancreas and functions locally to inhibit the secretion of insulin from other cells of the pancreas (see chapter 18).

Pheromones (fer′ō-mōnz) are chemical signals secreted into the environment that modify the behavior and the physiology of other individuals. For example, pheromones released in the urine of cats and dogs at certain times are olfactory signals that indicate fertility. Evidence supports the existence of pheromones produced by women that influence the length of menstrual cycles in other women (table 17.1).

Many intercellular chemical signals consistently fit one specific definition, but others do not. For example, norepinephrine functions both as a neurotransmitter and a neurohormone; and prostaglandins function as neurotransmitters, neuromodulators, parahormones, and autocrine chemical signals. The schemes used to classify chemicals on the basis of their functions are useful, but they don't indicate that a specific molecule always performs as the same type of chemical signal in every place it's found. For that reason, the study of endocrinology often includes the study of autocrine and paracrine chemical signals in addition to hormones.

1. *Define the terms endocrine gland, endocrine system, and hormone. Explain why a simple definition for hormone is difficult to create.*
2. *Contrast the endocrine system and the nervous system for the following: amplitude versus frequency modulation; speed and duration of target cell response.*
3. *Explain why, despite their differences, the nervous and endocrine systems cannot be completely separated.*
4. *Name and describe five intercellular chemical signals, other than hormones.*

Chemical Structure of Hormones

Objective

- ***Describe the categories of hormones based on their chemical structure.***

Hormones, including neurohormones, can be either proteins, short sequences of amino acids called polypeptides, derivatives of amino acids, or lipids. Some protein hormones, called glycoprotein hormones, are composed of one or more polypeptide chains and carbohydrate molecules. Lipid hormones are either steroids or derivatives of fatty acids. Table 17.2 and figure 17.3 provide information concerning the chemical structure of the major hormones.

5. *List six categories of hormones based on chemical structure, and give an example of each.*

Control of Secretion Rate

Objective

- ***Explain how regulation of hormone secretion is achieved.***

Most hormones are not secreted at a constant rate. Instead, most endocrine glands increase and decrease their secretory activity dramatically over time. The specific mechanisms that regulate the secretion rates for each hormone are presented in chapter 18, but the general patterns of regulation are introduced in this chapter. Hormones function to regulate the rates of many activities in the body. The secretion rate of each hormone is controlled by a negative-feedback mechanism (see chapter 1), so that the body activity it regulates is maintained within a normal range and homeostasis is maintained.

Hormones have three major patterns of regulation. One pattern involves the action of a substance other than a hormone on the endocrine gland. Figure 17.4 describes the influence of blood glucose on insulin secretion from the pancreas. An increasing blood glucose level causes an increase in insulin secretion from the pancreas. Insulin increases glucose movement into cells, resulting in a decrease in blood glucose levels, which in turn causes a decrease in insulin secretion. Thus insulin levels increase and decrease in response to changes in blood glucose levels.

A second pattern of hormone regulation involves neural control of the endocrine gland. Neurons synapse with the cells that produce the hormone, and, when action potentials result, the neurons release a neurotransmitter. In some cases, the neurotransmitter is stimulatory and causes the cells to increase hormone secretion. In other cases the neurotransmitter is inhibitory and decreases hormone secretion. Thus sensory input and emotions acting through the nervous system can influence hormone secretion. Figure 17.5 illustrates the neural control of epinephrine and norepinephrine secretion from the adrenal gland. In response to stimuli such as stress or exercise, the nervous system stimulates the adrenal gland to secrete epinephrine and norepinephrine, which help the body respond to the stimuli. When the stimuli are no longer present, secretion of epinephrine and norepinephrine decreases.

Table 17.1 Functional Classification of Intercellular Chemical Signals

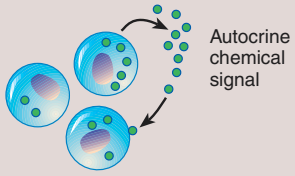
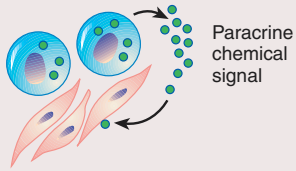
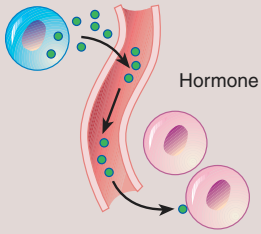
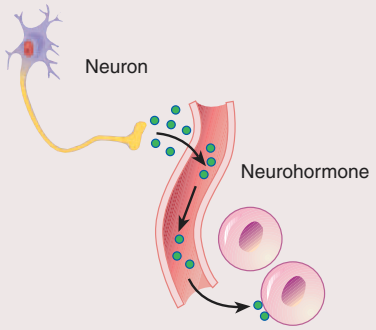
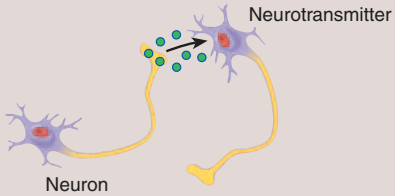
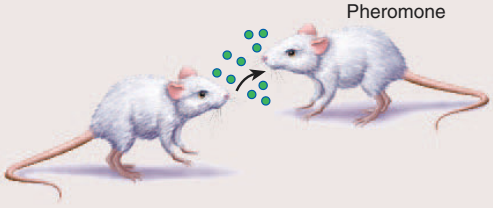
Intercellular Chemical Signal	Description	Example	
Autocrine	Secreted by cells in a local area and influences the activity of the same cell type from which it was secreted	Prostaglandins	
Paracrine	Produced by a wide variety of tissues and secreted into tissue spaces; usually has a localized effect on other tissues	Histamine prostaglandins	
Hormone	Secreted into the blood by specialized cells; travels some distance to target tissues; influences specific activities	Thyroxine, insulin	
Neurohormone	Produced by neurons and functions like hormones	Oxytocin, antidiuretic hormone	
Neurotransmitter or neuromodulator	Produced by neurons and secreted into extracellular spaces by presynaptic nerve terminals; travels short distances; influences postsynaptic cells	Acetylcholine, epinephrine	
Pheromone	Secreted into the environment; modifies physiology and behavior of other individuals	Sex pheromones are released by humans and many other animals. They are released in the urine of animals, such as dogs and cats. Pheromones produced by women influence the length of the menstrual cycle of other women.	

Table 17.2 Structural Categories of Hormones

Structural Category	Examples	Structural Category	Examples
Proteins	Growth hormone Prolactin Insulin	Amino acid derivatives	Epinephrine Norepinephrine Thyroid hormones (both T_4 and T_3) Melatonin
Glycoproteins (protein and carbohydrate)	Follicle-stimulating hormone Luteinizing hormone Thyroid-stimulating hormone Parathyroid hormone	Lipids	
Polypeptides	Thyrotropin-releasing hormone Oxytocin Antidiuretic hormone Calcitonin Glucagon Adrenocorticotropic hormone Endorphins Thymosin Melanocyte-stimulating hormones Hypothalamic hormones Lipotropins Somatostatin	Steroids (cholesterol is a precursor for all steroids)	Estrogens Progestins (progesterone) Testosterone Mineralocorticoids (aldosterone) Glucocorticoids (cortisol)
		Fatty acids	Prostaglandins Thromboxanes Prostacyclins Leukotrienes

Abbreviations: T_4 = tetraiodothyronine or thyroxine; T_3 = triiodothyronine.

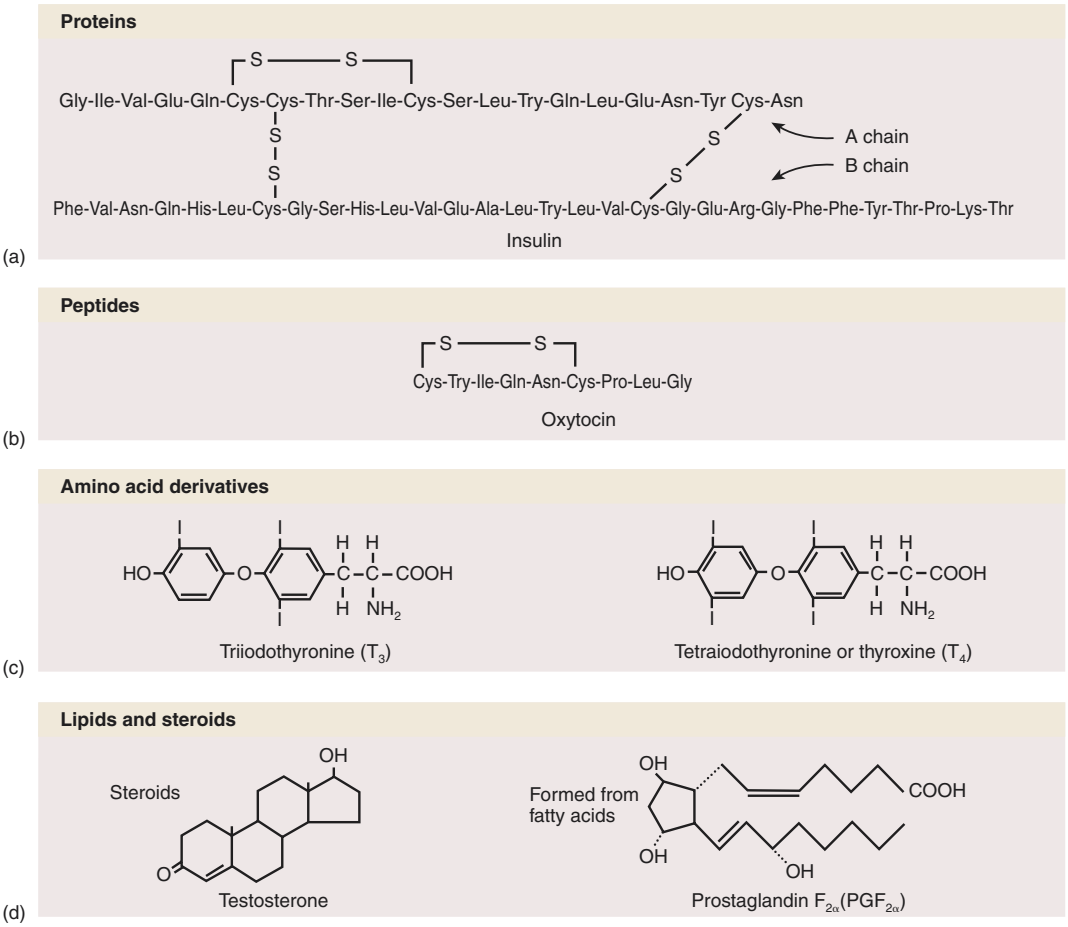
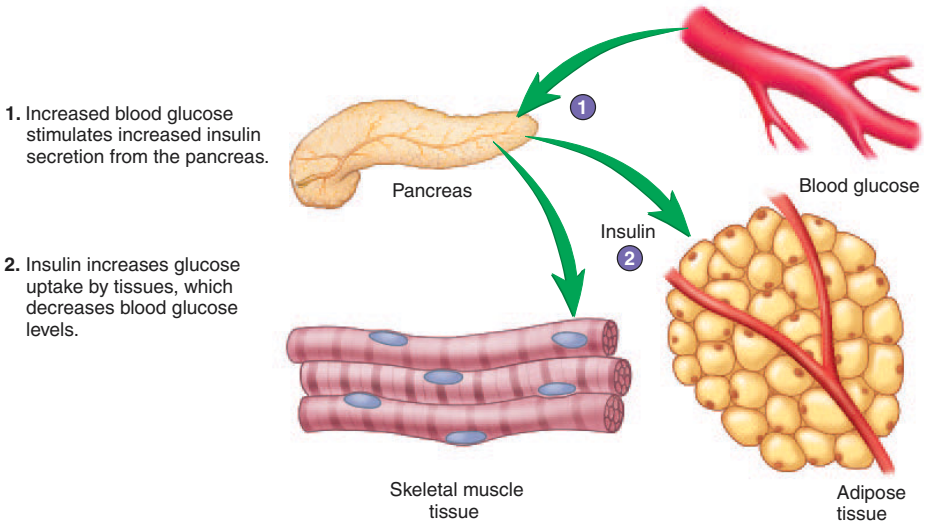


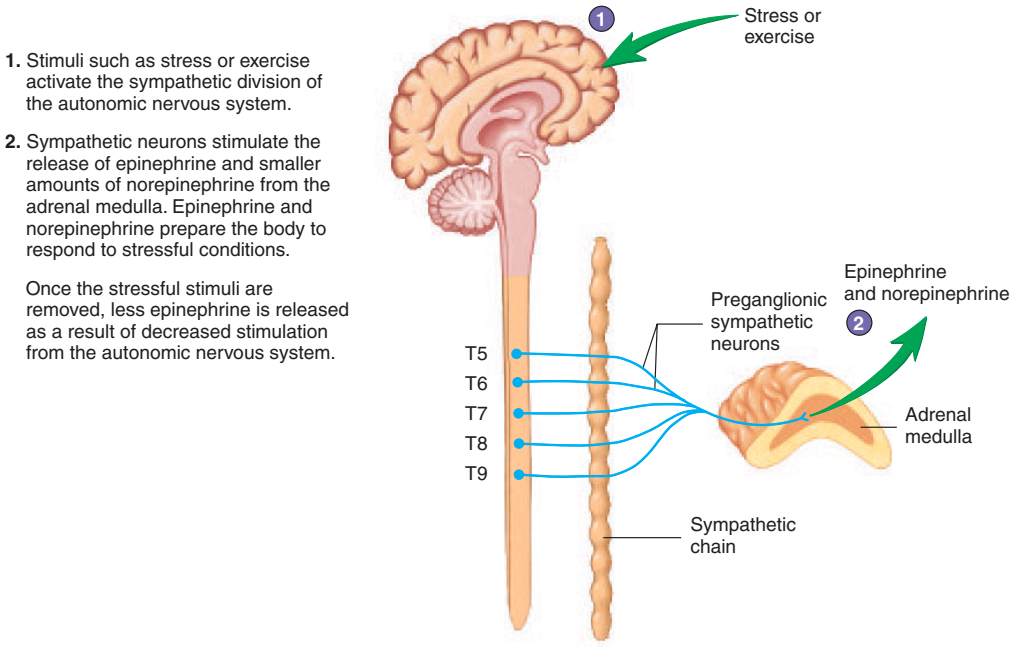
Figure 17.3 The Chemical Structure of Hormones

(*a*) Insulin is an example of a protein hormone. (*b*) Oxytocin is an example of a peptide hormone. (*c*) The thyroid hormones, triiodothyronine (T_3) and tetraiodothyronine (T_4), are examples of modified amino acid hormones. (*d*) Testosterone, a steroid, and prostaglandin $F_{2\alpha}$ are examples of lipid hormones.



Process Figure 17.4 Nonhormonal Regulation of Hormone Secretion

Glucose, which is not a hormone, regulates the secretion of insulin from the pancreas.



Process Figure 17.5 Nervous System Regulation of Hormone Secretion

The sympathetic division of the autonomic nervous system stimulates the adrenal gland to secrete epinephrine and norepinephrine.

A third pattern of hormone regulation involves the control of the secretory activity of one endocrine gland by a hormone or a neurohormone secreted by another endocrine gland. Figure 17.6 illustrates how thyroid-releasing hormone (TRH) from the hypothalamus of the brain stimulates the secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary gland, which, in turn, stimulates the secretion of thyroid hormones from the thyroid gland. A negative-feedback mechanism for regulating thyroid hormone secretion exists because thyroid hormones can inhibit the secretion of TRH and TSH. Thus, the concentrations of TRH, TSH, and thyroid hormone increase and decrease within a normal range (see chapter 18).

Neural Control of Insulin Secretion

Blood glucose levels regulate insulin secretion, but insulin secretion is also regulated by the nervous system. When action potentials in parasympathetic neurons that innervate the pancreas increase, the neurotransmitter acetylcholine is released. Acetylcholine causes depolarization of pancreatic cells, and insulin is secreted. When action potentials in sympathetic neurons that innervate the pancreas increase, the neurotransmitter norepinephrine is released. Norepinephrine causes hyperpolarization of pancreatic cells, and insulin secretion decreases. Thus, nervous stimulation of the pancreas can either increase or decrease insulin secretion.

P R E D I C T 1

For a person having normal thyroid function, the rate at which TSH and thyroid hormones are secreted remains within a normal range of concentrations. In some people, however, the immune system begins to produce large amounts of an abnormal substance that functions like TSH. Predict what that substance will do to the rate of TSH secretion and the rate of thyroid hormone secretion.

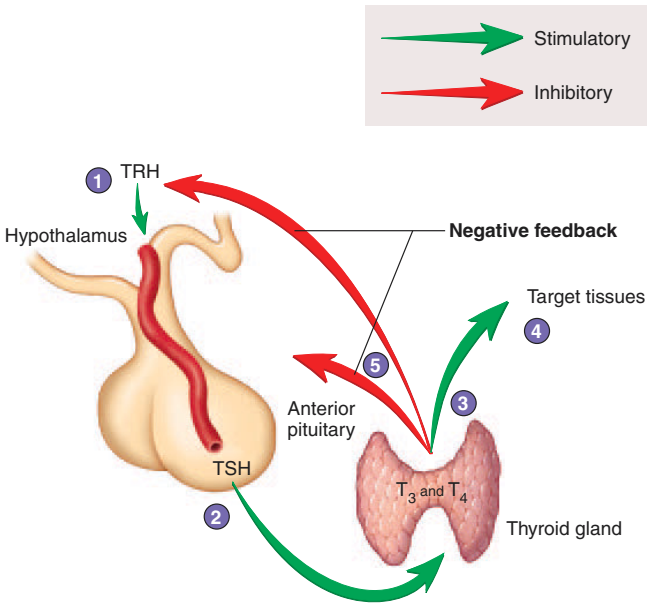
One of these three major patterns by which hormone secretion is regulated applies to each hormone, but the complete picture isn't quite so simple. The regulation of hormone secretion often involves more than one mechanism. For example, both the concentration of blood glucose and the autonomic nervous system influence insulin secretion from the pancreas.

A few examples of positive-feedback regulation in the endocrine system exist. Prior to ovulation, estrogen from the ovary stimulates luteinizing hormone (LH) secretion from the anterior pituitary gland. LH, in turn, stimulates estrogen secretion from the ovary. Consequently, blood levels of estrogen and LH increase prior to ovulation (figure 17.7*a*). The release of oxytocin during delivery of an infant is another example (see chapters 28 and 29). In cases of positive feedback, negative feedback limits the degree to which positive feedback proceeds (figure 17.7*b*). For example, after ovulation the ovary secretes progesterone, which inhibits LH secretion.

Some hormones are in the circulatory system at relatively constant levels, some change suddenly in response to certain stimuli, and others change in relatively constant cycles (figure 17.8). For example, thyroid hormones in the blood vary within a small range of concentrations that remain relatively constant. Epinephrine is released in large amounts in response to stress or physical exercise; thus its concentration can change suddenly. Reproductive hormones increase and decrease in a cyclic fashion in women during their reproductive years.

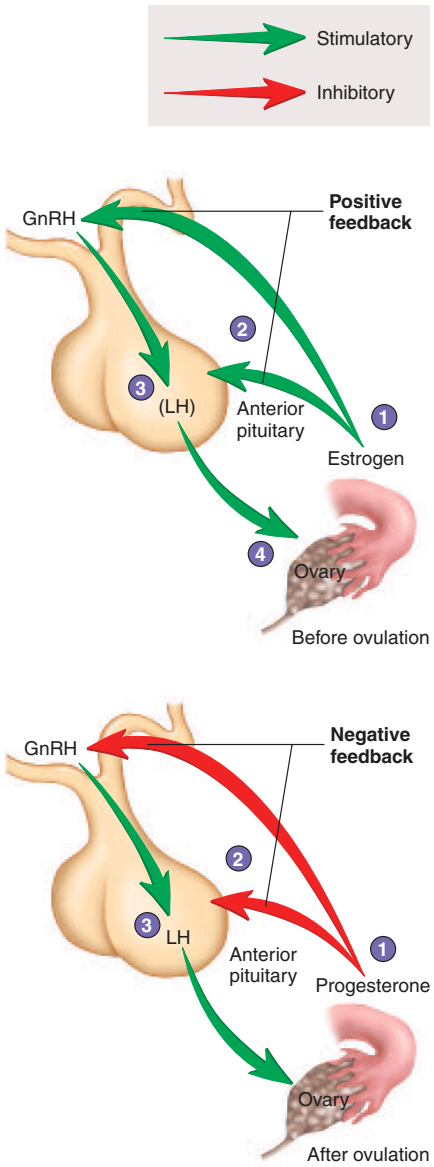
6. ***Describe and give examples of the three major patterns by which hormone secretion is regulated. Give an example of a hormone that is controlled by more than one mechanism.***
7. ***Is hormone secretion generally regulated by negative-feedback or positive-feedback mechanisms?***
8. ***Describe chronic, acute, and cyclic patterns of hormone secretion.***

1. Thyroid-releasing hormone (TRH) is released from neurons in the hypothalamus and travels in the blood to the anterior pituitary gland.
2. TRH stimulates the release of thyroid-stimulating hormone (TSH) from the anterior pituitary gland. TSH travels in the blood to the thyroid gland.
3. TSH stimulates the secretion of thyroid hormones (T_3 and T_4) from the thyroid gland into the blood.
4. Thyroid hormones act on tissues to produce responses.
5. Thyroid hormones also have a negative-feedback effect on the hypothalamus and the anterior pituitary to inhibit both TRH secretion and TSH secretion. The negative feedback helps keep blood thyroid hormone levels within a narrow range.



Process Figure 17.6 Hormonal Regulation of Hormone Secretion

Hormones can stimulate or inhibit the secretion of other hormones.



Process Figure 17.7 Positive and Negative Feedback

Transport and Distribution in the Body

Objective

- ***Describe how hormones are transported in the blood and delivered to cells.***

Hormones are dissolved in blood plasma and transported either in a free form or bound to plasma proteins. Hormones that are free in the plasma can diffuse from capillaries into interstitial spaces. As the concentration of free hormone molecules increases in the blood, more hormone molecules diffuse from the capillaries into the interstitial spaces and bind to target cells. As the concentration of the free hormone molecules decreases in the blood, fewer hormone molecules diffuse from the capillaries into the interstitial spaces and bind to target cells (figure 17.9).

Hormones that bind to plasma proteins do so in a reversible fashion. An equilibrium is established between the free plasma hormones and hormones bound to plasma proteins called binding proteins.

$$\underset{\text{Hormone}}{H} + \underset{\text{Binding protein}}{BP} \longleftrightarrow \underset{\text{Hormone bound to binding protein}}{HBP}$$

Many hormones bind only to certain types of plasma proteins. For example, a specific type of plasma protein binds to thyroid

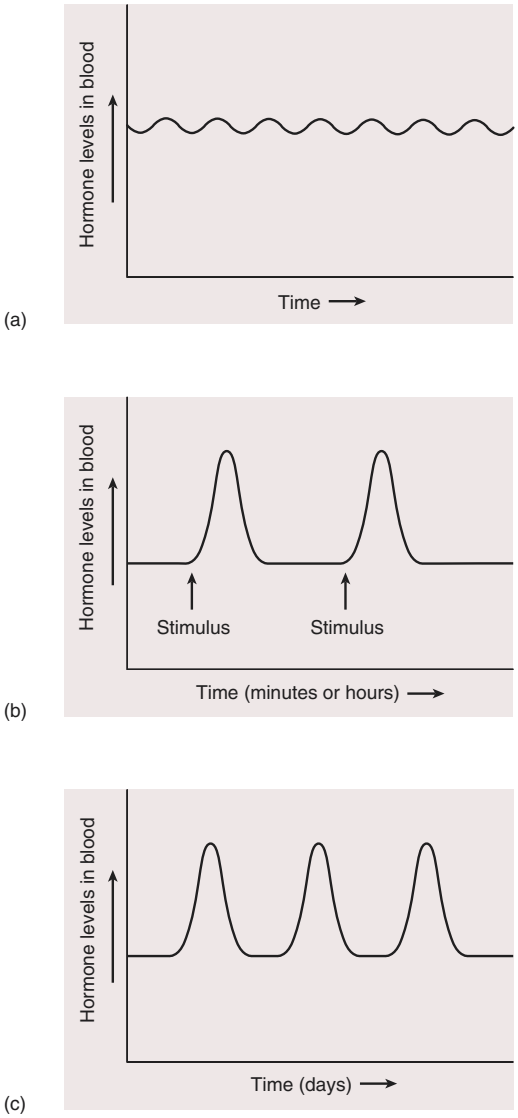


Figure 17.8 Changes in Hormone Secretion Through Time

At least three basic patterns of hormone secretion exist. (*a*) *Chronic hormone regulation*—the maintenance of a relatively constant concentration of hormone in the circulating blood over a relatively long period. (*b*) *Acute hormone regulation*—a hormone rapidly increases in the blood for a short time in response to a stimulus. (*c*) *Cyclic hormone regulation*—a hormone is regulated so that it increases and decreases in the blood at a relatively constant time and to roughly the same amount.

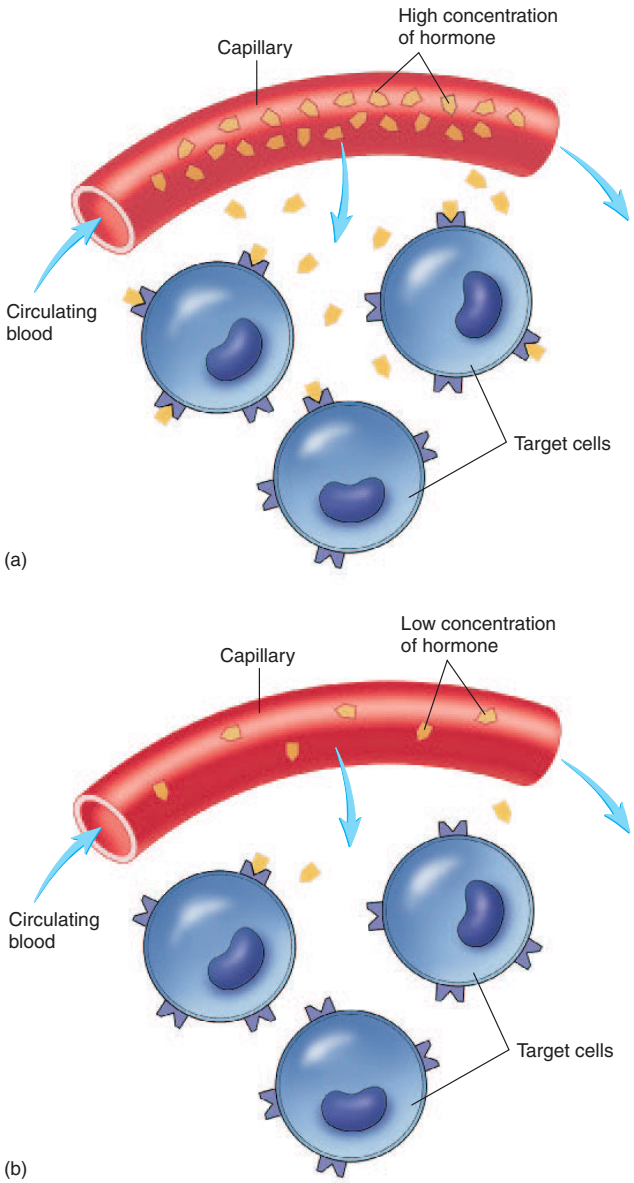


Figure 17.9 Hormone Concentrations at the Target Cell

Hormone molecules diffuse from the blood through the walls of the capillaries into the interstitial spaces. Once within the interstitial spaces, they diffuse to the target cells. (*a*) As the concentration of free hormone molecules increases in the blood, more molecules diffuse from the capillary to the target cells. (*b*) As the concentration of free hormone molecules decreases in the blood, fewer diffuse from the capillary to the target cells.

hormones, and a different type of plasma protein binds to sex hormones, such as testosterone. The equilibrium between the unbound hormone and the hormone bound to the plasma proteins is important because only the free hormone is able to diffuse through capillary walls and bind to target tissues. Hormones bound to plasma proteins tend to remain at a relatively constant level in the blood for longer periods of time (see next section). A large decrease in the plasma protein concentration can result in the loss of a hormone from the blood because free hormones are rapidly eliminated from the circulation through either the kidney or the liver (figure 17.10).

Because hormones circulate in the blood, they are distributed quickly throughout the body. They diffuse through the capillary endothelium and enter the interstitial spaces, although the rate at which this movement occurs varies from one hormone to the next. Lipid-soluble hormones readily diffuse through the walls of

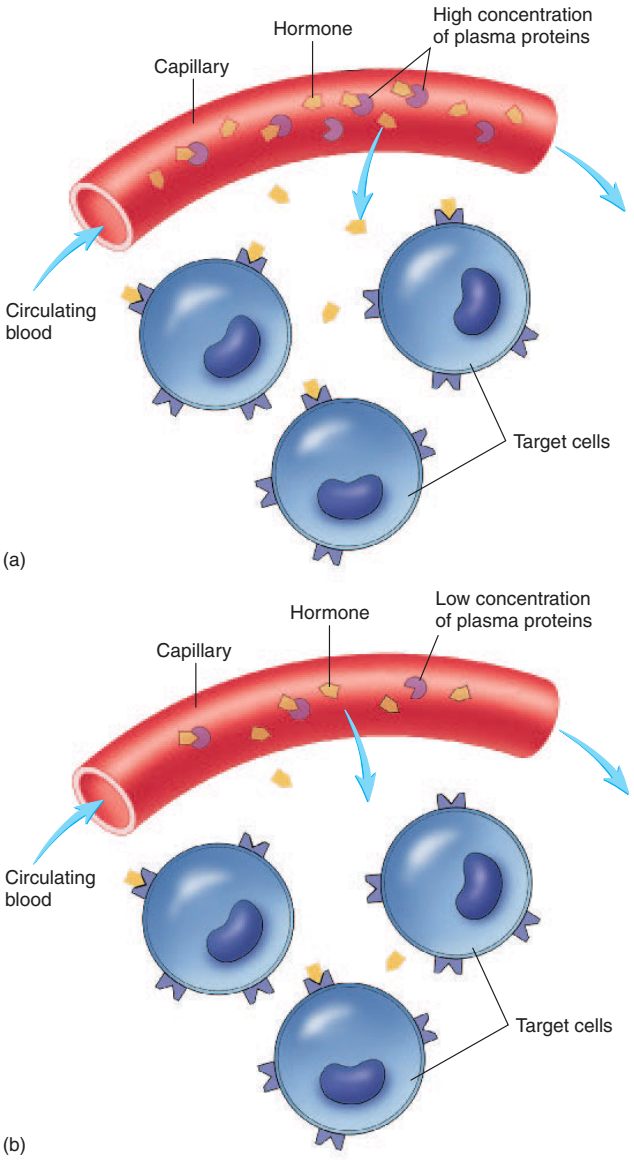


Figure 17.10 Effect of Changes in Plasma Protein Concentration on the Concentration of Free Hormone

(*a*) An equilibrium exists between free hormone molecules and hormone molecules bound to plasma proteins. The free hormone molecules can diffuse from the capillaries to the interstitial spaces. (*b*) A decrease in plasma protein concentration reduces the number of hormone molecules bound to plasma proteins. This increases the rate at which free hormone molecules diffuse from the capillaries. More importantly, hormones that diffuse from capillaries are eliminated from the blood by the kidney and liver. The rapid loss of hormone from the circulatory system reduces the hormone concentration in the body and fewer hormone molecules are available to bind to receptors.

all capillaries. In contrast, water-soluble hormones, such as proteins, must pass through pores called fenestrae (see chapter 21) in the capillary endothelium. The capillary endothelia of organs that are regulated by protein hormones have large pores.

9. *What effect does a hormone binding to a plasma protein have on the amount of free hormone in the blood? On the amount of time the hormone remains in the blood?*
10. *Why do the capillary endothelia of organs regulated by protein hormones have large pores?*

Metabolism and Excretion

Objective

- *Define half-life, and describe the major factors that increase and decrease the half-life of hormones.*

The destruction and elimination of hormones limit the length of time during which they are active, and body activities can increase and decrease quickly when hormones are secreted and remain active for only short periods. The length of time it takes for half a dose of a substance to be eliminated from the circulatory system is called its **half-life.** The half-life of a hormone is a standard measurement used by endocrinologists because it allows them to predict the rate at which hormones are eliminated from the body. The length of time required for total removal of a hormone from the body is not as useful because that measurement is influenced dramatically by the starting concentration. Water-soluble hormones, such as proteins, glycoproteins, epinephrine, and norepinephrine, have relatively short half-lives because they are degraded rapidly by enzymes within the circulatory system or organs, such as the kidneys, liver, or lungs. Hormones with short half-lives normally have concentrations that increase and decrease rapidly within the blood. They generally regulate activities that have a rapid onset and a short duration.

Hormones that are lipid-soluble, such as steroids and thyroid hormones, commonly circulate in the blood in combination with plasma proteins. The rate at which hormones are eliminated from the circulation is greatly reduced when the hormones bind to plasma proteins. The combination reduces the rate at which they diffuse through the wall of blood vessels and increases their half-life. Hormones with a long half-life have blood levels that are maintained at a relatively constant level through time. Table 17.3 outlines the ways hormone half-life is shortened or lengthened.

Hormones are removed from the blood in four major ways: excretion, metabolism, active transport, and conjugation. The kidney excretes hormones into the urine, or the liver excretes them into the bile. Enzymes in the blood or in tissues like the liver, kidney, lungs, or other target cells metabolize or chemically modify hormones. The end products can be excreted in the urine or bile, or they can be taken up by cells and used in metabolic processes. For example, epinephrine is modified enzymatically and then excreted by the kidney. Protein hormones are broken down to their amino acid building blocks. The amino acids can then be taken up by cells and used to synthesize new proteins. Some hormones can be actively transported into cells and recycled. For example, both epinephrine and norepinephrine can be actively transported into cells and secreted again.

The liver conjugates some hormones. **Conjugation** (kon-jŭ-gā′shŭn) is accomplished when cells in the liver attach water-soluble molecules to the hormone. These molecules are usually sulfate or glucuronic acid. Once they are conjugated, hormones are excreted by the kidney and liver at a greater rate.

Table 17.3 Factors That Influence the Half-Life of Hormones

A.	Means by which the half-life of hormones is shortened:
1.	**Excretion** Hormones are excreted by the kidney into the urine or excreted by the liver into the bile.
2.	**Metabolism** Hormones are enzymatically degraded in the blood, liver, kidney, lungs, or target tissues. End products of metabolism are either excreted in urine or bile or used in other metabolic processes by cells in the body.
3.	**Active Transport** Some hormones are actively transported into cells and are used again as either hormones or neurotransmitter substances.
4.	**Conjugation** Substances such as sulfate or glucuronic acid groups are attached to hormones primarily in the liver, normally making them less active as hormones and increasing the rate at which they are excreted in the urine or bile.
B.	Means by which the half-life of hormones is lengthened:
1.	Some hormones are protected from rapid excretion or metabolism by binding reversibly with plasma proteins.
2.	Some hormones are protected by their structure. The carbohydrate components of the glycoprotein hormones protect them from proteolytic enzymes in the circulatory system.

11. Define the half-life of a hormone. What happens to this half-life when a hormone binds to a plasma protein? What kinds of hormones bind to plasma proteins?

12. What kinds of activities do hormones with a short half-life regulate? With a long half-life?

13. What are the ways by which the half-life of a hormone is shortened or lengthened?

PREDICT 2

How is the half-life of a hormone affected by a decrease in the concentration of the specific plasma protein to which that hormone binds?

Interaction of Hormones with Their Target Tissues

Objectives

- *Describe how chemical signals (ligands) bind only to specific receptor sites.*
- *Contrast and give examples of down-regulation and up-regulation.*

Chemical signals, commonly called **ligands** (lig′and, lī′gand), are molecules that bind to proteins or glycoproteins and change their functions. Hormones make up one category of ligands; others include substances such as neurotransmitters and chemical mediators of inflammation. The portion of each protein or glycoprotein molecule where a ligand binds is called a **binding site.** If the protein or glycoprotein molecule is a receptor, the binding site called a **receptor site.** The shape and chemical characteristics of each receptor site allow only a specific type of ligand to bind to it (figure 17.11). The tendency for each type of ligand to bind to a specific type of receptor site, and not to others, is called **specificity.** Insulin therefore binds to insulin receptors but not to receptors for growth hormone. However, ligands, such as some hormones, can bind to a number of different receptors that are closely related. For example, epinephrine can bind to more than one type of epinephrine receptor.

Hormones are ligands that are secreted and distributed throughout the body by the circulatory system, but the presence or absence of specific receptor molecules in cells determines which cells will or will not respond to each hormone (figure 17.12). For example, there are receptors for TSH in cells of the thyroid gland, but there are no such receptors in most other cells of the body. Consequently, cells of the thyroid gland produce a response when exposed to TSH, but cells without receptor molecules do not respond to it.

Drugs with structures similar to specific ligands may compete with those ligands for their receptor sites (see chapter 3). Depending on the exact characteristics of a drug, it may either bind to a receptor site and activate the receptor or it may bind to a receptor site and inhibit the action of the receptor. For example, drugs exist that compete with the ligand, epinephrine, for its receptor sites. Some of these drugs activate epinephrine receptors and others inhibit them.

The response to a given concentration of a ligand is constant in some cases but variable in others. In some cells the response rapidly decreases through time. Fatigue of the target cells after prolonged stimulation explains some decreases in responsiveness. Also, the number of receptors can rapidly decrease after exposure to certain ligands—a phenomenon called **down-regulation** (figure 17.13*a*). Two known mechanisms are responsible for down-regulation. First, the rate at which receptors are synthesized decreases in some cells after the cells are exposed to a ligand. Because most receptor molecules are degraded after a time, a decrease in the

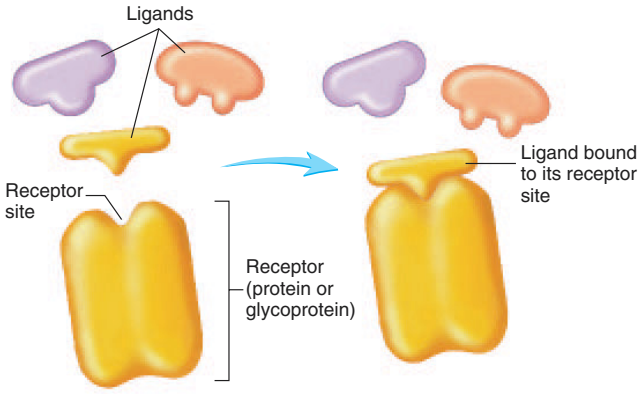


Figure 17.11 Specificity of Receptors for Ligands

The shape and chemical characteristics of receptor sites on receptor molecules make them very specific so that certain ligands can bind to a receptor site, but others cannot.

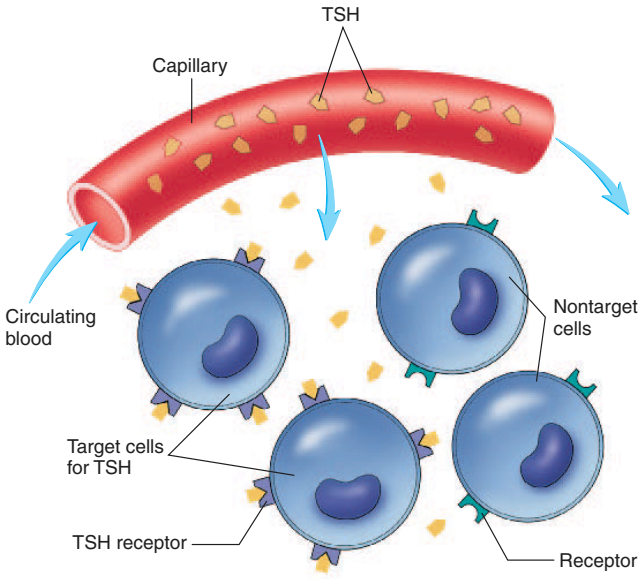


Figure 17.12 Response of Target Cells to Hormones

TSH is secreted into the blood and distributed throughout the body, where TSH diffuses from the blood into the interstitial fluid. Only target cells, however, have receptors for TSH; therefore, although TSH is distributed throughout the body, only target cells for that hormone can respond to it.

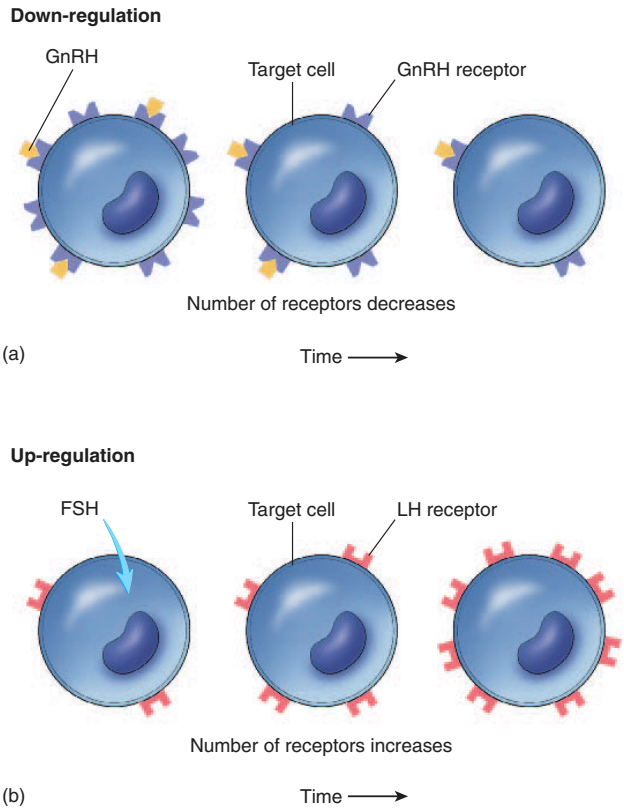


Figure 17.13 Down-Regulation and Up-Regulation

(*a*) Down-regulation occurs when the number of receptors for a hormone decreases within target cells. For example, gonadotropin-releasing hormone (GnRH) released from the hypothalamus binds to GnRH receptors in the anterior pituitary. GnRH bound to its receptors causes down-regulation of the GnRH receptors so that eventually the target cells become less sensitive to the GnRH. (*b*) Up-regulation occurs when some stimulus causes the number of receptors for a hormone to increase within a target cell. For example, FSH acts on cells of the ovary to up-regulate the number of receptors for LH. Thus the ovary becomes more sensitive to the effect of LH.

synthesis rate reduces the total number of receptor molecules in a cell. Second, the combination of ligands and receptors can increase the rate at which receptor molecules are degraded. In some cases, when a ligand binds to a receptor, both the ligand and the receptor are taken into the cell by phagocytosis. Once the hormone and receptor are inside the cell, the cell can break them down.

Gonadotropin-releasing hormone (GnRH), which is released from neurons of the hypothalamus, causes the secretion of LH and follicle-stimulating hormone (FSH) from the anterior pituitary cells. In addition, exposure of the anterior pituitary cells to GnRH causes the number of receptor molecules for GnRH in the pituitary gland cells to dramatically decrease several hours after exposure to the hormone. The down-regulation of GnRH receptors causes the pituitary gland to become less sensitive to additional GnRH. The normal response of the pituitary gland cells to GnRH, therefore, depends on periodic rather than constant exposure of the gland to the hormone.

In general, tissues that exhibit down-regulation of receptor molecules are adapted to respond to short-term increases in hormone concentrations, and tissues that respond to hormones maintained at constant levels normally do not exhibit down-regulation.

In addition to down-regulation, periodic increases in the sensitivity of some cells to certain hormones also occur. This is called **up-regulation,** and it results from an increase in the rate of receptor molecule synthesis (figure 17.13*b*). An example of up-regulation is the increased number of receptor molecules for LH in cells of the ovary during each menstrual cycle. FSH molecules secreted by the pituitary gland increase the rate of LH receptor molecule synthesis in cells of the ovary. Thus, exposure of a tissue to one hormone can increase its sensitivity to a second by causing up-regulation in the number of hormone receptors.

14. ***Define chemical signal (ligand) and receptor site. What characteristics of the receptor site make it specific for one type of ligand?***
15. ***What is down-regulation? What two mechanisms are responsible for down-regulation? Give an example of down-regulation in the body.***
16. ***What is up-regulation? Give an example of up-regulation in the body.***

P R E D I C T 3

Estrogen is a hormone secreted by the ovary. It is secreted in greater amounts after menstruation and a few days before ovulation. Among its many effects is causing up-regulation of receptors in the uterus for another hormone secreted by the ovary called progesterone. Progesterone is secreted after ovulation. A major effect of progesterone is to cause the uterus to become ready for the embryo to attach to its wall following ovulation. Pregnancy cannot occur unless the embryo attaches to the wall of the uterus. Predict the consequence if the ovary secretes too little estrogen.

Classes of Hormone Receptors

Objective

- ***List the two major categories into which ligands are placed.***

Hormones, like other ligands, can be placed into two major categories.

1. *Ligands that cannot pass through the plasma membrane.* These ligands include large molecules and water-soluble molecules that cannot pass through the plasma membrane. They interact with **membrane-bound receptors,** which are receptors that extend across the plasma membrane and have their receptor sites exposed to the outer surface of the plasma membrane (figure 17.14*a*). When a ligand binds to the receptor site on the outside of the plasma membrane, the receptor initiates a response inside the cell. These ligands include many large hormones that are proteins, glycoproteins, polypeptides, and some smaller molecules such as epinephrine and norepinephrine.
2. *Ligands that pass through the plasma membrane.* These ligands are lipid-soluble and relatively small. They diffuse through the plasma membrane and bind to **intracellular receptors,** which are receptors in the cytoplasm or in the nucleus of the cell (figure 17.14*b*). Subsequently, the receptors, with the ligands bound to their receptor sites, interact with DNA in the nucleus of the cell or interact with existing enzymes to produce a response. Thyroid hormones and steroid hormones, such as testosterone, estrogen, progesterone, aldosterone, and cortisol are examples.

17. Define membrane-bound receptor and intracellular receptor. Describe the types of molecules that bind to each type of receptor.

Membrane-Bound Hormone Receptors

Objectives

- ***Describe how ligands directly affect membrane permeability.***
- ***Explain how ligands interact with receptors to influence G proteins, and list the ways G proteins can produce a response to a ligand.***
- ***Describe how ligands interact with receptors to produce intracellular mediator molecules.***
- ***Describe how ligands bind with receptors and alter the activity of intracellular enzymes.***

Ligands bind in a reversible fashion to the receptor sites of membrane-bound receptor molecules. Hormone receptor molecules have peptide chains that cross the membrane once in the case of some receptors and several times for other receptors (see chapter 3). After a hormone binds to its receptor site, the intracellular part of the receptor initiates events that lead to a response. The mechanisms by which all membrane-bound receptors produce an intracellular response is not known, but evidence exists for at least three major mechanisms. The results of ligands binding to membrane-bound receptors are to (1) directly change the permeability of the plasma membrane by opening or closing ion channels, (2) alter the activity of G proteins at the inner surface of the plasma membrane,

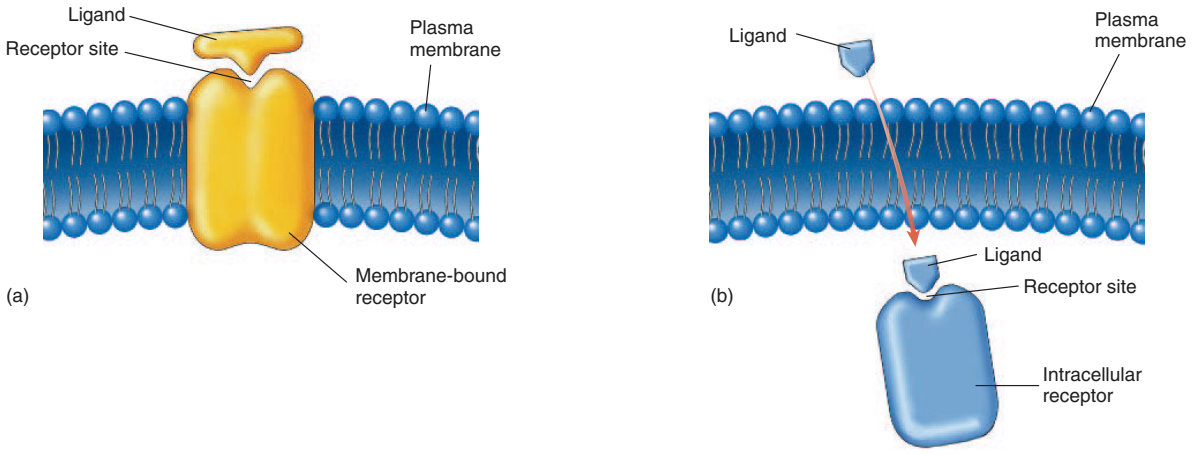
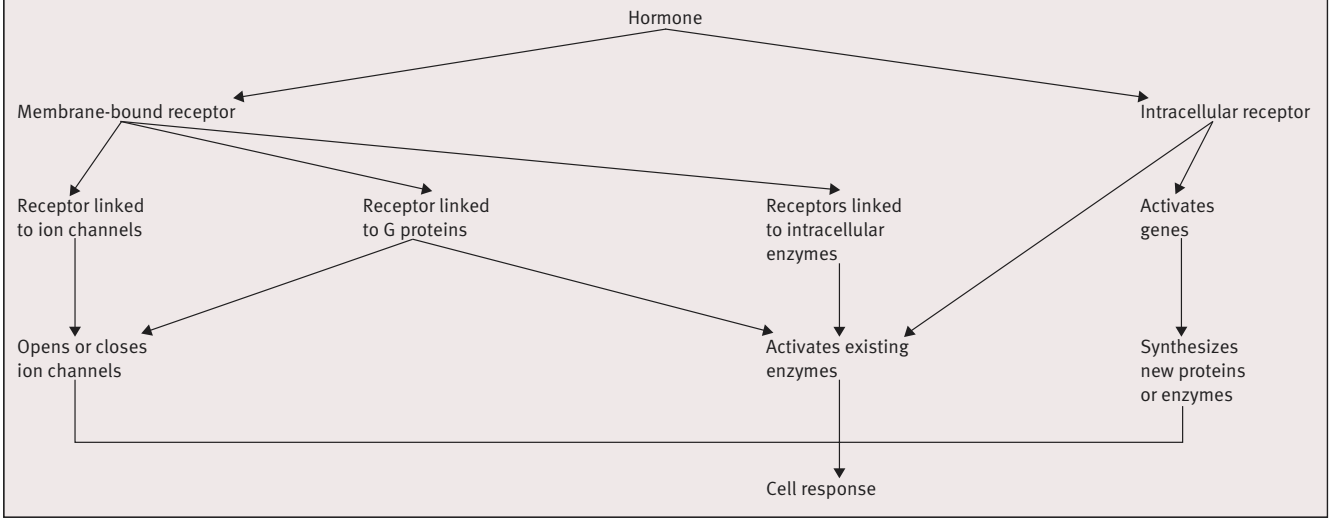


Figure 17.14 Membrane-Bound and Intracellular Receptors

(*a*) A ligand combines with the receptor site of a membrane-bound receptor. The receptor site is exposed to the outside of the cell, and the receptor extends across the plasma membrane. (*b*) The small, lipid-soluble ligand diffuses through the plasma membrane and combines with the receptor site of an intracellular receptor.

Table 17.4 Overview of Responses of Cells to Hormones Binding to Their Receptors



(3) or alter the activity of intracellular enzymes (table 17.4). The changes, initiated by the combination of ligands with their receptor sites, produce specific responses in cells.

Receptors That Directly Alter Membrane Permeability

Some membrane-bound receptors are protein molecules that make up part of ion channels in the plasma membrane (see chapter 3). When ligands bind to the receptor sites of this type of receptor, the combination alters the three-dimensional structure of the proteins of the ion channels, causing the channels either to open or close. These channels are called ligand-gated ion channels. The result is a change in the permeability of the plasma membrane to the specific ions passing through the ion channels (figure 17.15). For example, serotonin molecules bind to serotonin receptor sites that are part of a ligand-gated Na^+ channels and cause them to open. Na^+ diffuse into the cell and cause depolarization of the plasma membrane. Depolarization of target cells may lead to action potential initiation in those cells. Similarly, the neurotransmitter acetylcholine, released from nerve cells, is a ligand that combines with membrane-bound receptors of skeletal muscle cells. The combination of acetylcholine molecules with the receptor sites of the membrane-bound receptors for acetylcholine opens Na^+ channels in the plasma membrane. Consequently, Na^+ diffuse into the skeletal muscle cells causing depolarization and action potential initiation, and contraction (see chapter 9). Table 17.5 lists examples of ligand-gated ion channels. Many of these channels respond to neurotransmitters and not hormones, but some play important roles in regulating hormone secretion or mediating responses to paracrine chemical signals.

Receptors That Activate G Proteins

Many membrane-bound receptors produce responses through the action of a complex of proteins of the plasma membrane called **G proteins** (table 17.6 and figure 17.16). G proteins consist of three subunits; from the largest to smallest, they are called alpha (α), beta (β), and gamma (γ). The G proteins are so named because one of the subunits binds to guanine nucleotides. In the inactive state, a guanine diphosphate (GDP) molecule is bound to the α subunit of each G protein.

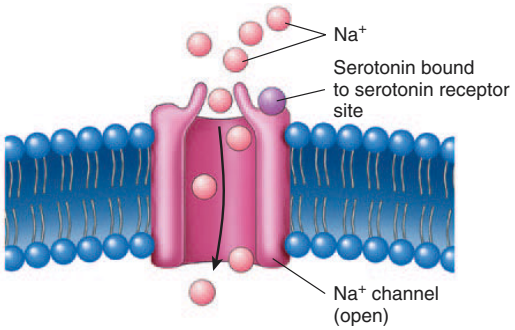


Figure 17.15 Membrane-Bound Receptors That Directly Control Membrane Channels

Membrane-bound receptors for serotonin are part of the Na^+ channel. When a serotonin molecule binds to its receptor site on the serotonin receptor, the Na^+ channel opens and the permeability of the membrane to Na^+ increases. Na^+ then diffuses through the channels into the cell.

Table 17.5 Chemical Signals, Including Paracrine, That Bind to Receptors and Directly Control Ion Channels

Ligand	Channel Type	Response
Acetylcholine	Cation channel (primarily Na^+ channels)	Excitatory
Serotonin	Cation channel (primarily Na^+ channels)	Excitatory
Glutamate	Cation channel (primarily Na^+ channels)	Excitatory
Glycine	Cl^- channels	Inhibitory
GABA	Cl^- channels	Inhibitory

Abbreviations: GABA = gamma(γ)-aminobutyric acid.

Table 17.6 Examples of Hormones That Bind to Membrane-Bound Receptors and Activate G Proteins

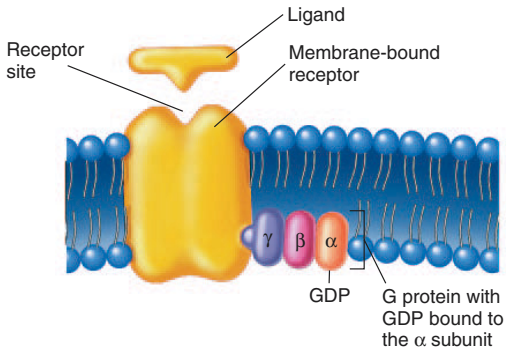
Hormone	Source	Target Tissue
Luteinizing hormone	Anterior pituitary	Ovary or testis
Follicle-stimulating hormone	Anterior pituitary	Ovary or testis
Prolactin	Anterior pituitary	Ovary or testis
Thyroid-stimulating hormone	Anterior pituitary	Thyroid gland
Adrenocorticotropic hormone	Anterior pituitary	Adrenal cortex
Oxytocin	Posterior pituitary	Uterus
Vasopressin	Posterior pituitary	Kidney
Calcitonin	Thyroid gland (parafollicular cells)	Osteoclasts and osteocytes
Parathyroid hormone	Parathyroid gland	Osteoclasts
Glucagon	Pancreas	Liver
Epinephrine	Medulla of adrenal gland	Cardiac muscle

G proteins can bind with receptors at the inner surface of the plasma membrane. After a ligand binds to the receptor on the outside of a cell, the receptor changes shape. As a result, the receptor combines with a G protein complex on the inner surface of the plasma membrane, and GDP is released from the α subunit. Guanine triphosphate (GTP), which is more abundant than GDP, binds to the α subunit, thereby activating it. The G proteins separate from the receptor and the activated α subunit separates from the β and γ subunits (see figure 17.16 *1* and *2*). The activated α subunit can alter the activity of molecules within the plasma membrane or inside the cell, thus producing cellular responses. After a short time, the activated α subunit is turned off because GTP is converted to GDP. The α subunit then recombines with the β and γ subunits (see figure 17.16 *3* and *4*).

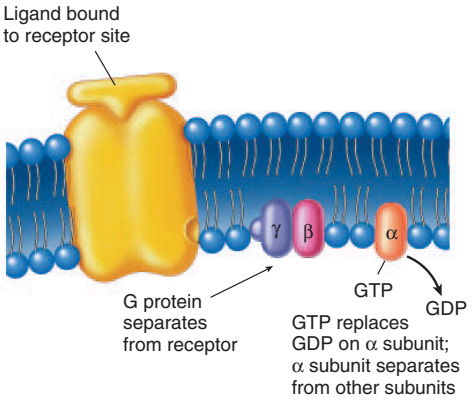
Some activated α subunits of G proteins can combine with ion channels, causing them to open or close (figure 17.17). For example, activated α subunits can open Ca^{2+} channels in smooth muscle cells resulting in the movement of Ca^{2+} into those cells. The Ca^{2+} function as intracellular mediators. The ions combine with calmodulin (kal-mod′ū-lin) molecules, and the calcium-calmodulin complexes activate enzymes that cause contraction of the smooth muscle cells (figure 17.17 *1* and *2*). After a short time, the activated α subunit is inactivated because GTP is converted to GDP. The α subunit then recombines with the β and γ subunits (see 17.17 *3* and *4*).

Other activated α subunits of G proteins alter the activity of enzymes inside of the cell. For example, activated α subunits can influence the rate of cyclic adenosine monophosphate (cAMP) formation (figure 17.18). The enzyme, adenylate cyclase (a-den′i-lāt sī′klās), can be activated by G proteins, thereby increasing the formation of cAMP from ATP. The cAMP molecules act as intracellular mediator molecules. They combine with enzymes and alter their activities inside of the cells, which, in turn, produce responses. The amount of time cAMP is present to produce a response in a cell is limited. An enzyme in the cytoplasm, called phosphodiesterase (fos′fō-dī-es′ter-ās), breaks down cAMP to AMP. The response of the cell is terminated after cAMP levels are reduced below a certain level.

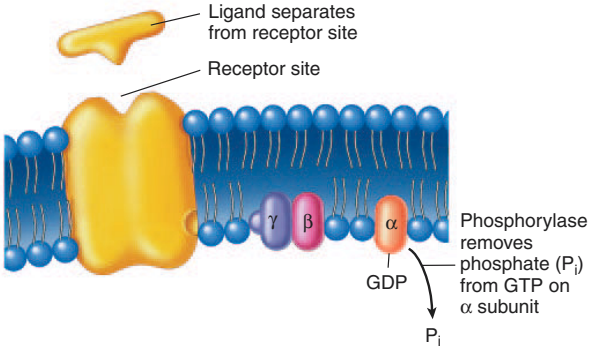
Cyclic AMP acts as an intracellular mediator in many cell types. The response in each cell type is different because the enzymes activated by cAMP in each cell type are different. For example, glucagon combines with receptors on the surface of liver cells,



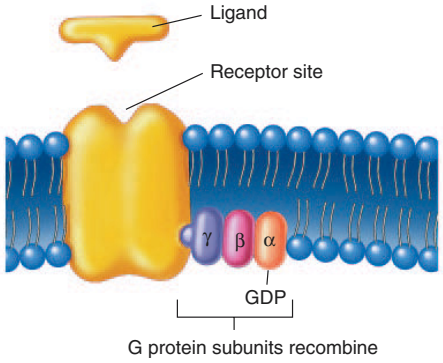
1. The membrane-bound receptor has a receptor site exposed to the outside of the cell. The portion of the receptor inside of the cell can bind to the G protein.



2. The ligand binds to the receptor site of the membrane-bound receptor. The combination alters the G protein. GTP replaces GDP on the α subunit, and the α subunit separates from the γ and β subunits. The α subunit can influence ion channels in the plasma membrane or the synthesis of intracellular mediators.



3. When the ligand separates from the receptor site, additional G proteins are no longer activated. Inactivation of the α subunit occurs when phosphorylase removes an inorganic phosphate (P_i) from the GTP, leaving GDP bound to the α subunit.



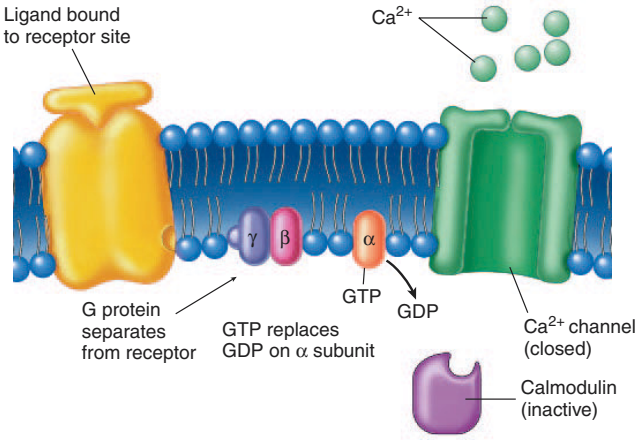
4. The subunits of the G protein recombine.

Process Figure 17.16 Membrane-Bound Receptors That Activate G Proteins

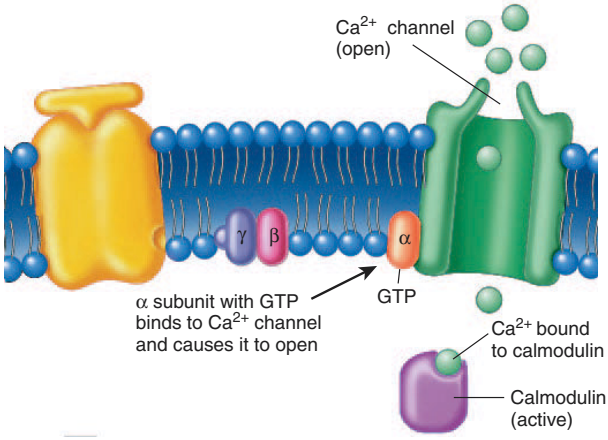
activating G proteins and causing an increase in cAMP synthesis, which increases the release of glucose from liver cells (see figure 17.18). In contrast, LH combines with receptors on the surface of cells of the ovary, activating G proteins, and increasing cAMP synthesis. The major response to the increased cAMP is ovulation.

The combination of ligands with their receptors doesn't always result in increased cAMP synthesis. There are other common intracellular mediators (table 17.7). In some cell types, the combination of ligands with their receptors causes the G proteins to inhibit the synthesis of cAMP, producing a response.

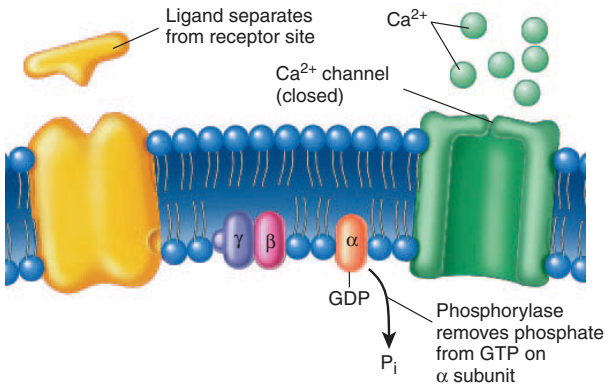
G proteins can also alter the concentration of intracellular mediators other than Ca^{2+} or cAMP (see table 17.7). For example, **diacylglycerol** (dī′as-il-glis′er-ol) **(DAG)** and **inositol** (in-ō′si-tōl, in-ō′si-tol) **triphosphate (IP_3)** are intracellular mediator molecules that are influenced by G proteins (figure 17.19). Epinephrine binds to certain membrane-bound receptors in some types of smooth muscle. The combination activates a G protein mechanism, which, in turn, increases the activity of phospholipase C. Phospholipase C converts phosphoinositol diphosphate (PIP_2) to DAG and IP_3. DAG activates enzymes that synthesize prostaglandins. Prostaglandins increase smooth muscle contraction. IP_3 releases Ca^{2+} from the endoplasmic reticulum or opens Ca^{2+} channels in the plasma membrane. The ions enter the cytoplasm and increase contraction of the smooth muscle cells.



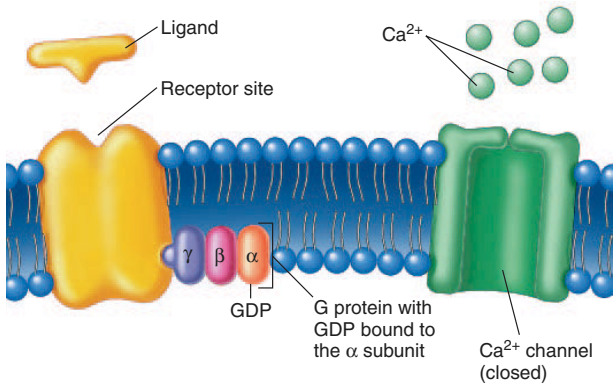
1. A ligand binds to the receptor site of the membrane-bound receptor. The combination alters the G protein. GTP replaces GDP on the α subunit, and the α subunit separates from the γ and β subunits.



2. The α subunit, with GTP bound to it, combines with the Ca^{2+} channel, and the combination causes the Ca^{2+} channel to open. The ions diffuse into the cell and combine with calmodulin. The combination of Ca^{2+} with calmodulin produces the response of the cell to the ligand.



3. Phosphorylase removes an inorganic phosphate from the GTP bound to the α subunit, leaving GDP bound to the α subunit. The α subunit can no longer stimulate a cellular response, it separates from the Ca^{2+} channel, and the channel closes.



4. The α subunit recombines with γ and β subunits.

Process Figure 17.17 Membrane-Bound Receptors, G Proteins, and Ca^{2+} Channels

Receptors That Alter the Activity of Intracellular Enzymes

Some ligands bind to membrane-bound receptors and directly change the activity of an intracellular enzyme. The altered enzyme activity either increases or decreases the synthesis of intracellular mediator molecules, or it results in the phosphorylation of intracellular proteins. The intracellular mediators or phosphorylated proteins activate processes that produce the response of cells to the ligands.

Intracellular enzymes that are controlled by membrane-bound receptors can be part of the membrane-bound receptor, or they may be separate molecules. The intracellular mediator molecules act as chemical signals that move from the enzymes that produce them into the cytoplasm of the cell, where they activate processes that produce the response of the cell.

Cyclic guanine (gwahn′ēn) **monophosphate (cGMP)** is an intracellular mediator molecule that is synthesized in response to a ligand binding with a membrane-bound receptor (figure 17.20). The ligand binds to its receptor, and the combination activates an

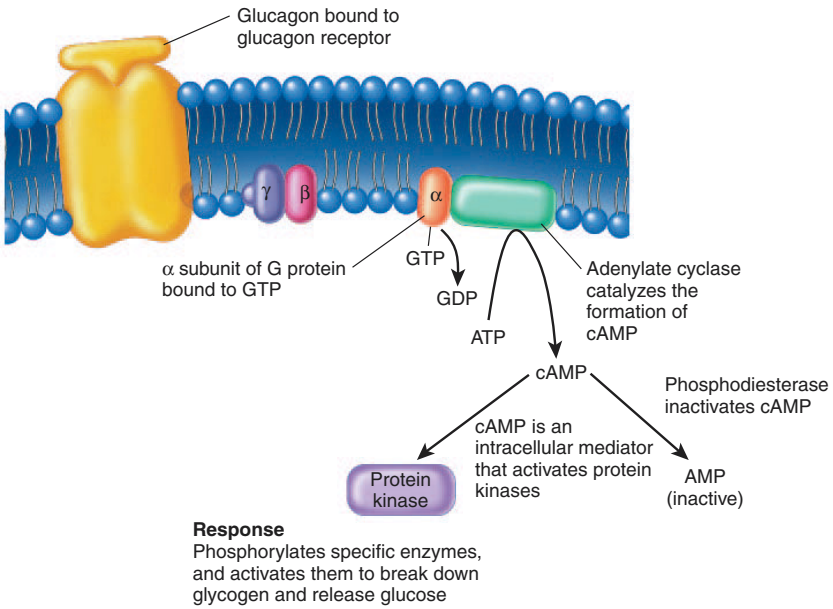


Figure 17.18 Membrane-Bound Receptors That Activate G Proteins and Increase the Synthesis of cAMP

Membrane-bound receptors for glucagon are associated with G proteins in liver cells. When glucagon binds to glucagon receptors, the α subunit of the G proteins dissociates from the other subunits and GTP binds to it. The α subunit then binds to adenylate cyclase and activates it. The resulting increase in cAMP activates protein kinase enzymes, which phosphorylate other specific enzymes that break down glycogen and release glucose from the liver cells.

Table 17.7 Common Intracellular Mediators

Intracellular Mediator	Example of Cell Type	Example of Response
Cyclic guanine monophosphate (cGMP)	Kidney cells	Increases Na^+ and water excretion by the kidney
Cyclic adenosine monophosphate (cAMP)	Liver cells	Increases the breakdown of glycogen and the release of glucose into the circulatory system
Calcium ions (Ca^{2+})	Smooth muscle cells	Contraction of smooth muscle cells
Inositol triphosphate (IP_3)	Smooth muscle cells	Contraction of certain smooth muscle cells in response to epinephrine
Diacylglycerol (DAG)	Smooth muscle cells	Contraction of certain smooth muscle cells in response to epinephrine
Nitric oxide (NO)	Smooth muscle cells	Relaxation of smooth muscle cells of blood vessels resulting in vasodilation

enzyme called **guanylyl cyclase** (gwahn′i-lil sī′klās) located at the inner surface of the plasma membrane. The guanylyl cyclase enzyme converts guanine triphosphate (GTP) to cGMP and two inorganic phosphate groups. The cGMP molecules then combine with specific enzymes in the cytoplasm of the cell and activate them. The activated enzymes, in turn, produce the response of the cell to the ligand. For example, atrial natriuretic hormone is a ligand that combines with its receptor in the plasma membrane of kidney cells. The result is an increase in the rate of cGMP synthesis at the inner surface of the plasma membranes (see figure 17.20). Cyclic GMP influences the action of enzymes in the kidney cells, which increase the rate of Na^+ and water excretion by the kidney (see chapter 26). The amount of time the cGMP is present to produce a response in the cell is limited. Phosphodiesterase breaks down cGMP to GMP. Consequently, the length of time a ligand increases cGMP synthesis and has an effect on a cell is brief after the ligand is no longer present.

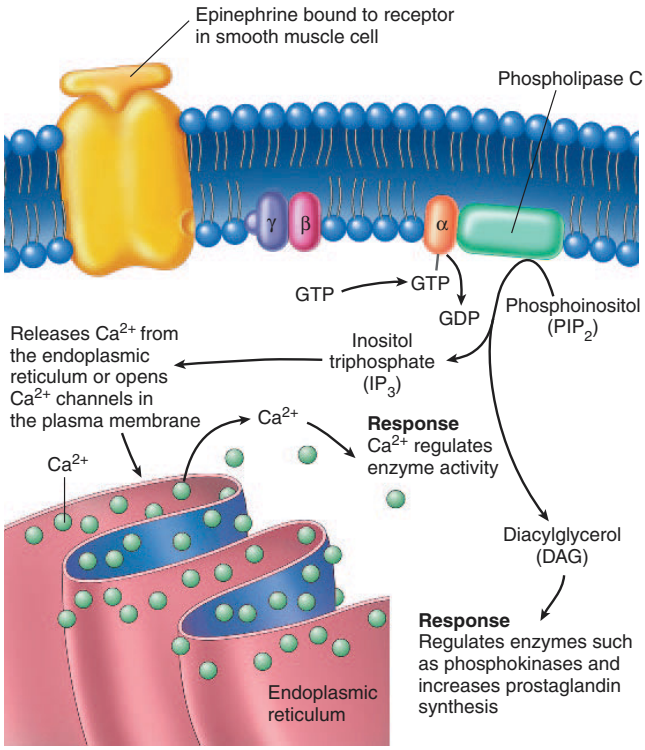


Figure 17.19 Membrane-Bound Receptors That Activate G Proteins and Increase the Synthesis of IP_3 and DAG

Epinephrine receptors in some smooth muscle cells are associated with G proteins. When epinephrine binds to the receptor, the G proteins dissociate and the α subunit binds to GTP. The α subunit then binds with phospholipase C, which acts on phosphoinositol (PIP_2) and produces inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 releases Ca^{2+} from the endoplasmic reticulum, and DAG regulates enzymes such as those that synthesize prostaglandin synthesis. These responses increase smooth muscle contraction.

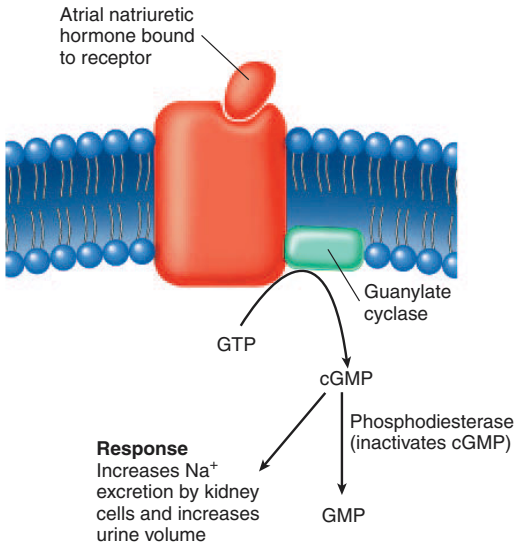


Figure 17.20 Membrane-Bound Receptor That Directly Synthesizes an Intracellular Mediator

Atrial natriuretic hormone binds with its receptor site. At the inner surface of the plasma membrane, guanylyl cyclase is activated to produce cGMP from GTP. Cyclic GMP is an intracellular mediator that mediates the response of the cell. Phosphodiesterase is an enzyme that breaks down cGMP to inactive GMP.

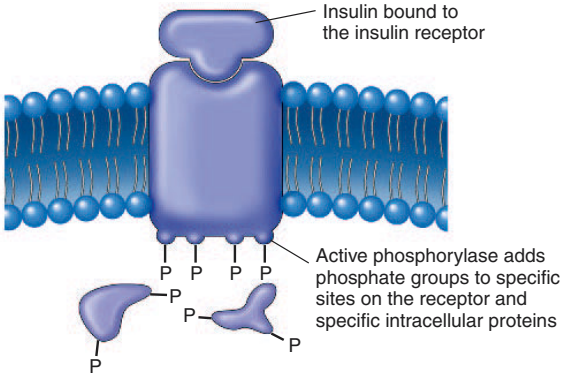


Figure 17.21 Membrane-Bound Receptors That Phosphorylate Intracellular Proteins

Insulin receptors are membrane-bound receptors. When insulin binds to the insulin receptor, the receptor acts as a phosphorylase enzyme and attaches phosphate groups from ATP to specific sites on the receptor and on intracellular proteins. The phosphorylated proteins produce the normal response to insulin.

Some ligands bind to membrane-bound receptors, and the portion of the receptor on the inner surface of the plasma membrane acts as an enzyme that adds phosphate groups, a process called **phosphorylation** (fos′fōr-i-lā′shŭn), to several specific proteins. Some of the phosphorylated proteins are part of the membrane-bound receptor, and others are in the cytoplasm of the cell (figure 17.21). The phosphorylated proteins influence the activity of other enzymes in the cytoplasm of the cell. For example, insulin binds to its membrane-bound receptor, resulting in the phosphorylation of parts of the receptor on the inner surface of the plasma membrane and the phosphorylation of certain other intracellular proteins. The phosphorylated proteins produce the responses of the cells to insulin. Some receptors for hormones that phosphorylate intracellular proteins are listed in table 17.8.

Hormones that stimulate the synthesis of an intracellular mediator molecule often produce rapid responses. This is possible because the mediator influences already-existing enzymes and causes a **cascade effect,** which results when a few mediator molecules activate several enzymes and each of the activated enzymes in

Table 17.8 Hormones That Bind to Receptors That Phosphorylate Intracellular Proteins

Hormone	Source	Target Tissue and Effect
Insulin	Pancreatic islets	Most cells; increases glucose and amino acid uptake
Growth hormone	Anterior pituitary gland	Most cells; increases protein synthesis and resists protein breakdown
Prolactin	Anterior pituitary gland	Mammary glands and ovary; initiates milk production following pregnancy and helps maintain the corpus luteum
Growth factors	Various tissues	Stimulate growth in certain cell types
Some intercellular immune signal molecules	Cells of the immune system	Immune-competent cells; help mediate responses of the immune system

turn activates several other enzymes that produce the final response. Thus, an amplification system exists in which a few molecules, such as cAMP, cGMP, or phosphorylated proteins, can control the activity of many enzymes within a cell (figure 17.22)

18. *Describe how membrane permeability can be changed when a hormone binds to a membrane-bound receptor. Give an example.*
19. *Explain how the combination of a ligand and its receptor can alter the G proteins on the inner surface of the plasma membrane. Which activated subunit of the G protein alters the activity of molecules inside the plasma membrane or inside the cell?*
20. *Describe how G proteins can alter the permeability of the plasma membrane and how they can alter the synthesis of an intracellular mediator molecule such as cAMP. Give examples.*
21. *Other than cAMP and Ca^{2+}, list two additional intracellular mediators affected by G proteins.*

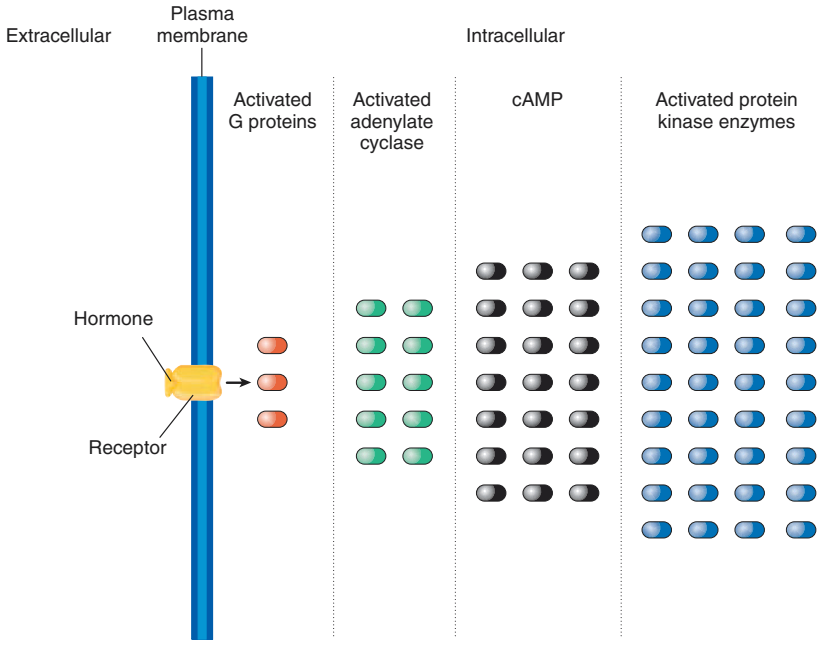


Figure 17.22 The Cascade Effect

The combination of a hormone with a membrane-bound receptor activates several G proteins. The G proteins, in turn, activate adenylyl cyclase enzymes, which cause the synthesis of a large number of cAMP molecules. The cAMP molecules, in turn, activate many protein kinase enzymes, which produce a rapid and amplified response.

22. *Describe how a ligand can combine with a membrane-bound receptor and change enzyme activity inside the cell and increase phosphorylation of intracellular proteins. Give examples.*
23. *What limits the activity of intracellular mediator molecules, such as cAMP, and phosphorylated proteins?*
24. *Explain what is meant by the cascade effect for the intracellular mediator model of hormone action. Does the intracellular mediator mechanism produce a slow or rapid response?*

P R E D I C T 4

When smooth muscle cells in the airways of the lungs contract, as in asthma, breathing becomes very difficult, whereas breathing is easy if the smooth muscle cells are relaxed. During asthma attacks, the smooth muscle cells in the airways of the lungs contract. Some of the drugs used to treat asthma increase cAMP in smooth muscle cells. Explain as many ways as possible how these drugs might work.

Intracellular Hormone Receptors

Objective

- *Explain how ligands that cross the plasma membrane can produce responses by binding to intracellular receptors.*

Intracellular receptors are either in the cytoplasm or in the nucleus of cells. Lipid-soluble ligands cross the plasma membrane into the cytoplasm or into the nucleus and bind to intracellular receptors by the process of diffusion (figure 17.23). After a ligand binds with an intracellular receptor, the receptor can alter the activity of enzymes in the cell, or it can bind to DNA to produce a response (see table 17.4). Some intracellular receptors that influence the expression of DNA are located in the cytoplasm. Once a ligand binds to its receptor, the receptor and ligand diffuse into the nucleus and bind to DNA. Other intracellular receptors are located in the nucleus. A ligand diffuses into the nucleus and binds to its receptor, and the receptor then binds to DNA.

Receptors that interact with DNA have specific "fingerlike" projections that interact with specific parts of a DNA molecule. The combination of the ligand and its receptor with DNA increases the synthesis of specific **messenger ribonucleic acid (mRNA)** molecules. The mRNA molecules then move to the cytoplasm and increase the synthesis of specific proteins at the ribosomes. The newly synthesized proteins produce the cell response to the ligand. For example, testosterone from the testes and estrogen from the ovaries stimulate the synthesis of proteins that are responsible for the secondary sex characteristics of males and females. The effect of the steroid aldosterone on its target cells in the kidney is to

1. Aldosterone is a lipid-soluble hormone and can easily diffuse through the plasma membrane.

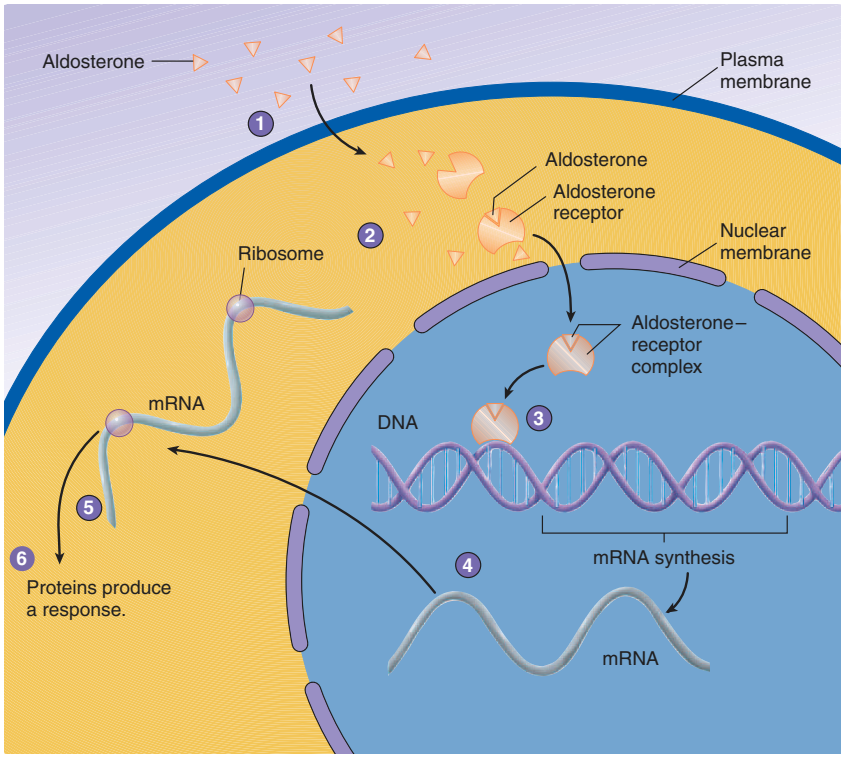
2. Aldosterone, once inside of the cell, binds with an aldosterone receptor molecule in the cytoplasm.

3. The aldosterone–receptor complex moves into the nucleus and binds to DNA.

4. The binding of the aldosterone-receptor complex to DNA stimulates the synthesis of messenger RNA (mRNA) which codes for specific proteins.

5. The mRNA leaves the nucleus, passes into the cytoplasm of the cell, and binds to ribosomes, where it directs the synthesis of the specific proteins.

6. The proteins synthesized on the ribosomes produce the response of the cell to aldosterone.



Process Figure 17.23 Intracellular Receptor Model

stimulate the synthesis of proteins that increase the rate of Na^+ transport. The result is an increase in the reabsorption of Na^+ from the filtrate in the kidney and a reduction in the amount of Na^+ lost in the urine. Other hormones that produce responses through intracellular receptor mechanisms include thyroid hormones and vitamin D (table 17.9).

Cells that synthesize new protein molecules in response to hormonal stimuli normally have a latent period of several hours between the time the hormones bind to their receptors and the time responses are observed. During this latent period, mRNA and new proteins are synthesized. Receptor–hormone complexes normally are degraded within the cell, limiting the length of time hormones influence the activities of cells, and the cells slowly return to their previous functional states.

Some cellular functions depend on the coordinated activity of ligands that bind to membrane-bound receptors and ligands that bind to intracellular receptors. For example, acetylcholine molecules, released from nerve cells, bind to membrane-bound receptors of endothelial cells in blood vessels, and the combination causes Ca^{2+} channels to open. The ions then enter the endothelial cell and activate enzymes that produce nitric oxide (NO). NO is a very toxic gas, but in the low concentrations found in cells, it functions as a ligand. NO diffuses from the endothelial cells to smooth muscle cells in the blood vessel. It could be appropriately classified as a paracrine chemical signal. NO binds to an intracellular receptor that is part of the enzyme guanylate cyclase. In response, guanylate cyclase catalyzes the synthesis of cGMP, which causes the smooth muscle cells to relax (figure 17.24) and blood vessels to dilate.

25. *Describe how a ligand that crosses the plasma membrane interacts with its receptor and how it alters the rate of protein synthesis. Why is there normally a latent period between the time hormones bind to their receptors and the time responses are observed?*
26. *What finally limits the processes activated by the intracellular receptor mechanism?*

PREDICT 5

Of membrane-bound receptors and intracellular receptors, which is better adapted for mediating a response that lasts a considerable length of time and which is better for mediating a response with a rapid onset and a short duration? Explain why.

Table 17.9 Major Hormones That Combine with Intracellular Receptors

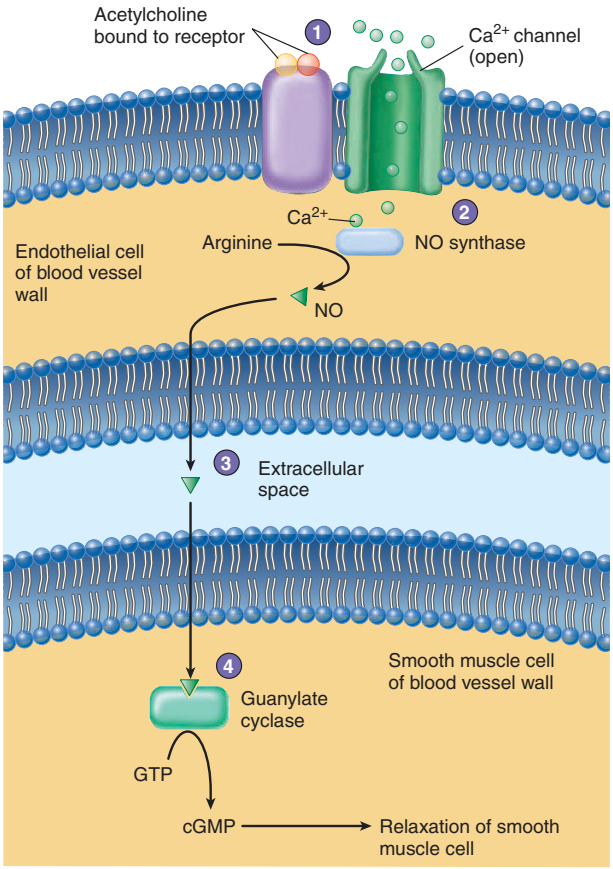
Category of Hormone	Hormone	Source	Target Tissue and Effect
Sex steroids	Testosterone	Testis	Responsible for development of the reproductive structures and development of male secondary sex characteristics
	Progesterone	Ovary	Causes increased size of cells lining the uterus
	Estrogen	Ovary	Causes increased cell division in the lining of the uterus
Mineralocorticoid steroids	Aldosterone	Adrenal cortex	Increased reabsorption of Na^+ and increased secretion of K^+ in the kidney
Glucocorticoid steroid hormones	Cortisol	Adrenal cortex	Increased breakdown of proteins and fats and increased blood levels of glucose
Thyroid hormones	Triiodothyronine (T_3)	Thyroid gland	Regulate development and metabolism
Vitamin D	1,25-dihydroxycholecalciferol	Combination of the skin, liver, and kidney	Increased reabsorption of Ca^{2+} in the kidney and absorption of Ca^{2+} in the gastrointestinal tract

1. Acetylcholine binds to the acetylcholine receptor site on an acetylcholine receptor. The combination causes a Ca^{2+} channel to open, allowing Ca^{2+} to diffuse into the endothelial cell of the blood vessel wall.

2. Ca^{2+} binds to a receptor site on nitric oxide (NO) synthase, an enzyme that acts on arginine to produce NO.

3. NO diffuses out of the endothelial cell and into a smooth muscle cell of the blood vessel wall.

4. NO combines with a receptor site on the enzyme, guanylate cyclase, which converts GTP to cGMP. cGMP causes the smooth muscle cell to relax.



Process Figure 17.24 Combined Membrane-Bound and Intracellular Receptor Mechanism

Combination of a ligand with its membrane-bound receptor results in the production of nitric oxide (NO) in one cell (e.g., an endothelial cell of blood vessels). The NO diffuses into another cell (e.g., a smooth muscle cell of the blood vessel) and binds to an intracellular receptor, increasing the synthesis of an intracellular signal molecule (cAMP), which produces a response (e.g., relaxation of the smooth muscle cells).

S U M M A R Y

General Characteristics of the Endocrine System (p. 572)

1. Endocrine glands produce hormones that are released into the interstitial fluid, diffuse into the blood, and travel to target tissues, where they cause a specific response.
2. Endocrine glands produce other chemical messengers, including neurohormones, neurotransmitters, neuromodulators, parahormones, and pheromones.
3. Generalizations about the differences between the endocrine and nervous systems include the following: (a) the endocrine system is amplitude-modulated, whereas the nervous system is frequency-modulated; and (b) the response of target tissues to hormones is usually slower and of longer duration than that to neurons.

Chemical Structure of Hormones (p. 573)

Hormones are proteins, glycoproteins, polypeptides, derivatives of amino acids, or lipids (steroids or derivatives of fatty acids).

Control of Secretion Rate (p. 573)

1. Most hormones are not secreted at a constant rate.
2. Negative-feedback mechanisms that function to maintain homeostasis control most hormone secretion.
3. Hormone secretion from an endocrine tissue is regulated by one or more of three mechanisms: a nonhormone substance, stimulation by the nervous system, or a hormone from another endocrine tissue.

Transport and Distribution in the Body (p. 578)

Hormones are dissolved in plasma or bind to plasma proteins. The blood quickly distributes hormones throughout the body.

Metabolism and Excretion (p. 580)

1. Nonpolar, readily diffusible hormones bind to plasma proteins and have an increased half-life.
2. Water-soluble hormones, such as proteins, epinephrine, and norepinephrine, do not bind to plasma proteins or readily diffuse out of the blood. Instead, they are broken down by enzymes or are taken up by tissues. They have a short half-life.
3. Hormones with a short half-life regulate activities that have a rapid onset and a short duration.

4. Hormones with a long half-life regulate activities that remain at a constant rate through time.
5. Hormones are eliminated from the blood by excretion from the kidneys and liver, enzymatic degradation, conjugation, or active transport.

Interaction of Hormones with Their Target Tissues (p. 581)

1. Target tissues have receptor molecules that are specific for a particular hormone.
2. Hormones bound with receptors affect the rate at which already existing processes occur.
3. Down-regulation is a decrease in the number of receptor molecules in a target tissue, and up-regulation is an increase in the number of receptor molecules.

Classes of Hormone Receptors (p. 583)

1. Membrane-bound receptors bind to water-soluble or large-molecular-weight hormones.
2. Intracellular receptors bind to lipid-soluble hormones.

Membrane-Bound Hormone Receptors

1. Membrane-bound receptors are proteins or glycoproteins that have polypeptide chains that are folded to cross the cell several times.
2. When a hormone binds to a membrane-bound receptor:
   - A change in the structure of membrane channels can result in a change in permeability of the plasma membrane to ions.
   - G proteins are activated. The α subunit of the G protein can bind to ion channels and cause them to open or change the rate of synthesis of intracellular mediator molecules, such as cAMP, cGMP, IP_3, and DAG.
   - Intracellular enzymes can be directly activated, which in turn synthesizes intracellular mediators, such as cGMP, or adds a phosphate group to intracellular enzymes, which alters their activity.
3. Intracellular mediator mechanisms are rapid-acting because they act on already-existing enzymes and produce a cascade effect.

Intracellular Hormone Receptors

1. Intracellular receptors are proteins in the cytoplasm or nucleus.
2. Hormones bind with the intracellular receptor, and the receptor–hormone complex activates genes. Consequently, DNA is activated to produce mRNA. The mRNA initiates the production of certain proteins (enzymes) that produce the response of the target cell to the hormone.
3. Intracellular receptor mechanisms are slow-acting because time is required to produce the mRNA and the protein.
4. Intracellular receptor–activated processes are limited by the breakdown of the receptor–hormone complex.

REVIEW AND COMPREHENSION

1. When comparing the endocrine system and the nervous system, generally speaking, the endocrine system
   a. is faster-acting than the nervous system.
   b. produces effects that are of shorter duration.
   c. uses amplitude-modulated signals.
   d. produces more localized effects.
   e. relies less on chemical signals.
2. A chemical signal released from a cell that has a local effect on the same cell type from which the chemical signal is released is a(n)
   a. paracrine chemical signal.
   b. pheromone.
   c. autocrine chemical signal.
   d. hormone.
   e. intracellular mediator.
3. Given this list of molecule types:
   1. nucleic acid derivatives
   2. fatty acid derivatives
   3. polypeptides
   4. proteins
   5. phospholipids

   Which could be hormone molecules?
   a. 1,2,3
   b. 2,3,4
   c. 1,2,3,4
   d. 2,3,4,5
   e. 1,2,3,4,5
4. Which of these regulates secretion of a hormone from an endocrine tissue?
   a. other hormones
   b. negative-feedback mechanisms
   c. nonhormone substance in the blood
   d. the nervous system
   e. all of the above
5. Hormones are released into the blood
   a. at relatively constant levels.
   b. in large amounts in response to a stimulus.
   c. increasing and decreasing in a cyclic fashion.
   d. all of the above.
6. Lipid-soluble hormones readily diffuse through capillary walls, whereas water-soluble hormones, such as proteins, must
   a. pass through capillary cells.
   b. pass through pores in the capillary endothelium.
   c. be moved out of the capillary by active transport.
   d. remain in the blood.
   e. be broken down to amino acids before leaving the blood.
7. Concerning the half-life of hormones,
   a. lipid-soluble hormones generally have a longer half-life.
   b. hormones with shorter half-lives regulate activities with a slow onset and long duration.
   c. hormones with a shorter half-life are maintained at more constant levels in the blood.
   d. lipid-soluble hormones are degraded rapidly by enzymes in the circulatory system.
   e. water-soluble hormones usually combine with plasma proteins.
8. Given these observations:
   1. A hormone will affect only a specific tissue (not all tissues).
   2. A tissue can respond to more than one hormone.
   3. Some tissues respond rapidly to a hormone, whereas others take many hours to respond.

   Which of these observations can be explained by the characteristics of hormone receptors?
   a. 1
   b. 1,2
   c. 2,3
   d. 1,3
   e. 1,2,3

9. Which of these is *not* a means by which hormones are eliminated from the circulatory system?
   a. excreted into urine or bile
   b. bound to plasma proteins
   c. metabolism (enzymatically degraded in the blood)
   d. actively transported into cells
   e. conjugated with sulfate or glucuronic acid
10. Down-regulation
   a. produces a decrease in the number of receptors in the target cells.
   b. produces an increase in the sensitivity of the target cells to a hormone.
   c. is found in target cells that respond to hormones that are maintained at constant levels.
   d. occurs partly because of an increase in receptor synthesis by the target cell.
   e. all of the above.
11. A ligand
   a. can function as an enzyme.
   b. is also a G protein.
   c. can bind to a receptor site.
   d. is an intracellular mediator.
   e. all of the above.
12. Activated G proteins can
   a. cause ion channels to open or close.
   b. activate adenylyl cyclase.
   c. inhibit the synthesis of cAMP.
   d. alter the activity of IP_3.
   e. all of the above.
13. Given these events:
   1. GTP is converted to GDP.
   2. The α subunit separates from the β and γ units.
   3. GDP is released from the α subunit.

   List the order in which the events occur after a ligand binds to a membrane-bound receptor.
   a. 1,2,3
   b. 1,3,2
   c. 2,3,1
   d. 3,2,1
   e. 3,1,2
14. Which of these can limit the response of a cell to a ligand?
   a. phosphodiesterase
   b. converting GTP to GDP
   c. decreasing the number of receptors
   d. blocking binding sites
   e. all of the above
15. Given these events:
   1. Na^+ channels open.
   2. Na^+ channels close.
   3. The plasma membrane depolarizes.
   4. The plasma membrane hyperpolarizes.

   Choose the arrangement that lists the events in the order they occur after serotonin binds to its receptor.
   a. 1,3
   b. 1,4
   c. 2,3
   d. 2,4
16. Given these events:
   1. The α subunit of a G protein interacts with Ca^{2+} channels.
   2. Ca^{2+} diffuse into the cell.
   3. The α subunit of a G protein is activated.

   Choose the arrangement that lists the events in the order they occur after a ligand combines with a receptor on a smooth muscle cell.
   a. 1,2,3
   b. 1,3,2
   c. 2,1,3
   d. 3,1,2
   e. 3,2,1
17. Given these events:
   1. cAMP is synthesized.
   2. The α subunit of G protein is activated.
   3. Phosphodiesterase breaks down cAMP.

   Choose the arrangement that lists the events in the order they occur after a ligand binds to a receptor.
   a. 1,2,3
   b. 1,3,2
   c. 2,1,3
   d. 2,3,1
   e. 3,2,1
18. Which of these events can occur after a G protein activates phospholipase C?
   a. DAG and IP_3 are synthesized from PIP_2.
   b. IP_3 causes Ca^{2+} channels to open.
   c. DAG activates enzymes that synthesize prostaglandins.
   d. All of the above.
19. When a ligand binds to an intracellular receptor
   a. DNA produces mRNA.
   b. G proteins are activated.
   c. the receptor–hormone complex causes ion channels to open or close.
   d. the cell's response is faster than when a ligand binds to a membrane-bound receptor.
   e. the ligand is usually a large, water-soluble molecule.
20. Given these events:
   1. activation of cAMP
   2. activation of genes
   3. enzyme activity altered

   Which of these events can occur when a hormone binds to an intracellular hormone receptor?
   a. 1
   b. 1,2
   c. 2,3
   d. 1,2,3

Answers in Appendix F

CRITICAL THINKING

1. Consider a hormone that is secreted in large amounts at a given interval, modified chemically by the liver, and excreted by the kidney at a rapid rate, thus making the half-life of the hormone in the circulatory system very short. The hormone therefore rapidly increases in the blood and then decreases rapidly. Predict the consequences of liver and kidney disease on the blood levels of that hormone.
2. Consider a hormone that controls the concentration of some substance in the circulatory system. If a tumor begins to produce that substance in large amounts in an uncontrolled fashion, predict the effect on the secretion rate for the hormone.
3. How could you determine whether or not a hormone-mediated response resulted from the intracellular mediator mechanism or the intracellular receptor mechanism?
4. If the effect of a hormone on a target tissue is through a membrane-bound receptor that has a G protein associated with it, predict the consequences if a genetic disease causes the α subunit of the G protein to have a structure that prevents it from binding to GTP.
5. Prostaglandins are a group of hormones produced by many cells of the body. Unlike other hormones, they don't circulate but usually have their effect at or very near their site of production. Prostaglandins apparently affect many body functions, including blood pressure, inflammation, induction of labor, vomiting, fever, and inhibition of the clotting process. Prostaglandins also influence the formation of cAMP. Explain how an inhibitor of prostaglandin synthesis could be used as a therapeutic agent. Inhibitors of prostaglandin synthesis can produce side effects. Why?
6. For a hormone that binds to a membrane-bound receptor and has cAMP as the intracellular mediator, predict and explain the consequences if a drug is taken that strongly inhibits phosphodiesterase.
7. When an individual is confronted with a potentially harmful or dangerous situation, epinephrine (adrenaline) is released from the adrenal gland. Epinephrine prepares the body for action by increasing the heart rate and blood glucose levels. Explain the advantages or disadvantages associated with a short half-life for epinephrine and those associated with a long half-life.
8. Thyroid hormones are important in regulating the basal metabolic rate of the body. What are the advantages or disadvantages of
   a. a long half-life for thyroid hormones?
   b. a short half-life?
9. An increase in thyroid hormones causes an increase in metabolic rate. If liver disease results in reduced production of the plasma proteins to which thyroid hormones normally bind, what is the effect on metabolic rate? Explain.
10. Predict the effect on LH and FSH secretion if a small tumor in the hypothalamus of the brain secretes large concentrations of GnRH continuously. Given that LH and FSH regulate the function of the male and female reproductive systems, predict whether the condition increases or decreases the activity of these systems.
11. Insulin levels normally change in order to maintain normal blood sugar levels, despite periodic fluctuations in sugar intake. A constant supply of insulin from a skin patch might result in insulin levels that are too low when blood sugar levels are high (after a meal) and might be too high when blood sugar levels are low (between meals). In addition, insulin is a protein hormone that would not readily diffuse through the lipid barrier of the skin (see chapter 5). Estrogen is a lipid soluble steroid hormone.

Answers in Appendix G

ANSWERS TO PREDICT QUESTIONS

1. Because the abnormal substance acts like TSH, it acts on the thyroid gland to increase the rate of secretion of the thyroid hormones, which increase in concentration in the circulatory system. The thyroid hormones have a negative-feedback effect on the secretion of TSH, thereby decreasing the concentration of TSH in the circulatory system to low levels. Because the abnormal substance is not regulated, it can cause thyroid hormone levels to become very elevated.
2. A major function of plasma proteins, to which hormones bind, is to increase the half-life of the hormone. If the concentration of the plasma protein decreases, the half-life and, consequently, the concentration of the hormone in the circulatory system decrease. The half-life of the hormone decreases because the rate hormone leaves the circulatory system increases. If the secretion rate for the hormone does not increase, its concentration in the blood declines.
3. If too little estrogen is secreted, the up-regulation of receptors in the uterus for progesterone cannot occur. As a result, the uterus is not prepared for the embryo to attach to its wall following ovulation, and pregnancy cannot occur. Because of the lack of up-regulation, the uterus probably will not respond to progesterone, regardless of how much is secreted. If some progesterone receptors are present, however, the uterus will require a much larger amount of progesterone to produce the normal response.
4. A drug could increase the cAMP concentration in a cell by stimulating its synthesis or by inhibiting its breakdown. Drugs that bind to a receptor that increases adenylate cyclase activity will increase cAMP synthesis. Because phosphodiesterase normally causes the breakdown of cAMP, an inhibitor of phosphodiesterase decreases the rate of cAMP breakdown and causes cAMP to increase in the smooth muscle cells of the airway and produces relaxation.
5. Intracellular receptor mechanisms result in the synthesis of new proteins that exist within the cell for a considerable amount of time. Intracellular receptors are therefore better adapted for mediating responses that last a relatively long time (i.e., for many minutes, hours, or longer). On the other hand, membrane-bound receptors that increase the synthesis of intracellular mediators such as cAMP normally activate enzymes already existing in the cytoplasm of the cell for shorter periods. The synthesis of cAMP occurs quickly, but the duration is short because cAMP is broken down quickly, and the activated enzymes are then deactivated. Membrane-bound receptor mechanisms are therefore better adapted to short-term and rapid responses.