THE ENDOCRINE SYSTEM AND HORMONE FUNCTION: AN OVERVIEW

Compared to other organs of the body, the organs of the endocrine system are small and unimpressive. Indeed, to collect 1 kg (2.2 lbs) of hormone-producing tissue, you would need to collect all of the endocrine tissue from eight or nine adults! In addition, the anatomical continuity typical of most organ systems does not exist between the endocrine organs. Instead, endocrine organs are widely scattered about the body (Figure 17.1).

As explained in Chapter 4, there are two kinds of glands: endocrine and exocrine. Exocrine glands have ducts through which their nonhormonal products are routed to a membrane surface. In contrast, endocrine glands, also called ductless glands, lack ducts. They release hormones into the blood or lymph (endo = within; crine = to secrete), and they typically have a rich vascular and lymphatic drainage. Most hormone-producing cells are arranged in cords and branching networks in a manner that maximizes the contact between them and the capillaries that receive their secretions. The endocrine glands of the body include the pituitary, thyroid, parathyroid, adrenal, pineal, and thymus glands. In addition, several organs of the body contain discrete areas of endocrine tissue and produce hormones as well as exocrine products. Such organs, which include the pancreas and gonads (the ovaries and testes), are also major endocrine glands. The hypothalamus also falls into this latter category. Along with its neural functions, it produces and releases hormones, so we can consider the hypothalamus a neuroendocrine organ.

Besides the major endocrine organs, various other tissues and organs produce hormones. For example, pockets of hormone-producing cells are found in the walls of the small intestine, stomach, kidneys, and heart—organs whose chief functions have little to do with hormone production. These other endocrine structures are described on page 576.

Additionally, certain tumor cells, such as those of some cancers of the lung or pancreas, synthesize hormones identical to those made in normal endocrine glands, but in an excessive and uncontrolled fashion. •

Hormones have widespread and diverse effects. The major processes controlled and integrated by these “mighty molecules” are reproduction; growth and development; mobilization of body defenses against stressors; maintenance of electrolyte, water, and nutrient balance of the blood; and regulation of cellular metabolism and energy balance. As you can

FIGURE 17.1
Location of the major endocrine organs of the body.
see, the endocrine system orchestrates processes that go on for relatively long periods and, in some instances, continuously.

**HORMONES**

**The Chemistry of Hormones**

Hormones may be defined as chemical substances, secreted by cells into the extracellular fluids, that regulate the metabolic function of other cells in the body. Although a large variety of hormones are produced, nearly all of them can be classified chemically into one of two large groups of biochemical molecules: **amino acid–based hormones** and **steroids**.

Most hormones belong to the first group. Molecular size varies widely in this group—from the simple amino acid derivatives, which include the amines and thyroxine, to peptides (short chains of amino acids), to protein macromolecules (long polymers of amino acids). Hormones of the second group, the steroids, are synthesized from cholesterol. Of the hormones produced by the major endocrine organs, only the gonadal hormones and adrenocortical hormones are steroids.

If we also consider the **eicosanoids** (i-ko’sa-noyds), which include **leukotrienes** and **prostaglandins**, we must add a third chemical class. These **paracrines**, or local hormones, are biologically active lipids (made from arachidonic acid) released from nearly all cell membranes. Leukotrienes are signaling chemicals that mediate inflammation and some allergic reactions. Prostaglandins have multiple targets and myriad effects, ranging from raising blood pressure and increasing the expansive uterine contractions of birth (via stimulation of smooth muscle) to enhancing blood clotting and inflammation. Since the effects of eicosanoids are typically highly localized, they do not quite fit the definition of true circulating hormones, which influence distant targets. Hence, this class of hormonelike chemicals will not be considered further here.

**Hormone–Target Cell Specificity**

Although all major hormones circulate to virtually all tissues, a given hormone influences the activity of only certain tissue cells, referred to as its **target cells**. For a target cell to respond to a hormone, it must have specific protein **receptors** on its plasma membrane or in its interior, to which that hormone can bind. For example, receptors for adrenocorticotropic hormone (ACTH) are normally found only on certain cells of the adrenal cortex. By contrast, thyroxine is the principal hormonal stimulant of cellular metabolism, and nearly all body cells have thyroxine receptors. An analogy can be drawn between the endocrine gland–target cell response and a radio’s transmitter–receiver system. The endocrine gland is the “transmitter,” sending signals to the rest of the body, and the receptors on target cells are the “receivers.” Like a radio tuned to a single station, the receptors respond only to its particular signal, even though many other signals may be present at the same time. A radio receiver responds to the radio signal by producing sound; a hormone receptor responds to hormone binding by prompting the cell to perform, or “turn on,” some genetically determined “preprogrammed” function. Hence, hormones are molecular “triggers” rather than informational molecules.

Although hormone–receptor binding is the crucial first step, the extent of target cell activation by hormone–receptor interaction depends equally on three factors: (1) blood levels of the hormone, (2) the relative numbers of receptors for that hormone on or in the target cells, and (3) the **affinity** (strength) of the union between the hormone and the receptor. Changes in all three factors occur rapidly in response to various stimuli and changes within the body. As a rule, a large number of high-affinity receptors produces a pronounced hormonal effect, whereas a smaller number of low-affinity receptors results in reduced target cell response or outright endocrine dysfunction at the same blood hormone levels. Furthermore, receptors are dynamic structures. In some instances, the target cells form more receptors in response to increasingly higher levels of the specific hormones to which they respond, a phenomenon called **up-regulation**. But in other cases, prolonged exposure to high hormone concentrations desensitizes the target cells, so that they respond less vigorously to hormonal stimulation. This **down-regulation** is thought to involve loss of receptors and effectively prevents the target cells from overreacting to persistently high hormone levels. In addition, hormones may influence the number and affinity not only of their own receptors, but also of receptors responsive to other hormones. For example, progesterone induces a loss of estrogen receptors in the uterus, thus antagonizing estrogen's actions. Conversely, estrogen promotes production of more progesterone receptors in the same cells, enhancing their ability to respond to progesterone.

**Mechanisms of Hormone Action**

Hormones bring about their characteristic effects on target cells by altering cell activity; that is, by increasing or decreasing the rates of normal cellular processes. The precise response is dictated by the target cell type. For example, epinephrine binding to smooth muscle cells in blood vessel walls stimulates them to contract. Epinephrine binding to cells other than muscle cells may have a different effect, but it will not cause those noncontractile cells to shorten.

A hormonal stimulus typically produces one or more of the following changes:
1. Changes in plasma membrane permeability and/or electrical state (membrane potential) by opening or closing ion channels.

2. Synthesis of proteins or certain regulatory molecules (such as enzymes) within the cell.

3. Enzyme activation or deactivation.

4. Induction of secretory activity.

5. Stimulation of mitosis.

In general, there are two major mechanisms that harness hormone receptor binding to the specific intracellular machinery needed for hormone action. One involves the services of regulatory molecules called G proteins and one or more intracellular second messengers, which mediate the target cell's response to the hormone. The other involves direct gene (DNA) activation by the hormone itself.

**Second-Messenger Systems**

Because proteins and peptides cannot penetrate the plasma membranes of tissue cells, virtually all of the amino acid–based hormones exert their effects through intracellular **second messengers** generated by hormone binding to plasma membrane receptors. Of the second messengers, **cyclic AMP**, which also mediates the effects of certain neurotransmitters, is by far the best understood, so it will receive most of our attention.

Intracellular levels of cyclic AMP are determined by interaction of three plasma membrane components of the target cell (Figure 17.2a): (1) the hormone receptor, (2) the signal transducer (a G protein), and (3) the effector enzyme (adenylate cyclase). In this scheme, the hormone, functioning as the **first messenger**, binds to its receptor. The catalytic subunit of the **G protein** then acts as an intermediary to deliver the signal to **adenylate cyclase** to generate cyclic AMP from ATP. The energy for converting the first (hormonal) message into the second (cyclic AMP) is provided by hydrolyzing the high-energy compound **GTP**. (The G protein possesses GTPase activity and cleaves the terminal phosphate group off GTP in much the same way as ATPase enzymes hydrolyze ATP.)

Now that we know how cyclic AMP is generated, we can consider how this “messenger,” which is free to diffuse throughout the cell, mediates target cell responses to a hormone. Perhaps its best-known ability is that of initiating a cascade of chemical reactions in which one or more different enzymes, called **protein kinases**, are activated. A given cell may have several types of protein kinases, each of which has distinct substrates. The protein kinases **phosphorylate** (add a phosphate group to) different proteins, many of which are other enzymes. Since phosphorylation activates some of these proteins and inhibits others, a variety of reactions may occur in the same target cell at the same time. For example, a fat cell responds to epinephrine binding by breaking down glycogen and stored fat, reactions mediated by different enzymes.

This type of intracellular enzymatic cascade has a huge amplification effect because G proteins, once activated, detach from the receptor to “go about their business”; each activated adenylate cyclase generates large numbers of cyclic AMP molecules; and a single kinase enzyme can catalyze literally hundreds of reactions. Hence, as the reaction cascades through one enzyme intermediate after another, the number of product molecules increases dramatically at each step. Theoretically, receptor binding of a single hormone molecule could generate millions of the final product molecules!

**FIGURE 17.2**

**Second-messenger mechanisms of protein-peptide hormones.** (a) Mechanisms that generate cyclic AMP by activation of adenylate cyclase are mediated by G proteins which are activated when the hormone binds to the external membrane receptors. The G proteins exhibit GTPase activity, which catalyzes energy release by hydrolysis of GTP. Cyclic AMP acts intracellularly to activate protein kinase enzymes that mediate the cell's responses to the hormone.
The sequence of biochemical reactions set into motion by cyclic AMP depends on the target cell type, the specific protein kinases it contains, and the hormone acting as first messenger. For example, in thyroid cells, cyclic AMP generated in response to the binding of thyroid-stimulating hormone promotes the synthesis of the thyroid hormone thyroxine; in bone and muscle cells, cyclic AMP generated in response to growth hormone binding activates anabolic reactions in which amino acids are built into tissue proteins. Note also that not all G proteins activate adenylyl cyclase; some inhibit it (see Figure 17.2a), thus reducing the cytoplasmic concentration of cyclic AMP. Such opposing effects permit a target cell to respond to even slight changes in levels of antagonistic hormones that influence its activity.

Since cyclic AMP is rapidly degraded by the intracellular enzyme phosphodiesterase, its action persists only briefly. Waile at first glance, this may appear to be a problem, it is quite the opposite. Because of the amplification effect just explained, most hormones need to be present for only short periods to promote the desired results. Continued hormone production prompts continued cellular activity; no extracellular controls are necessary to stop the activity.

Although cyclic AMP is the activating second messenger in some tissues for at least 10 of the amino acid–based hormones, some of the same hormones (e.g., epinephrine) act through a different second-messenger system in other tissues. In one such mechanism, hormone docking to the receptor activates a membrane-bound phospholipase enzyme that splits PIP$_2$ (phosphatidyl inositol biphosphate) into diacylglycerol and IP$_3$ (inositol triphosphate) (Figure 17.2b), and both of these molecules act as second messengers. Diacylglycerol activates specific protein kinases, whereas IP$_3$ triggers the release of Ca$^{2+}$ from the endoplasmic reticulum (ER) and other intracellular storage sites. The calcium ions then act as a third messenger, either by directly altering the activity of specific enzymes and plasma membrane ion (Ca$^{2+}$) channels or by binding to the intracellular regulatory protein calmodulin.

Hormones known to act on their target cells via cyclic AMP or the PIP mechanism are listed in Figure 17.2. Other hormones act on their target cells through different (and in some cases, unknown) mechanisms or messengers. For example, cyclic GMP (cyclic guanosine 3',5'-monophosphate) is a second messenger for atrial natriuretic factor, a hormone released by heart tissue. Insulin appears to work “solo” without a G protein intermediary or second messengers. Its receptor is a tyrosine kinase enzyme that is directly activated by insulin binding. In certain instances, any of the second messengers mentioned—and the hormone receptor itself—can cause changes in intracellular calcium ion levels.

**Direct Gene Activation**

Being lipid soluble, steroid hormones (and, strangely, thyroid hormone, a small iodinated amine) can diffuse easily into their target cells. Once inside, they bind to an intracellular receptor that is activated by the interaction. The activated hormone-receptor complex then translocates to the nuclear chromatin, where the hormone binds to a DNA-associated receptor protein specific for it. This interaction “turns on” a gene, that is, it prompts transcription of DNA to produce a messenger RNA (mRNA). The mRNA is then translated on the cytoplasmic ribosomes, producing specific protein molecules. These protein products include enzymes that promote the metabolic activities induced by that particular hormone and, in some
What is the crucial difference between the signaling mechanism depicted here and that shown in Figure 17.2?

**FIGURE 17.3**

Direct gene activation mechanism of steroid hormones. Lipid-soluble steroids diffuse through the plasma membrane of the target cell and bind to intracellular receptors, located in the nucleus (as shown) or cytoplasm. Once formed, the hormone-receptor complex binds to specific receptor proteins on the chromatin, initiating transcription of certain genes. The messenger RNA formed migrates into the cytoplasm, where it directs synthesis of specific proteins.

cases, synthesis of structural proteins or proteins that are exported by the target cell. The steroidal gene activation mechanism is depicted in Figure 17.3.

**Half-Life, Onset, and Duration of Hormone Activity**

Hormones are exceptionally potent chemicals, and they exert profound effects on their target organs at very low concentrations. The concentration of a hormone in blood at any time reflects (1) its rate of release, and (2) the speed of its inactivation and removal from the body. Some hormones are rapidly degraded by enzymes within their target cells, but most are removed from the blood by kidney and liver enzyme systems, and their breakdown products are quickly excreted from the body in urine or, to a lesser extent, in feces. As a result, the persistence of a hormone in the blood, referred to as its half-life, is usually brief—from a fraction of a minute to 30 minutes.

The time required for onset of hormone effects varies greatly. Some hormones provoke target organ responses almost immediately. Others, particularly the steroid hormones, may require hours to days before their effects are seen. Additionally, some hormones, such as testosterone secreted by the testes, are secreted in a relatively inactive (prohormone) form and must be activated in the target cells.

The duration of hormone action is limited, ranging from 20 minutes to several hours, depending on the hormone. Effects may disappear rapidly as blood levels drop, or they may persist for hours after very low levels have been reached. Because of these many variations, hormonal blood levels must be precisely and individually controlled to meet the continuously changing needs of the body.

**Control of Hormone Release**

The synthesis and release of most hormones are regulated by some type of negative feedback system (see Chapter 1, pp. 10–12). In such a system, hormone secretion is triggered by some internal or external stimulus, after which rising hormone levels (even while causing target organ effects) inhibit further hormone release. As a result, blood levels of many hormones vary only within a very narrow range.

**Endocrine Gland Stimuli**

The various endocrine glands of the body are stimulated to manufacture and release their hormones by three major types of stimuli: humoral (hu’mer-ul), neural, and hormonal.

**Humoral Stimuli.** Some endocrine glands secrete their hormones in direct response to changing blood levels of certain ions and nutrients. These stimuli are called humoral stimuli to distinguish them from hor-
1. Capillary blood contains low concentration of Ca\(^{2+}\), which stimulates...

2. ...secretion of parathyroid hormone (PTH)

3. The hypothalamus secretes hormones that...

(a) Humoral

(b) Neural

(c) Hormonal

**FIGURE 17.4**

**Endocrine gland stimuli: Three different mechanisms.**

(a) Humoral stimulus of endocrine gland activity. Low blood calcium levels trigger parathyroid hormone (PTH) release from the parathyroid glands. PTH causes blood calcium levels to rise by stimulating release of Ca\(^{2+}\) from bone.

(b) Neural stimulus of endocrine gland activity. The stimulation of adrenal medullary cells by sympathetic nervous system (SNS) fibers triggers the release of catecholamines (epinephrine and norepinephrine) to the blood.

(c) Hormonal stimulus of endocrine gland activity. In the example illustrated, hormones released by the hypothalamus stimulate the anterior pituitary gland to release hormones that stimulate other endocrine organs to secrete hormones. In this way, the hypothalamus regulates much of endocrine system activity.

Consequently, the stimulus for PTH secretion ends.

Neural stimuli, which are also blood-borne chemicals. The term *humoral* harks back to the ancient use of the term *humor* to refer to various body fluids (blood, bile, and others). This is the simplest of the endocrine control systems. For example, cells of the parathyroid glands directly monitor the concentration of calcium ions in blood and, when they detect a decline in the normal Ca\(^{2+}\) range, they respond by secreting parathyroid hormone (PTH). Since PTH acts by several routes to reverse that decline, blood Ca\(^{2+}\) levels soon rise, ending the initiative for PTH release (Figure 17.4a). Other hormones released in response to humoral stimuli include insulin, produced by the pancreas, and aldosterone, one of the adrenal cortex hormones.

**Neural Stimuli.** In a few cases, nerve fibers stimulate hormone release. The classic example is sympathetic nervous system stimulation of the adrenal medulla to release catecholamines (norepinephrine and epinephrine) during periods of stress (Figure 17.4b). In addition, oxytocin and antidiuretic hormone are released from the posterior pituitary in response to nerve impulses from hypothalamic neurons.

**Hormonal Stimuli.** Finally, many endocrine glands release their hormones in response to hormones produced by other endocrine organs. For example, release of most anterior pituitary hormones is regulated by releasing and inhibiting hormones produced by the hypothalamus, and many anterior pituitary hormones in turn stimulate other endocrine organs to release their hormones into the blood (Figure 17.4c). As the hormones produced by the final target glands increase in the blood, they inhibit the release of anterior pituitary hormones and thus their own release. This hypothalamic–pituitary–target endocrine organ feedback loop lies at the very core of the science of
endocrinology, and it will be considered many times in this chapter. Hormone release promoted by the hormonal mechanism tends to be rhythmic, with hormone blood levels rising and falling in a specific pattern.

While these three mechanisms typify most systems that control hormone release, they are by no means all-inclusive or mutually exclusive, and some endocrine organs respond to multiple stimuli.

**Nervous System Modulation**

Both “turn on” factors (hormonal, humoral, and neural stimuli) and “turn off” factors (feedback inhibition and others) may be modified or modulated by the activity of the nervous system. Without this added safeguard, endocrine system activity would be strictly mechanical, much like a household thermostat. A thermostat can maintain the house temperature at or around its set value, but it cannot sense that your grandmother visiting from Florida feels cold at that temperature and reset itself accordingly. You must make that adjustment. Similarly, the nervous system can, in certain cases, override normal endocrine controls as necessary to maintain homeostasis. For example, blood sugar levels are normally kept within a range of 80–120 mg glucose per 100 ml of blood by the action of insulin and several other hormones. However, when the body is under severe stress, blood sugar levels rise much higher because the hypothalamus and sympathetic nervous system centers are strongly activated. This ensures that body cells will have sufficient fuel for the more vigorous activity required of them during such periods.

Remember that the hypothalamus is an autonomic center concerned with homeostatic control of such body functions as water balance and temperature as well as an integrating center for biological rhythms and emotions. This helps explain how a single external stimulus, such as acute blood loss or severe physical trauma, can be followed by bodywide neuroendocrine adjustments.

**MAJOR ENDOCRINE ORGANS**

**The Pituitary Gland (Hypophysis)**

Securely seated in the sella turcica of the sphenoid bone, the tiny pituitary gland, or hypophysis (hi-pof'sis; “to grow under”), secretes at least nine major hormones. Usually said to be the size and shape of a pea, the pituitary gland is more accurately described as a pea on a stalk. Its stalk, the funnel-shaped infundibulum, connects it to the hypothalamus superiorly (Figure 17.5a). In humans, the pituitary gland has two major lobes, one neural tissue, the other glandular. The posterior lobe, or neurohypophysis (nu'tro-hi-pof'sis), is composed largely of neuroglia and nerve fibers. It releases neurohormones that it receives ready-made from the hypothalamus. Thus, the neurohypophysis is a hormone-storage area and not a true endocrine gland in the precise sense. The anterior lobe, or adenohypophysis (ad'ë-no-hi-pof'sis), is composed of glandular tissue (aden = gland), and it manufactures and releases a number of hormones (Table 17.1 on pp. 556–557).

Arterial blood is delivered to the pituitary via two branches of the internal carotid artery. The superior hypophysial artery supplies the anterior pituitary and the infundibulum; the inferior hypophysial artery supplies the posterior lobe. The veins leaving the pituitary drain into the cavernous sinus (p. 683) and other nearby dural sinuses.

**Pituitary-Hypothalamic Relationships**

The contrasting histology of the two pituitary lobes reflects the dual origin of this tiny gland. The neurohypophysis is actually part of the brain. It derives from a downgrowth of hypothalamic (nervous) tissue, and maintains its connection with the hypothalamus via a nerve bundle called the hypothalamic-hypophysial tract (Figure 17.5), which runs through the infundibulum. This tract arises from neurons in the supraoptic and paraventricular nuclei of the hypothalamus (see Figure 12.14c, p. 394). These neurosecretory cells synthesize two neurohormones, which are transported along their length to their axon terminals in the neurohypophysis. Oxytocin is made by the paraventricular neurons and antidiuretic hormone (ADH) is synthesized by the supraoptic neurons. When these hypothalamic neurons fire, they release the stored hormones into a capillary bed in the posterior pituitary for distribution throughout the body.

In contrast, the anterior lobe originates from a superior outpocketing of the oral mucosa (Rathke’s pouch) and is formed from the epithelial tissue. After touching the posterior lobe, the adenohypophysis loses its connection with the oral mucosa and adheres to the neurohypophysis to form the composite organ. There is no direct neural connection between the adenohypophysis and hypothalamus, but there is a vascular connection. Specifically, the primary capillary plexus in the infundibulum communicates inferiorly via the small hypophysial portal veins with a secondary capillary plexus in the adenohypophysis. The primary and secondary capillary plexuses and the intervening hypophysal portal veins make up the hypophysal portal system (Figure 17.5). Via this portal system, releasing and inhibiting hormones secreted by neurons in the ventral hypothalamus circulate directly to the adenohypophysis, where they regulate the secretory activity of its hormone-

*A portal system is a somewhat unique arrangement of blood vessels in which a capillary bed feeds into veins which, in turn, feed into another capillary bed.
producing cells. All of these hypothalamic regulatory hormones are amino acid–based, but they vary widely in size from amines to polypeptides.

**Adenohypophyseal Hormones**

The adenohypophysis has traditionally been called the “master endocrine gland” because of its numerous hormonal products, many of which regulate the activity of other endocrine glands. Although the adenohypophysis has been dethroned by the hypothalamus, which is now known to control anterior pituitary activity, six distinct adenohypophyseal hormones with specific physiological actions in humans are known. All of these are proteins. In addition, a large molecule with the tongue-twisting name pro-opiomelanocortin (pro"op-e-o-mah-lan'o-kor"tin) (POMC) has been isolated from the anterior pituitary. POMC is a prohormone, that is, a large precursor molecule from which other active molecules are split by enzymatic cleavage. POMC is the source of adrenocorticotropic hormone, two natural opiates (an enkephalin and beta-endorphin, described in Chapter 11), and melanocyte-stimulating hormone (MSH). MSH stimulates melanocytes to increase their synthesis of melanin pigment, but in humans its plasma levels are insignificant and it is probably more important as a CNS neurotransmitter (neuropeptide) than a hormone. Additionally, MSH release is stimulated by dopamine-releasing hypothalamic neurons rather than releasing hormones.

When the adenohypophysis receives an appropriate chemical stimulus from the hypothalamus, one or more of its hormones is released by certain of its cells. Although many different releasing and inhibiting hormones pass from the hypothalamus to the anterior lobe, the individual anterior pituitary target cells distinguish the messages directed to them and respond
in kind—synthesizing and secreting the proper hormones in response to specific releasing hormones, and closing down hormone release in response to inhibiting hormones. The releasing hormones are far more important as regulatory factors because little hormone is stored by the secretory cells of the anterior lobe.

Four of the six anterior pituitary lobe hormones—thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)—are tropins or tropic hormones. Tropic (tropi = turn on, change) hormones regulate the secretory action of other endocrine glands. The three cell types that produce tropic hormones (thyrotropes, gonadotropes, and corticotropes) are stained blue by basic dyes and thus are collectively classed as basophil ("base-loving") cells of the anterior pituitary (Figure 17.5b). The remaining two adenohypophyseal hormones—growth hormone (GH) and prolactin (PRL)—exert their major effects on nonendocrine targets. Since these cell types (somatotropes and lactotropes) stain red with acidic dyes, they constitute the acidophil ("acid-loving") cells of the anterior pituitary (Figure 17.5b). (The role of the colorless chromophobes ("color fearing") is controversial, but some assume they are still-immature glandular cells.)

With the possible exception of growth hormone and prolactin, for which the mechanism is unknown, all adenohypophyseal hormones affect their target cells via a cyclic AMP second-messenger system. (The adenohypophyseal hormones, their effects, and their relationships to hypothalamic regulatory factors are summarized briefly in Table 17.1.)

**Growth Hormone (GH).** Growth hormone (GH) is produced by the somatotrophic cells or somatotropes. Although GH stimulates most body cells to increase in size and divide, its major targets are the bones and skeletal muscles. Stimulation of the epiphyseal plate leads to long bone growth; its effects on skeletal muscles promote increased muscle mass.

Essentially an anabolic hormone, GH promotes protein synthesis, and it encourages the use of fats for fuel, thus conserving glucose (Figure 17.6). The second-messenger system through which GH influences its target cells is still controversial, but the growth-promoting effects of GH are known to be mediated indirectly by somatomedins (so"mah-to-me’dinz), a family of growth-promoting proteins produced by the liver and perhaps by the kidneys and muscles as well. Somatomedin C, also known as insulin-like growth factor 1 (IGF-1), is believed to be the active factor. Specifically, GH (1) stimulates uptake of amino acids from the blood and their incorporation into cellular proteins; (2) stimulates uptake of sulfur (needed for the synthesis of chondroitin sulfate) into cartilage matrix; (3) mobilizes fats from fat depots for transport to cells, increasing blood levels of fatty acids; and (4) decreases the rate of glucose uptake and metabolism. In the liver, it encourages glycogen breakdown and release of glucose to the blood. The elevation in blood sugar levels that subsequently occurs is called the diabetogenic effect of GH, because it mimics the high blood sugar levels typical of diabetes mellitus (see p. 573).

Secretion of GH is regulated chiefly by two hypothalamic hormones with antagonistic effects. Growth hormone–releasing hormone (GHRH) stimulates GH