UNIT Eight

Alterations in the Endocrine System

CHAPTER 30

Organization and Control of the Endocrine System

The endocrine system is involved in all of the integrative aspects of life, including growth, sex differentiation, metabolism, and adaptation to an ever-changing environment. This chapter focuses on general aspects of endocrine function, organization of the endocrine system, hormone receptors and hormone actions, and regulation of hormone levels.

THE ENDOCRINE SYSTEM

The endocrine system uses chemical substances called *hormones* as a means of regulating and integrating body functions. The endocrine system participates in the regulation of digestion, use, and storage of nutrients; growth and development; electrolyte and water metabolism; and reproductive functions. Although the endocrine system once was thought to consist solely of discrete endocrine glands, it is now known that a number of other tissues release chemical messengers that modulate body processes. The functions of the endocrine system are closely linked with those of the nervous system and the immune system. For example, neurotransmitters such as epinephrine can act as neurotransmitters or as hormones. The functions of the immune system also are closely linked with those of the endocrine system. The immune system responds to foreign agents by means of chemical messengers (cytokines, *e.g.*, interleukins, interferons) and complex receptor mechanisms (see Chapter 8). The immune system also is extensively regulated by hormones such as the adrenal corticosteroid hormones.

Hormones

Hormones generally are thought of as chemical messengers that are transported in body fluids. They are highly specialized organic molecules produced by endocrine organs that exert their action on specific target cells. Hormones do not initiate reactions; they are modulators of systemic and cellular responses. Most hormones are present in body fluids at all times but in greater or lesser amounts, depending on the needs of the body.

A characteristic of hormones is that a single hormone can exert various effects in different tissues or, conversely, a single function can be regulated by several hormones. For example, estradiol, which is produced by the ovary, can act on the ovarian follicles to promote their maturation, on the uterus to stimulate its growth and maintain the cyclic changes in the uterine mucosa, on the mammary gland to stimulate ductal growth, on the hypothalamic-pituitary system to regulate the secretion of gonadotropins and prolactin, and on general metabolic processes to affect adipose tissue distribution. Lipolysis, which is the release of free fatty acids from adipose tissue, is an example of a single function that is regulated by several hormones, including the catecholamines, glucagon, and secretin. Table 30-1 lists the major functions and sources of body hormones.

Paracrine and Autocrine Actions

In the past, hormones were described as chemical substances that were released into the bloodstream and transported to distant target sites, where they exerted their action (Fig. 30-1). Although many hormones travel by this mechanism, some hormones and hormone-like substances never enter the bloodstream but instead act locally in the vicinity in which they are released. When they act locally on cells other than those that produced the hormone, the action is called *paracrine*. The action of sex steroids on the ovary is a paracrine action. Hormones also can exert an *autocrine* action on the cells from which they were produced. For example, the release of insulin from pancreatic beta cells can inhibit its release from the same cells. *Juxtacrine* refers to a mechanism whereby a cytokine that is embedded in, bound to, or associated with the plasma membrane of one cell interacts with a specific receptor in a juxtaposed cell.

KEY CONCEPTS

HORMONES

- Hormones function as chemical messengers, moving through the blood to distant target sites of action, or acting more locally as paracrine or autocrine messengers that incite more local effects.
- Most hormones are present in body fluids at all times but in greater or lesser amounts, depending on the needs of the body.
- Hormones exert their actions by interacting with high-affinity receptors, which in turn are linked to one or more effector systems in the cell. Some hormone receptors are located on the surface of the cell and act through second messenger mechanisms, and others are located in the cell, where they modulate the synthesis of enzymes, transport proteins, or structural proteins.

Eicosanoids and Retinoids

A group of compounds that have a hormone-like action are the eicosanoids, which are derived from polyunsaturated fatty acids in the cell membrane. Among these, *arachidonic acid* is the most important and abundant precursor of the various eicosanoids. The most important of the eicosanoids are the prostaglandins, leukotrienes, and thromboxanes. These fatty acid derivatives are produced by most body cells, are rapidly cleared from the circulation, and are thought to act mainly by paracrine and autocrine mechanisms. Eicosanoid synthesis often is stimulated in response to hormones, and they serve as mediators of hormone action. Retinoids (*e.g.*, retinoic acid) also are derived from fatty acids and have an important role in regulating nuclear receptor action.

Structural Classification

Hormones have diverse structures, ranging from single amino acids to complex proteins and lipids. Hormones usually are divided into four categories according to their structures: (1) amines and amino acids; (2) peptides, polypeptides, glycoproteins, and proteins; (3) steroids; and (4) fatty acid derivatives (Table 30-2). The first category, the amines, includes norepinephrine and epinephrine, which are derived from a single amino acid (*i.e.*, tyrosine), and the thyroid hormones, which are derived from two iodinated tyrosine amino acid residues. The second category, the peptides, polypeptides, glycoproteins, and proteins, can be as small as thyrotropin-releasing hormone (TRH), which contains three amino acids, and as large and complex as growth hormone (GH) and follicle-stimulating hormone (FSH), which have approximately 200 amino acids. Glycoproteins are large peptide hormones associated with a carbohydrate (*e.g.*, FSH). The third category comprises the steroid hormones, which are derivatives of cholesterol. The fourth category, the fatty acid derivatives, includes the eicosanoids and retinoids.

Synthesis and Transport

The mechanisms for hormone synthesis vary with hormone structure. Protein and peptide hormones are synthesized and stored in granules or vesicles in the cytoplasm of the cell until secretion is required. The lipid-soluble steroid hormones are released as they are synthesized.

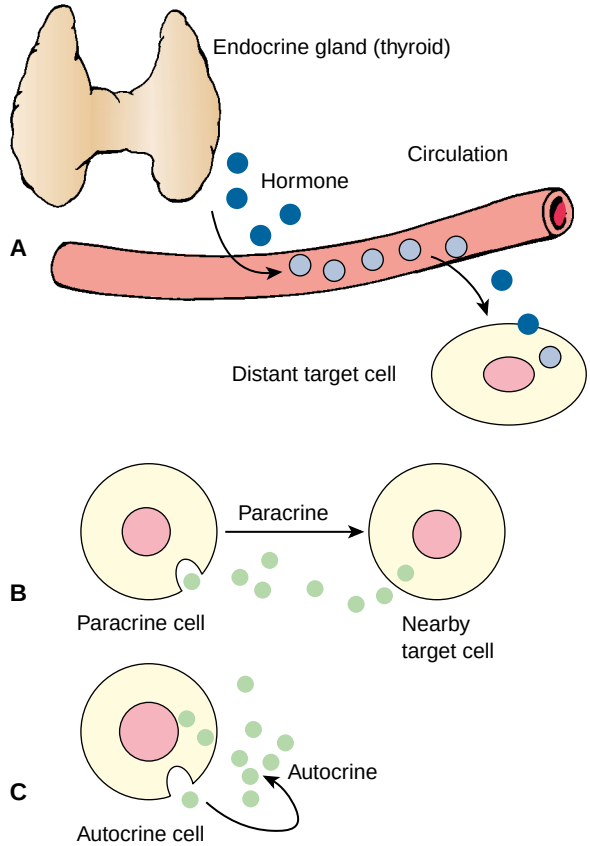
Protein and peptide hormones are synthesized in the rough endoplasmic reticulum in a manner similar to the synthesis of other proteins (see Chapter 1). The appropriate amino acid sequence is dictated by messenger RNAs from the nucleus. Usually, synthesis involves the production of a precursor hormone, which is modified by the addition of peptides or sugar units. These precursor hormones often contain extra peptide units that ensure proper folding of the molecule and insertion of essential linkages. If extra amino acids are present, as in insulin, the precursor hormone is called a prohormone. After synthesis and sequestration in the endoplasmic reticulum, the protein and peptide hormones move into the Golgi complex, where they are packaged in granules or vesicles. It is in the Golgi complex that prohormones are converted into hormones.

TABLE 30-1 Major Action and Source of Selected Hormones

Source	Hormone	Major Action
Hypothalamus	Releasing and inhibiting hormones Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TRH) Growth hormone-releasing hormone (GHRH) Gonadotropin-releasing hormone (GnRH)	Controls the release of pituitary hormones
Anterior pituitary	Growth hormone (GH)	Stimulates growth of bone and muscle, promotes protein synthesis and fat metabolism, decreases carbohydrate metabolism
	Adrenocorticotropic hormone (ACTH)	Stimulates synthesis and secretion of adrenal cortical hormones
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormone
	Follicle-stimulating hormone (FSH)	Female: stimulates growth of ovarian follicle, ovulation Male: stimulates sperm production
	Luteinizing hormone (LH)	Female: stimulates development of corpus luteum, release of oocyte, production of estrogen and progesterone Male: stimulates secretion of testosterone, development of interstitial tissue of testes
Posterior pituitary	Antidiuretic hormone (ADH)	Increases water reabsorption by kidney
	Oxytocin	Stimulates contraction of pregnant uterus, milk ejection from breasts after childbirth
Adrenal cortex	Mineralocorticosteroids, mainly aldosterone	Increases sodium absorption, potassium loss by kidney
	Glucocorticoids, mainly cortisol	Affects metabolism of all nutrients; regulates blood glucose levels, affects growth, has anti-inflammatory action, and decreases effects of stress
	Adrenal androgens, mainly dehydroepiandrosterone (DHEA) and androstenedione	Have minimal intrinsic androgenic activity; they are converted to testosterone and dihydrotestosterone in the periphery
Adrenal medulla	Epinephrine Norepinephrine	Serve as neurotransmitters for the sympathetic nervous system
Thyroid (follicular cells)	Thyroid hormones: triiodothyronine (T_3), thyroxine (T_4)	Increase the metabolic rate; increase protein and bone turnover; increase responsiveness to catecholamines; necessary for fetal and infant growth and development
Thyroid C cells	Calcitonin	Lowers blood calcium and phosphate levels
Parathyroid glands	Parathyroid hormone	Regulates serum calcium
Pancreatic islet cells	Insulin	Lowers blood glucose by facilitating glucose transport across cell membranes of muscle, liver, and adipose tissue
	Glucagon	Increases blood glucose concentration by stimulation of glycogenolysis and glyconeogenesis
	Somatostatin	Delays intestinal absorption of glucose
Kidney	1,25-Dihydroxyvitamin D	Stimulates calcium absorption from the intestine
Ovaries	Estrogen	Affects development of female sex organs and secondary sex characteristics
	Progesterone	Influences menstrual cycle; stimulates growth of uterine wall; maintains pregnancy
Testes	Androgens, mainly testosterone	Affect development of male sex organs and secondary sex characteristics; aid in sperm production

Steroid hormones are synthesized in the smooth endoplasmic reticulum, and steroid-secreting cells can be identified by their large amounts of smooth endoplasmic reticulum. Certain steroids serve as precursors for the production of other hormones. For example, in the adrenal cortex, progesterone and other steroid intermediates are enzymatically converted into aldosterone, cortisol, or androgens (see Chapter 31).

Hormones that are released into the bloodstream circulate as either free, unbound molecules or as hormones attached to transport carriers (Fig. 30-2). Peptide hormones and protein hormones usually circulate unbound in the blood. Steroid hormones and thyroid hormone are carried by specific carrier proteins synthesized in the liver. The extent of carrier binding influences the rate at which hormones leave the blood and enter the cells. The half-life of a hormone—the time it takes for the body to reduce the concentration of the hormone by one half—is positively correlated with its percentage of protein binding. Thyroxine, which is more than 99% protein bound, has a half-life of 6 days. Aldosterone, which is only 15% bound, has a half-life of only 25 minutes. Drugs that compete with a hormone for binding with transport carrier molecules increase hormone action by increasing the availability of the active unbound hormone. For example, aspirin competes with thyroid hormone for binding to transport proteins; when the

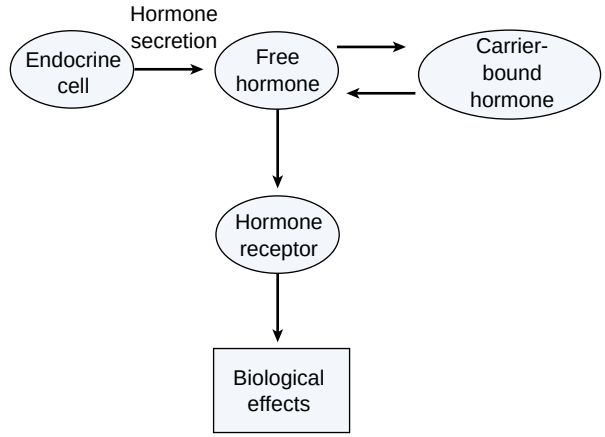


■ **FIGURE 30-1** ■ Examples of endocrine (**A**), paracrine (**B**), and autocrine (**C**) secretions.

drug is administered to persons with excessive levels of circulating thyroid hormone, such as during thyroid crisis, serious effects may occur.

Metabolism and Elimination

Metabolism of hormones and their precursors can generate more or less active products or it can degrade them to inactive forms. In some cases, hormones are eliminated in the intact



■ **FIGURE 30-2** ■ Relationship of free and carrier-bound hormone.

form. Hormones secreted by endocrine cells must be inactivated continuously to prevent their accumulation. Intracellular and extracellular mechanisms participate in the termination of hormone function. Some hormones are enzymatically inactivated at receptor sites where they exert their action. The catecholamines, which have a very short half-life, are degraded by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). Because of their short half-life, their production is measured by some of their metabolites. In general, peptide hormones also have a short life span in the circulation. Their major mechanism of degradation is through binding to cell surface receptors, with subsequent uptake and degradation by enzymes in the cell membrane or inside the cell. Peptide hormones have a short life span and are inactivated by enzymes that split peptide bonds. Steroid hormones are bound to protein carriers for transport and are inactive in the bound state. Their activity depends on the availability of transport carriers. Unbound adrenal and gonadal steroid hormones are conjugated in the liver, which renders them inactive, and then excreted in the bile or urine. Thyroid hormones also are transported by carrier molecules. The free hormone is rendered inactive by the removal of amino acids (*i.e.*, deamination) in the tissues, and the hormone is conjugated in the liver and eliminated in the bile.

TABLE 30-2 Classes of Hormones Based on Structure

Amines and Amino Acids	Peptides, Polypeptides, and Proteins	Steroids	Fatty Acid Compounds
Dopamine	Corticotropin-releasing hormone (CRH)	Aldosterone	Eicosanoids
Epinephrine	Growth hormone–releasing hormone (GHRH)	Glucocorticoids	Retinoids
Norepinephrine	Thyrotropin-releasing hormone (TRH)	Estrogens	
Thyroid hormone	Adrenocorticotropic hormone (ACTH)	Testosterone	
	Follicle-stimulating hormone (FSH)	Progesterone	
	Luteinizing hormone (LH)	Androstenedione	
	Thyroid-stimulating hormone (TSH)	1,25-Dihydroxyvitamin D	
	Growth hormone (GH)	Dihydrotestosterone (DHT)	
	Antidiuretic hormone (ADH)	Dehydroepiandrosterone (DHEA)	
	Oxytocin		
	Insulin		
	Glucagon		
	Somatostatin		
	Calcitonin		
	Parathyroid hormone		

Mechanisms of Action

Hormones produce their effects through interaction with high-affinity receptors, which in turn are linked to one or more effector systems within the cell. These mechanisms involve many of the cell's metabolic activities, ranging from ion transport at the cell surface to stimulation of nuclear transcription of complex molecules. The rate at which hormones react depends on their mechanism of action. The neurotransmitters, which control the opening of ion channels, have a reaction time of milliseconds. Thyroid hormone, which functions in the control of cell metabolism and synthesis of intracellular signaling molecules, requires days for its full effect to occur.

Receptors. Hormones exert their action by binding to high-affinity receptors located either on the surface or inside the target cells. The function of these receptors is to recognize a specific hormone and translate the hormonal signal into a cellular response. The structure of these receptors varies in a manner that allows target cells to respond to one hormone and not to others. For example, receptors in the thyroid are specific for thyroid-stimulating hormone, and receptors on the gonads respond to the gonadotropic hormones.

The response of a target cell to a hormone varies with the *number* of receptors present and with the *affinity* of these receptors for hormone binding. A variety of factors influence the number of receptors that are present on target cells and their affinity for hormone binding.

There are approximately 2000 to 100,000 hormone receptor molecules per cell. The number of hormone receptors on a cell may be altered for any of several reasons. Antibodies may destroy or block the receptor proteins. Increased or decreased hormone levels often induce changes in the activity of the genes that regulator receptor synthesis. For example, decreased hormone levels often produce an increase in receptor numbers by means of a process called *up-regulation*; this increases the sensitivity of the body to existing hormone levels. Likewise, sustained levels of excess hormone often bring about a decrease in receptor numbers by *down-regulation*, producing a decrease in hormone sensitivity. In some instances, the reverse effect occurs, and an increase in hormone levels appears to recruit its own receptors, thereby increasing the sensitivity of the cell to the hormone. The process of up-regulation and down-regulation of receptors is regulated largely by inducing or repressing the transcription of receptor genes.

The affinity of receptors for binding hormones also is affected by a number of conditions. For example, the pH of the body fluids plays an important role in the affinity of insulin receptors. In ketoacidosis, a lower pH reduces insulin binding.

Some hormone receptors are located on the surface of the cell and act through second messenger mechanisms, and others are located within the cell, where they modulate the synthesis of enzymes, transport proteins, or structural proteins. The receptors for thyroid hormones, which are found in the nucleus, are thought to be directly associated with controlling the activity of genes located on one or more of the chromosomes. Chart 30-1 lists hormones that act through the two types of receptors.

Surface Receptors. Because of their low solubility in the lipid layer of cell membranes, peptide hormones and catecholamines cannot readily cross the cell membrane. Instead, these hormones interact with surface receptors in a manner that incites the generation of an intracellular signal or message. The intracellular signal system is termed the *second messenger*, and the hormone is considered to be the first messenger (Fig. 30-3). For example, the first messenger glucagon binds to surface receptors on liver cells to incite glycogen breakdown by way of the second messenger system.

The most widely distributed second messenger is cyclic adenosine monophosphate (cAMP). cAMP is formed from

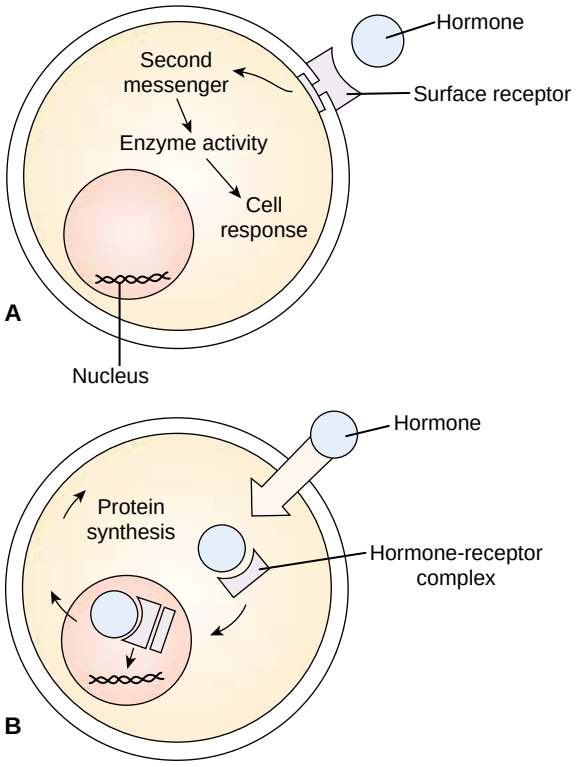
CHART 30-1 Hormone–Receptor Interactions

Surface (Second Messenger) Receptors

Glucagon
Insulin
Epinephrine
Parathyroid hormone
Thyroid-stimulating hormone (TSH)
Adrenocorticotropic hormone (ACTH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Antidiuretic hormone (ADH)
Secretin

Intracellular Interactions

Estrogens
Testosterone
Progesterone
Adrenal cortical hormones
Thyroid hormones



■ **FIGURE 30-3** ■ The two types of hormone–receptor interactions: the surface receptor **(A)** and the intracellular receptor **(B)**.

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cellular adenosine triphosphate (ATP) by the enzyme adenylate cyclase, a membrane-bound enzyme that is located on the inner aspect of the cell membrane. Adenylate cyclase is functionally coupled to various cell surface receptors by the regulatory actions of G proteins (see Chapter 1 and Fig. 1-12). A second messenger similar to cAMP is cyclic GMP, derived from guanine triphosphate (GTP). As a result of binding to specific cell receptors, many peptide hormones incite a series of enzymatic reactions that produce an almost immediate increase in cAMP. Some hormones act to decrease cAMP levels and have an opposite effect.

In some cells, the binding of hormones or neurotransmitters to surface receptors acts directly, rather than through a second messenger, to open ion channels in the cell membrane. The influx of ions serves as an intracellular signal to convey the hormonal message to the cell interior. In many instances, the activation of hormone receptors results in the opening of calcium channels. The increasing cytoplasmic concentration of calcium may result in direct activation of calcium-dependent enzymes or calcium-calmodulin complexes with their attendant effects.

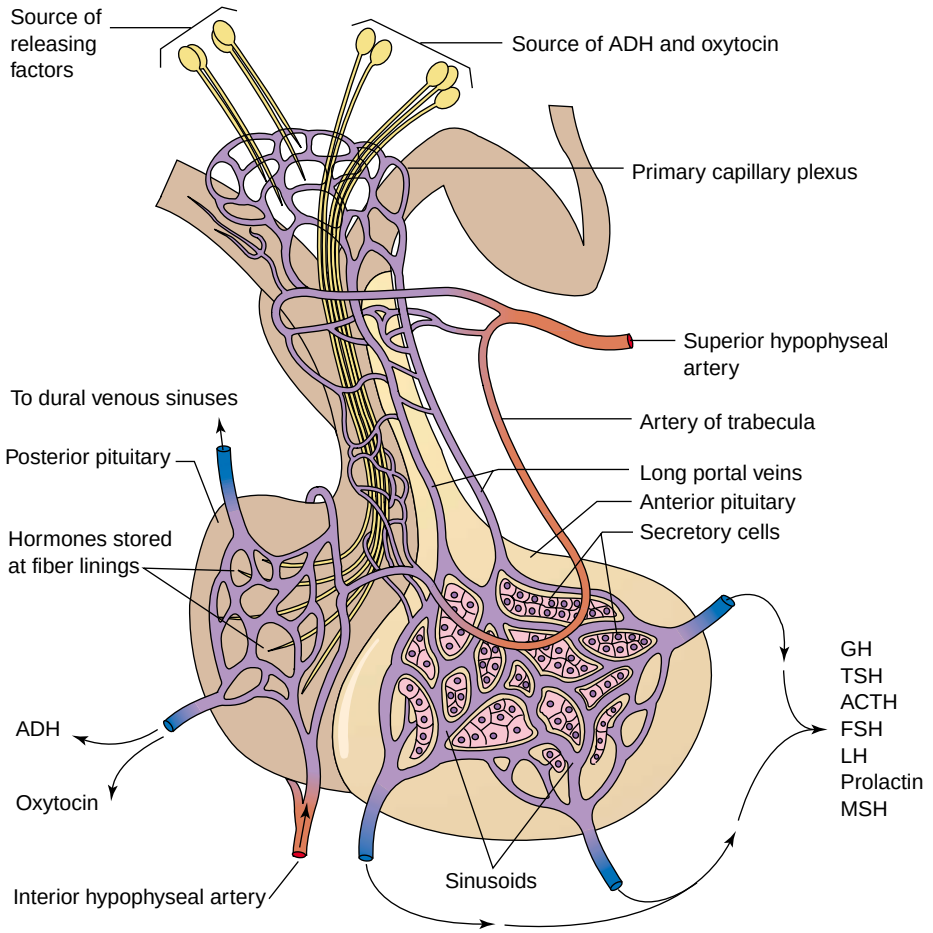
Intracellular Receptors. A second type of receptor mechanism is involved in mediating the action of hormones such as the steroid and thyroid hormones (see Fig. 30-3). These hormones are lipid soluble and pass freely through the cell membrane. They then attach to intracellular receptors and form a hormone-receptor complex that travels to the cell nucleus. The hormone-messenger complex then activates or suppresses intracellular mechanisms such as gene activity, with subsequent production or inhibition of messenger RNA and protein synthesis.

Control of Hormone Levels

Hormone secretion varies widely during a 24-hour period. Some hormones, such as growth hormone (GH) and adrenocorticotropic hormone (ACTH), have diurnal fluctuations that vary with the sleep-wake cycle. Others, such as the female sex hormones, are secreted in a complicated cyclic manner. The levels of hormones such as insulin and antidiuretic hormone (ADH) are regulated by feedback mechanisms that monitor substances such as glucose (insulin) and water (ADH) in the body. The levels of many of the hormones are regulated by feedback mechanisms that involve the hypothalamic-pituitary-target cell system.

Hypothalamic-Pituitary Regulation

The hypothalamus and pituitary (*i.e.*, hypophysis) form a unit that exerts control over many functions of several endocrine glands as well as a wide range of other physiologic functions. These two structures are connected by blood flow in the hypophyseal portal system, which begins in the hypothalamus and drains into the anterior pituitary gland, and by the nerve axons that connect the supraoptic and paraventricular nuclei of the hypothalamus with the posterior pituitary gland (Fig. 30-4).

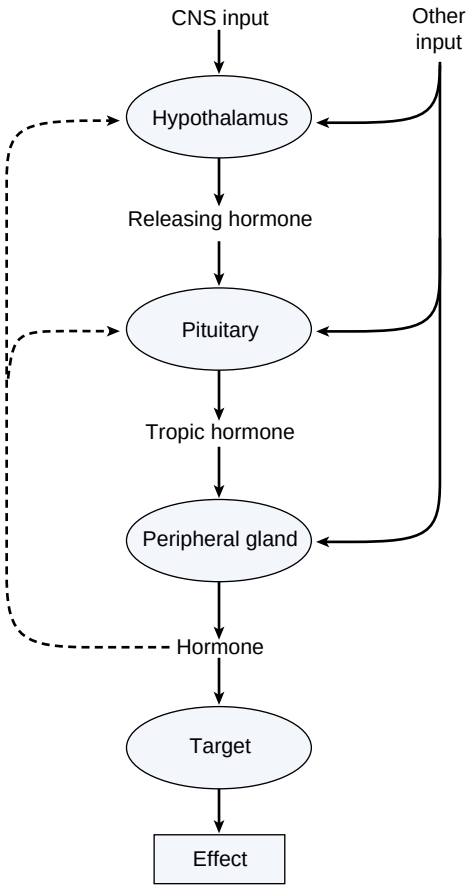


■ **FIGURE 30-4** ■ The hypothalamus and the anterior and posterior pituitary. The hypothalamic releasing or inhibiting hormones are transported to the anterior pituitary by way of the portal vessels. ADH and oxytocin are produced by nerve cells in the supraoptic and paraventricular nuclei of the hypothalamus and then transported through the nerve axon to the posterior pituitary, where they are released into the circulation.

The pituitary is enclosed in the bony sella turcica ("Turkish saddle") and is bridged by the diaphragma sellae. Embryologically, the anterior pituitary gland developed from glandular tissue and the posterior pituitary developed from neural tissue.

Hypothalamic Hormones. The synthesis and release of anterior pituitary hormones are largely regulated by the action of releasing or inhibiting hormones from the hypothalamus, which is the coordinating center of the brain for endocrine, behavioral, and autonomic nervous system function. It is at the level of the hypothalamus that emotion, pain, body temperature, and other neural input are communicated to the endocrine system (Fig. 30-5). The posterior pituitary hormones, ADH and oxytocin, are synthesized in the cell bodies of neurons in the hypothalamus that have axons that travel to the posterior pituitary. The release and function of ADH are discussed in Chapter 31.

The hypothalamic hormones that regulate the secretion of anterior pituitary hormones include GH-releasing hormone (GHRH), somatostatin, dopamine, thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and gonadotropin-releasing hormone (GnRH). With the exception of GH and prolactin, most of the pituitary hormones are regulated by hypothalamic stimulatory hormones. GH secretion is stimulated by GHRH; thyroid-stimulating hormone (TSH) by TRH; ACTH by CRH; and luteinizing hormone (LH) and FSH by GnRH. Somatostatin functions as an inhibitory hormone for GH and TSH. Prolactin secretion is inhibited by dopamine; thus, persons receiving antipsychotic drugs that block dopamine often have increased prolactin levels.



■ **FIGURE 30-5** ■ Hypothalamic-pituitary control of hormone levels. The *dashed* line represents feedback control.

The activity of the hypothalamus is regulated by both hormonally mediated signals (*e.g.*, negative feedback signals) and by neuronal input from a number of sources. Neuronal signals are mediated by neurotransmitters such as acetylcholine, dopamine, norepinephrine, serotonin, γ-aminobutyric acid, and opioids. Cytokines that are involved in immune and inflammatory responses, such as the interleukins, also are involved in the regulation of hypothalamic function. This is particularly true of the hormones involved in the hypothalamic-pituitary-adrenal axis. Thus, the hypothalamus can be viewed as a bridge by which signals from multiple systems are relayed to the pituitary gland.

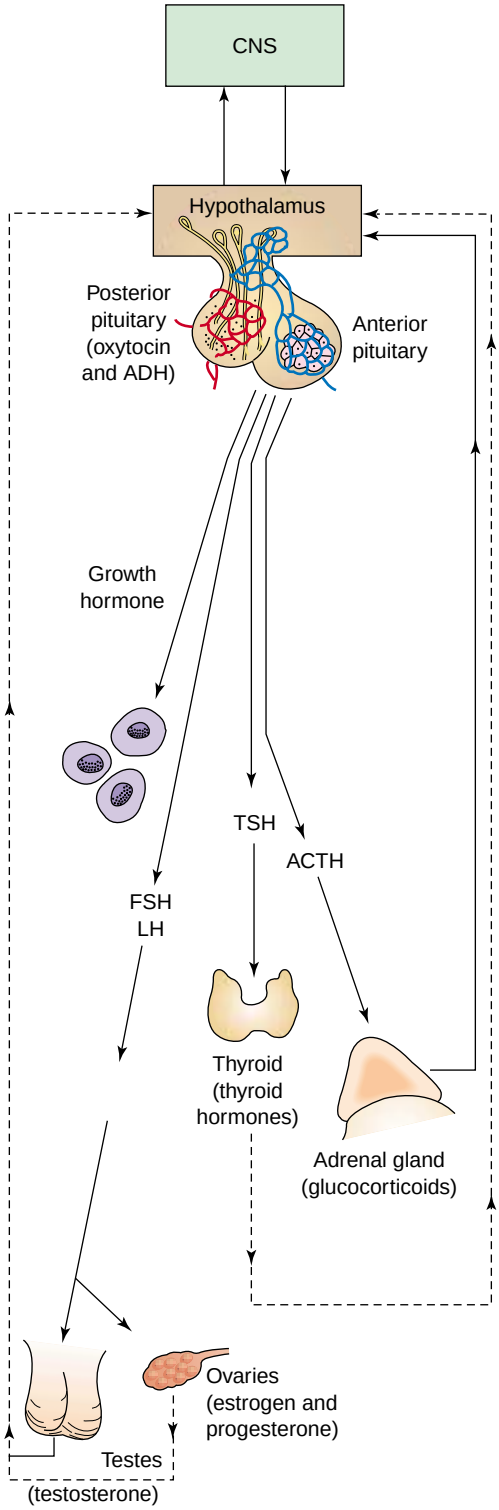
Pituitary Hormones. The pituitary gland has been called the master gland because its hormones control the functions of many target glands and cells. Hormones produced by the anterior pituitary control body growth and metabolism (GH), function of the thyroid gland (TSH), glucocorticoid hormone levels (ACTH), function of the gonads (FSH and LH), and breast growth and milk production (prolactin). Melanocyte-stimulating hormone, which is involved in the control of pigmentation of the skin, is produced by the pars intermedia of the pituitary gland. The functions of many of these hormones are discussed in other parts of this book (*e.g.*, thyroid hormone, GH, and the corticosteroids in Chapter 31, the sex hormones in Chapters 33 and 34, and ADH from the posterior pituitary in Chapter 6).

Feedback Regulation

The level of many of the hormones in the body is regulated by negative feedback mechanisms. The function of this type of system is similar to that of the thermostat in a heating system. In the endocrine system, sensors detect a change in the hormone level and adjust hormone secretion so that body levels are maintained within an appropriate range. When the sensors detect a decrease in hormone levels, they initiate changes that cause an increase in hormone production; when hormone levels rise above the set point of the system, the sensors cause hormone production and release to decrease. For example, an increase in thyroid hormone is detected by sensors in the hypothalamus or anterior pituitary gland, and this causes a reduction in the secretion of TSH, with a subsequent decrease in the output of thyroid hormone from the thyroid gland. The feedback loops for the hypothalamic-pituitary feedback mechanisms are illustrated in Figures 30-5 and 30-6.

Exogenous forms of hormones (given as drug preparations) can influence the normal feedback control of hormone production and release. One of the most common examples of this influence occurs with the administration of the corticosteroid hormones, which causes suppression of the hypothalamic-pituitary-target cell system that regulates the production of these hormones.

Although the levels of most hormones are regulated by negative feedback mechanisms, a small number are under positive feedback control, in which increasing levels of a hormone cause another gland to release a hormone that is stimulating to the first. However, there must be a mechanism for shutting off the release of the first hormone, or its production would



■ **FIGURE 30-6** ■ Control of hormone production by hypothalamic-pituitary–target cell feedback mechanism. Hormone levels from the target glands regulate the release of hormones from the anterior pituitary by means of a negative feedback system. The *dashed line* represents feedback control.

continue unabated. An example of such a system is that of the female ovarian hormone estradiol. Increased estradiol production during the follicular stage of the menstrual cycle causes increased gonadotropin (FSH) production by the anterior pituitary gland. This stimulates further increases in estradiol levels until the demise of the follicle, which is the source of estradiol, results in a decrease in gonadotropin levels.

In addition to positive and negative feedback mechanisms that monitor changes in hormone levels, some hormones are regulated by the level of the substance they regulate. For example, insulin levels normally are regulated in response to blood glucose levels and those of aldosterone in response to body levels of sodium and potassium. Other factors such as stress, environmental temperature, and nutritional status can alter feedback regulation of hormone levels.

Diagnostic Tests

Several techniques are available for assessing endocrine function and hormone levels. One technique measures the effect of a hormone on body function. For example, measurement of blood glucose reflects insulin levels and is an indirect method of assessing insulin availability. Another method is to measure hormone levels.

Blood Tests

Hormones circulating in the plasma were first detected by bioassays using the intact animal or a portion of tissue from the animal. At one time, female rats or male frogs were used to test women's urine for the presence of human chorionic gonadotropin, which is produced by the placenta during pregnancy. Unfortunately, most bioassays lack the precision, sensitivity, and specificity to measure low concentrations of hormones in plasma, and they are inconvenient to perform.

Blood hormone levels provide information about hormone levels at a specific time. For example, blood insulin levels can be measured along with blood glucose after administration of a challenge dose of glucose to measure the time course of change in blood insulin levels.

Real progress in measuring plasma hormone levels came more than 40 years ago with the use of competitive binding and the development of radioimmunoassay (RIA) methods. This method uses a radiolabeled form of the hormone and a hormone antibody that has been prepared by injecting an appropriate animal with a purified form of the hormone. The unlabeled hormone in the sample being tested competes with the radiolabeled hormone for attachment to the binding sites of the antibody. Measurement of the radiolabeled hormone-antibody complex then provides a means of arriving at a measure of the hormone level in the sample. Because hormone binding is competitive, the amount of radiolabeled hormone-antibody complex that is formed decreases as the amount of unlabeled hormone in the sample is increased. Newer techniques of RIA have been introduced, including the immunoradiometric assay (IRMA). IRMA uses two antibodies instead of one. These two antibodies are directed against two different parts of the molecule, so IRMA assays are more specific. RIA has several disadvantages, including limited shelf-life of the radiolabeled hormone and the cost for the disposal of radioactive waste.

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Nonradiolabeled methods have been developed in which the antigen of the hormone being measured is linked to an enzyme-activated label (*e.g.*, fluorescent label, chemiluminescent label) or latex particles that can be agglutinated with an antigen and measured. The enzyme-linked immunosorbent assays (ELISA) use antibody-coated plates and an enzyme-labeled reporter antibody. Binding of the hormone to the enzyme-labeled reporter antibody produces a colored reaction that can be measured using a spectrophotometer.

Urine Tests

Measurements of urinary hormone or hormone metabolite excretion often are done on a 24-hour urine sample and provide a better measure of hormone levels during that period than hormones measured in an isolated blood sample. The advantages of a urine test include the relative ease of obtaining urine samples and the fact that blood sampling is not required. The disadvantage is that reliably timed urine collections often are difficult to obtain. For example, a person may be unable to urinate at specific timed intervals, and urine samples may be accidentally discarded or inaccurately preserved. Because many urine tests involve the measure of a hormone metabolite, rather than the hormone itself, drugs or disease states that alter hormone metabolism may interfere with the test result. Some urinary hormone metabolite measurements include hormones from more than one source and are of little value in measuring hormone secretion from a specific source. For example, urinary 17-ketosteroids are a measure of both adrenal and gonadal androgens.

Stimulation and Suppression Tests

Stimulation tests are used when hypofunction of an endocrine organ is suspected. A tropic or stimulating hormone can be administered to test the capacity of an endocrine organ to increase hormone production. The capacity of the target gland to respond is measured by an increase in the appropriate hormone. For example, the function of the hypothalamic-pituitary-thyroid system can be evaluated through stimulation tests using TRH and measuring TSH response. Failure to effect an increase in TSH after a TRH stimulation test suggests inadequate production of TSH by the pituitary.

Suppression tests are used to determine if negative feedback control mechanisms are intact. For example, a glucocorticoid hormone can be administered to persons suspected of having hypercortisolism to assess the capacity to inhibit CRH.

Genetic Tests

Deoxyribonucleic acid (DNA) analysis is being increasingly used for the identification of affected family members in a kindred harboring a known mutation (*e.g.*, looking for the RET proto-oncogene in certain multiple endocrine neoplasia syndromes).

Imaging

Imaging studies are gaining increasing importance in the diagnosis and follow-up of endocrine diseases. Magnetic resonance imaging (MRI) and computed tomography scans are especially useful for imaging endocrine glands and endocrine tumors. Nuclear scanning also is widely used for assessing thyroid, parathyroid, and adrenal disorders. Ultrasound scanning is recommended for managing thyroid nodules. Positron emission tomography scanning is being used more widely for parathyroid detection after failed parathyroid surgery for hyperparathyroidism.

In summary, the endocrine system acts as a communication system that uses chemical messengers, or hormones, for the transmission of information from cell to cell and from organ to organ. Hormones act by binding to receptors that are specific for the different types of hormones. Many of the endocrine glands are under the regulatory control of other parts of the endocrine system. The hypothalamus and the pituitary gland form a complex integrative network that joins the nervous system and the endocrine system; this central network controls the output from many of the other glands in the body.

Endocrine function can be assessed directly by measuring hormone levels or indirectly by assessing the effects that a hormone has on the body (*e.g.*, assessment of insulin function through blood glucose). Imaging techniques are increasingly used to visualize endocrine structures, and genetic techniques are used to determine the presence of genes that contribute to the development of endocrine disorders.

REVIEW QUESTIONS

- Characterize a hormone.
- State a difference between the synthesis of protein hormones and that of steroid hormones.
- Describe mechanisms of hormone transport and inactivation.
- State the function of a hormone receptor, and state the difference between cell surface hormone receptors and intracellular hormone receptors.
- Describe the role of the hypothalamus in regulating pituitary control of endocrine function.
- State the major difference between positive and negative feedback control mechanisms.
- Describe methods used in the diagnosis of endocrine disorders.

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