45

Hormones and the Endocrine System

▲ **Figure 45.1 What signals caused this butterfly to grow within the body of a caterpillar?**

KEY CONCEPTS

OVERVIEW

The Body's Long-Distance Regulators

To say that a butterfly, such as the anise swallowtail (*Papilio zelicaon*) in **Figure 45.1**, was once a caterpillar is only partly true. The adult cells that form the butterfly begin growing in the embryo. Within the larval caterpillar, they are nourished as islands of tissues that will eventually become the eyes, wings, brain, and other structures of the butterfly. Once the plump, crawling caterpillar becomes a stationary pupa, the adult cells take over. They complete their program of development, while many larval tissues undergo programmed cell death. The end result is a butterfly, a delicate, free-flying adult that bears little resemblance to the larval and pupal forms from which it arose.

What brings about such a complete change of body form, or *metamorphosis*? The answer for this and many other biological processes is a type of molecule called a **hormone** (from the Greek *horman*, to excite). In animals, hormones are secreted into the extracellular fluid, circulate in the hemolymph or blood, and communicate regulatory messages throughout the body. In the case of the caterpillar, a hormone called **ecdysteroid** stimulates the growth of adult cells, the programmed death of larval cells, and even the behaviors that bring about the motionless pupal stage. Communication within the body by ecdysteroid and other hormones also regulates the timing of metamorphosis and ensures that different parts of the swallowtail's adult body develop in unison.

Each hormone has specific receptors in the body. Although a given hormone can reach all cells of the body, only some cells have receptors for that hormone. A hormone elicits a response—such as a change in metabolism—only from specific *target cells*, those that have the matching receptor. Cells lacking a receptor for that particular hormone are unaffected.

Chemical signaling by hormones is the function of the **endocrine system**, one of the two basic systems of communication and regulation throughout the body. Hormones secreted by endocrine cells regulate reproduction, development, energy metabolism, growth, and behavior. The other major communication and control system is the **nervous system**, a network of specialized cells—neurons—that transmit signals along dedicated pathways. These signals in turn regulate neurons, muscle cells, and endocrine cells. Because signaling by neurons can regulate the release of hormones, the nervous and endocrine systems often overlap in function.

In this chapter, we'll begin with an overview of the different types of chemical signaling in animals and the ways in which the activities of the endocrine and nervous systems are coordinated. We will then explore how hormones regulate target cells, how hormone secretion is regulated, and how hormones help maintain homeostasis. We'll conclude by examining the role of hormones in regulating growth, development, and reproduction, topics we'll return to in Chapters 46 and 47.

CONCEPT 45.1

Hormones and other signaling molecules bind to target receptors, triggering specific response pathways

Endocrine signaling is just one of several ways information is transmitted between animal cells. Let's consider the similarities and differences in these various signaling processes.

Intercellular Communication

The ways in which signals are transmitted between animal cells are often classified by two criteria: the type of secreting cell and the route taken by the signal in reaching its target.

Endocrine Signaling

As illustrated in **Figure 45.2a**, hormones secreted into extracellular fluids by endocrine cells reach target cells via the bloodstream (or hemolymph). Endocrine signaling maintains homeostasis, mediates responses to environmental stimuli, and regulates growth and development. For example, hormones coordinate the body's responses to stress, dehydration, and low blood glucose levels. They also trigger behavioral and physical changes underlying sexual maturity and reproduction.

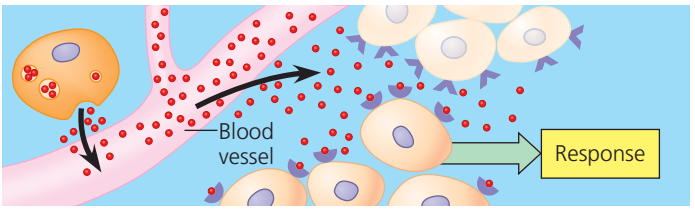
Paracrine and Autocrine Signaling

Many types of cells produce and secrete **local regulators**, molecules that act over short distances and reach their target cells solely by diffusion. Cytokines, for example, are local regulators that enable communication between immune cells (see Figures 43.16 and 43.18). Depending on the target cell, signaling by local regulators can be either paracrine or autocrine. In **paracrine** signaling (from the Greek *para*, to one side of), target cells lie near the secreting cell **(Figure 45.2b)**. In **autocrine** signaling (from the Greek *auto*, self), the target cell is the secreting cell itself **(Figure 45.2c)**. As we will discuss later in this chapter, paracrine and autocrine signaling play roles in many physiological processes, including blood pressure regulation, nervous system function, and reproduction.

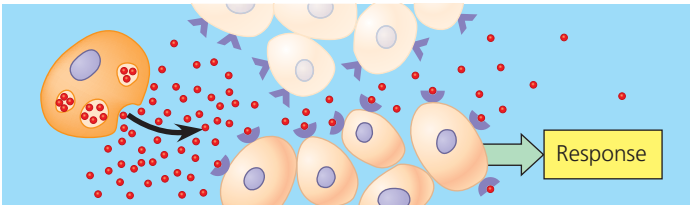
Synaptic and Neuroendocrine Signaling

Secreted molecules are crucial for two types of signaling by neurons. In *synaptic signaling*, neurons form specialized junctions called synapses with target cells, such as other neurons and muscle cells. At synapses, neurons secrete molecules called **neurotransmitters** that diffuse a very short distance to bind to receptors on the target cells **(Figure 45.2d)**. Neurotransmitters are central to sensation, memory, cognition, and movement, as we will explore in Chapters 48–50.

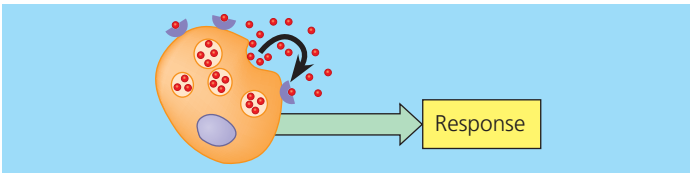
In *neuroendocrine signaling*, specialized neurons called neurosecretory cells secrete molecules that diffuse from nerve cell endings into the bloodstream **(Figure 45.2e)**. These molecules, which travel through the bloodstream to target cells, are a class of hormone called **neurohormones**. One example is antidiuretic hormone, also known as vasopressin, a hormone essential to kidney function and water balance (see Chapter 44).



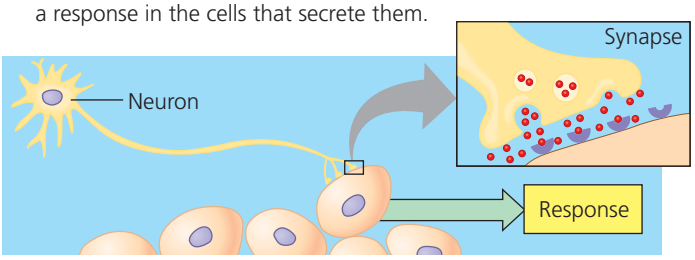
(a) In **endocrine signaling**, secreted molecules diffuse into the bloodstream and trigger responses in target cells anywhere in the body.



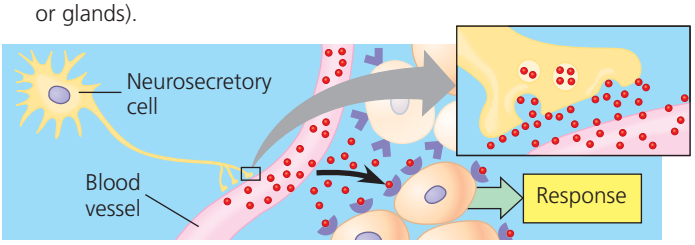
(b) In **paracrine signaling**, secreted molecules diffuse locally and trigger a response in neighboring cells.



(c) In **autocrine signaling**, secreted molecules diffuse locally and trigger a response in the cells that secrete them.



(d) In **synaptic signaling**, neurotransmitters diffuse across synapses and trigger responses in cells of target tissues (neurons, muscles, or glands).



(e) In **neuroendocrine signaling**, neurohormones diffuse into the bloodstream and trigger responses in target cells anywhere in the body.

▲ Figure 45.2 Intercellular communication by secreted molecules. In each type of signaling, secreted molecules (•) bind to a specific receptor protein (◡) expressed by target cells. Some receptors are located inside cells, but for simplicity here, all are drawn on the cell surface.

▲ **Figure 45.3 Signaling by pheromones.** Using their lowered antennae, these Asian army ants (*Leptogenys distinguenda*) follow a pheromone-marked trail as they carry pupae and larvae to a new nest site.

Signaling by Pheromones

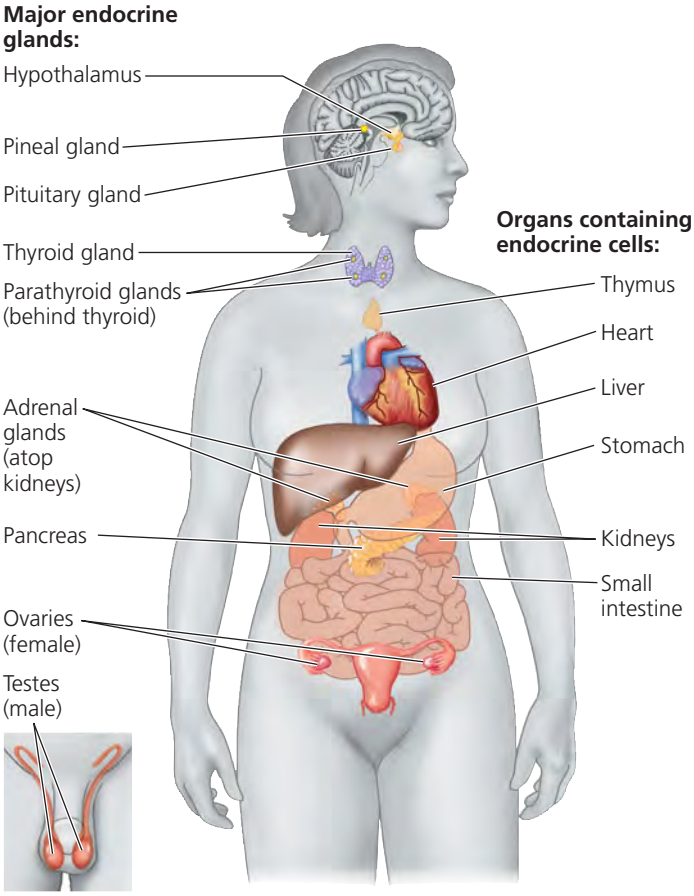
Not all secreted signaling molecules act within the body. Members of the same animal species sometimes communicate via **pheromones**, chemicals that are released into the external environment. For example, when a foraging ant discovers a new food source, it marks its path back to the nest with a pheromone. Ants also use pheromones for guidance when a colony migrates to a new location **(Figure 45.3)**.

Pheromones serve a wide range of functions that include defining territories, warning of predators, and attracting potential mates. The giant silk moth (*Antheraea polyphemus*) provides a noteworthy example: The sex pheromone released into the air by a female enables her to attract a male of the species from up to 4.5 km away.

Endocrine Tissues and Organs

Some endocrine system cells are found in organs that are part of other organ systems. For example, in the human digestive system, the stomach contains isolated endocrine cells in addition to the predominant cell and tissue types. In other cases, endocrine cells are grouped in ductless organs called **endocrine glands**, such as the thyroid and parathyroid glands of the neck. The various human glands and organs with endocrine function are illustrated in **Figure 45.4**, which will serve as a useful point of reference as you move through the chapter.

Note that endocrine glands secrete hormones directly into the surrounding fluid. Endocrine glands thus contrast with *exocrine glands*, such as salivary glands, which have ducts that carry secreted substances onto body surfaces or into body cavities. This distinction is reflected in their names: The Greek *endo* ("within") and *exo* ("out of") reflect secretion into or out of body fluids, while *crine* (from the Greek for "separate") reflects movement away from the secreting cell.

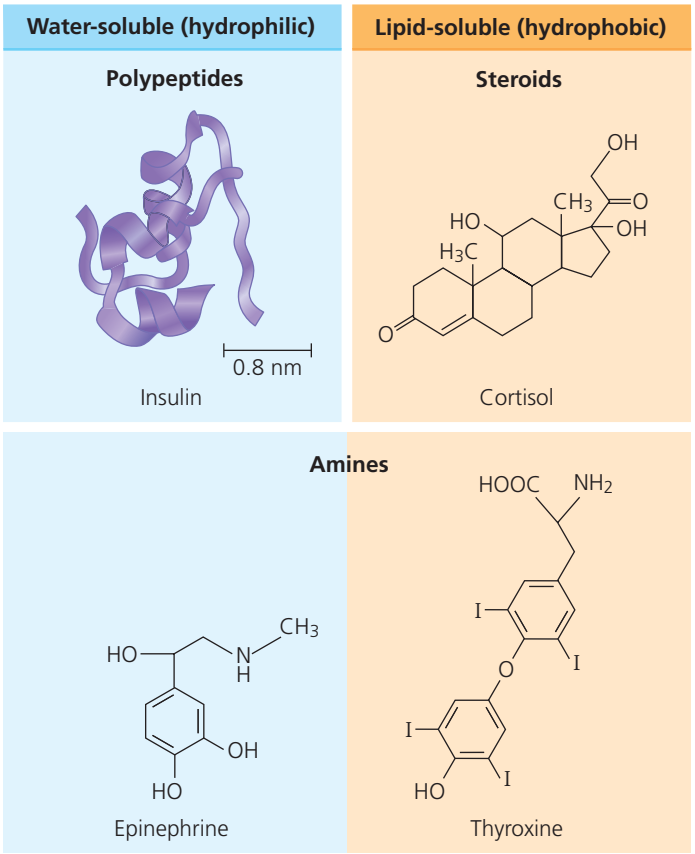


▲ **Figure 45.4 Major human endocrine glands.**

Chemical Classes of Hormones

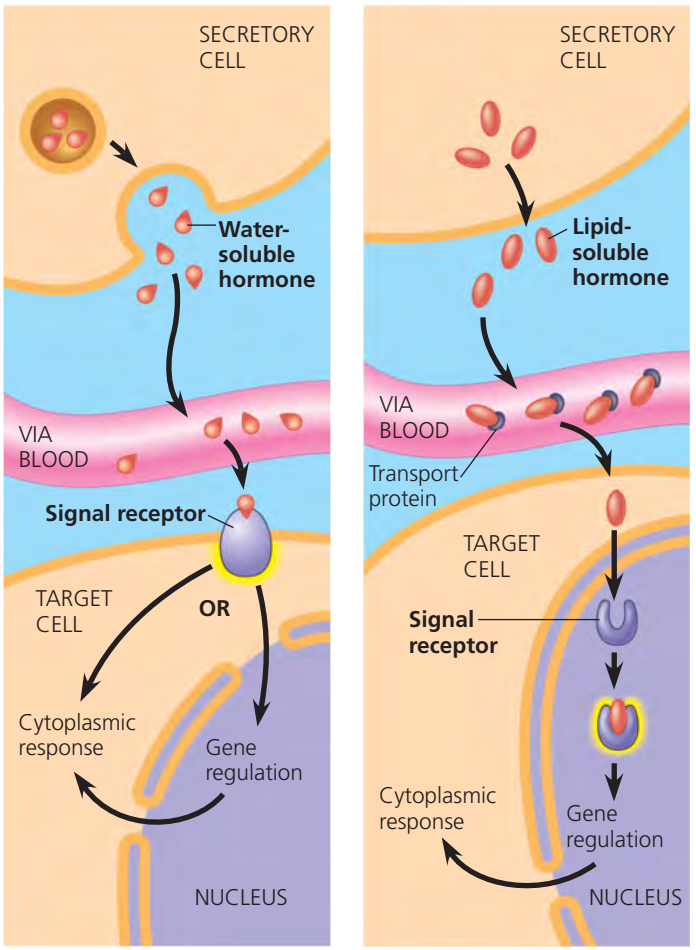
Hormone molecules vary substantially in size and chemical properties. Some of these differences are apparent in examples drawn from the three major chemical classes of hormones: polypeptides (proteins and peptides), steroids, and amines **(Figure 45.5)**. The polypeptide hormone insulin is made up of two polypeptide chains. Like most hormones in this group, insulin is formed by cleavage of one long polypeptide chain. Steroid hormones, such as cortisol and ecdysteroid, are lipids that contain four fused carbon rings. All are derived from the steroid cholesterol (see Figure 5.14). Epinephrine and thyroxine are amine hormones, each synthesized from a single amino acid, either tyrosine or tryptophan.

As Figure 45.5 indicates, hormones vary in their solubility in aqueous and lipid-rich environments. Polypeptides and most amine hormones are water-soluble. Being insoluble in lipids, these hormones cannot pass through the plasma membranes of cells. Instead, they bind to cell-surface receptors that relay information to the nucleus through intracellular pathways. In contrast, steroid hormones, as well as other largely nonpolar (hydrophobic) hormones, such as thyroxine, are lipid-soluble and can pass through cell membranes readily. Receptors for lipid-soluble hormones typically reside in the cytoplasm or nucleus.



▲ **Figure 45.5 Hormones differ in structure and solubility.**

MAKE CONNECTIONS *The biosynthesis of epinephrine involves breaking just one carbon-carbon bond in the amino acid tyrosine (see Figure 5.16, p. 79). Which bond is it?*



(a) Receptor in plasma membrane **(b) Receptor in cell nucleus**

▲ **Figure 45.6 Receptor location varies with hormone type.** **(a)** A water-soluble hormone binds to a signal receptor protein on the surface of a target cell. This interaction triggers events that lead to either a change in cytoplasmic function or a change in gene transcription in the nucleus. **(b)** A lipid-soluble hormone penetrates the target cell's plasma membrane and binds to an intracellular signal receptor, either in the cytoplasm or in the nucleus (shown here). The hormone-receptor complex acts as a transcription factor, typically activating gene expression.

? *Suppose you were studying a cell's response to a particular hormone, and you observed that the cell continued to respond to the hormone even when treated with a chemical that blocks transcription. What could you surmise about the hormone and its receptor?*

Cellular Response Pathways

There are several differences between the response pathways for water-soluble and lipid-soluble hormones. One difference is the location of the target cells' signal receptors **(Figure 45.6)**. Water-soluble hormones are secreted by exocytosis, travel freely in the bloodstream, and bind to cell-surface signal receptors. Binding of such hormones to receptors induces changes in cytoplasmic molecules and sometimes alters gene transcription (synthesis of messenger RNA molecules). In contrast, lipid-soluble hormones diffuse out across the membranes of endocrine cells. Outside the cell, they bind to transport proteins that keep them soluble in the aqueous environment of the bloodstream. Upon leaving the bloodstream, they diffuse into target cells, bind to intracellular signal receptors, and trigger changes in gene transcription.

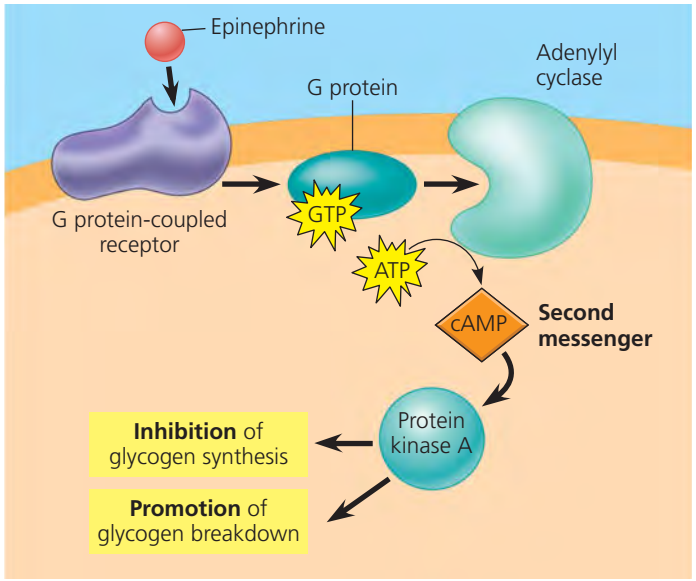
To follow the distinct cellular responses to water-soluble and lipid-soluble hormones, we'll examine the two response pathways in turn.

Pathway for Water-Soluble Hormones

The binding of a water-soluble hormone to a signal receptor protein triggers events at the plasma membrane that result in a cellular response. The response may be the activation of an enzyme, a change in the uptake or secretion of specific molecules, or a rearrangement of the cytoskeleton. In addition, some cell-surface receptors cause proteins in the cytoplasm to move into the nucleus and alter transcription of specific genes.

The series of changes in cellular proteins that converts the extracellular chemical signal to a specific intracellular response is called **signal transduction**. As described in Chapter 11, a signal transduction pathway typically involves multiple steps, each involving specific molecular interactions.

To explore the role of signal transduction in hormone signaling, consider one response to short-term stress. When you find yourself in a stressful situation, perhaps running to catch a bus, your adrenal glands secrete **epinephrine**, a hormone also



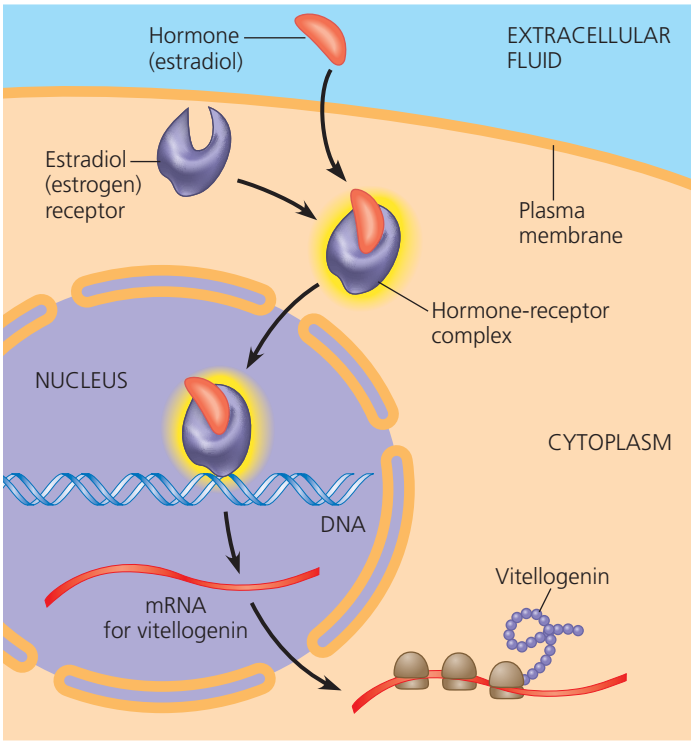
▲ **Figure 45.7 Cell-surface hormone receptors trigger signal transduction.**

called *adrenaline*. When epinephrine reaches the liver, it binds to a G protein-coupled receptor in the plasma membrane of target cells, as discussed in Chapter 11 and reviewed in **Figure 45.7**. The binding of hormone to receptor triggers a cascade of events involving synthesis of cyclic AMP (cAMP) as a short-lived *second messenger*. Activation of protein kinase A by cAMP leads to activation of an enzyme required for glycogen breakdown and inactivation of an enzyme necessary for glycogen synthesis. The net result is that the liver releases glucose into the bloodstream, providing the fuel you need to chase the departing bus.

Pathway for Lipid-Soluble Hormones

Intracellular receptors for lipid-soluble hormones perform the entire task of transducing a signal within a target cell. The hormone activates the receptor, which then directly triggers the cell's response. In most cases, the response to a lipid-soluble hormone is a change in gene expression.

Steroid hormone receptors are located in the cytosol prior to binding to a hormone. When a steroid hormone binds to its cytosolic receptor, a hormone-receptor complex forms, which moves into the nucleus. There, the receptor portion of the complex alters transcription of particular genes by interacting with a specific DNA-binding protein or response element in the DNA (see Figure 18.9). Consider, for example, estrogens, steroid hormones necessary for female reproductive function in vertebrates. In female birds and frogs, estradiol, a form of estrogen, has a specific receptor in liver cells. Binding of estradiol to this receptor activates transcription of the gene for the protein vitellogenin **(Figure 45.8)**. Following translation of the messenger RNA, vitellogenin is secreted and transported in the blood to the reproductive system, where it is used to produce egg yolk.



▲ **Figure 45.8 Steroid hormone receptors directly regulate gene expression.**

Thyroxine, vitamin D, and other lipid-soluble hormones that are not steroid hormones have receptors that are typically located in the nucleus. These receptors bind hormone molecules that diffuse from the bloodstream across both the plasma membrane and nuclear envelope. Once bound by a hormone, the receptor binds to specific sites in the cell's DNA and stimulates the transcription of specific genes.

There is now substantial evidence that estrogens and some other lipid-soluble hormones sometimes trigger responses at the cell surface without entering the nucleus. How and when these responses arise are currently the subjects of active study.

Multiple Effects of Hormones

Many hormones elicit more than one type of response in the body. The effects brought about by a particular hormone can vary if target cells differ in the molecules that receive or produce the response to that hormone. Consider the effects of epinephrine in mediating the body's response to short-term stress **(Figure 45.9)**. Epinephrine simultaneously triggers glycogen breakdown in the liver, increased blood flow to major skeletal muscles, and decreased blood flow to the digestive tract. These varied effects enhance the rapid reactions of the body in emergencies.

Tissues vary in their response to epinephrine because they vary in their receptors or in their signal transduction pathways. Target cell recognition of epinephrine involves G protein-coupled receptors. Liver cells have a β-type epinephrine receptor that activates the enzyme protein kinase A, which in turn

regulates enzymes in glycogen metabolism **(Figure 45.9a)**. In blood vessels supplying skeletal muscle, the same kinase activated by the same epinephrine receptor inactivates a muscle-specific enzyme. The result is smooth muscle relaxation and hence increased blood flow **(Figure 45.9b)**. In contrast, intestinal blood vessels have an α-type epinephrine receptor **(Figure 45.9c)**. Rather than activate protein kinase A, the α receptor triggers a distinct signaling pathway involving a different G protein and different enzymes. The result is smooth muscle contraction and restricted blood flow to the intestines.

Lipid-soluble hormones often exert different effects on different target cells as well. For example, the estrogen that stimulates a bird's liver to synthesize the yolk protein vitellogenin also stimulates its reproductive system to synthesize proteins that form the egg white.

Signaling by Local Regulators

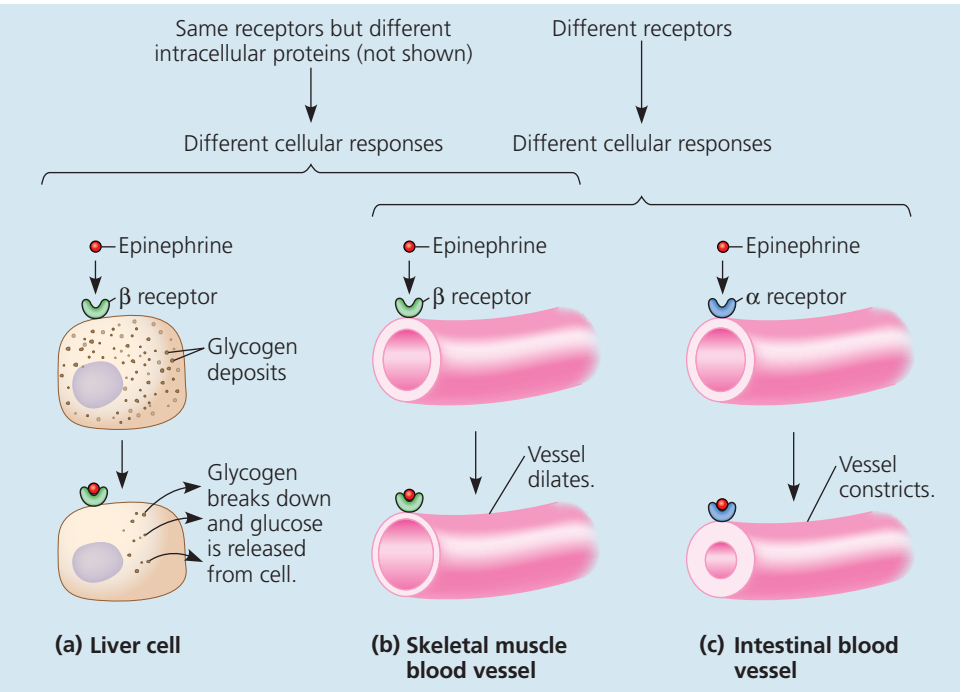
Recall that local regulators are secreted molecules that link neighboring cells (paracrine signaling) or directly regulate the secreting cell (autocrine signaling). Once secreted, local regulators act on their target cells within seconds or even milliseconds, eliciting responses more quickly than do hormones. Nevertheless, the pathways by which local regulators trigger responses are the same as those activated by hormones. (Although the definition of hormones is sometimes broadened to include local regulators, in this chapter we use *hormone* to refer to chemicals that reach target cells through the bloodstream or hemolymph.)

Several types of chemical compounds function as local regulators. Polypeptide local regulators include cytokines, as mentioned, and also most **growth factors**, which stimulate cell proliferation and differentiation. Many types of cells grow, divide, and develop normally only when growth factors are present in their extracellular environment.

The gas **nitric oxide (NO)** functions in the body as both a neurotransmitter and a local regulator. When the level of oxygen (O_2) in the blood falls, endothelial cells in blood vessel walls synthesize and release NO. Nitric oxide activates an enzyme that relaxes the surrounding smooth muscle cells, resulting in vasodilation, which improves blood flow to tissues. Highly reactive and potentially toxic, NO usually triggers changes in a target cell within a few seconds of contact and then breaks down. In human males, NO's ability to promote vasodilation enables sexual function by increasing blood flow into the penis, producing an erection. The drug Viagra (sildenafil citrate), a treatment for male erectile dysfunction, sustains an erection by prolonging activity of the NO response pathway.

A group of local regulators called **prostaglandins** are modified fatty acids. They are so named because they were first discovered in prostate gland secretions that contribute to semen. Prostaglandins are produced by many cell types and have varied activities. In semen that reaches the reproductive tract of a female, prostaglandins stimulate the smooth muscles of the female's uterine wall to contract, helping sperm reach an egg. At the onset of childbirth, prostaglandin-secreting cells of the placenta cause the nearby muscles of the uterus to become more excitable, helping to induce labor (see Figure 46.18).

In the immune system, prostaglandins promote fever and inflammation and also intensify the sensation of pain. The anti-inflammatory and pain-relieving effects of aspirin and ibuprofen are due to the inhibition of prostaglandin synthesis by these drugs. Prostaglandins also help regulate the aggregation of platelets, one step in the formation of blood clots. Because blood clots can cause a heart attack by blocking blood flow in vessels that supply the heart (see Chapter 42), some physicians recommend that people at risk for a heart attack take aspirin on a regular basis. However, because prostaglandins also help maintain a protective lining in the stomach, long-term aspirin therapy can cause debilitating stomach irritation.



▲ **Figure 45.9 One hormone, different effects.** Epinephrine, the primary "fight-or-flight" hormone, produces different responses in different target cells. Target cells with the same receptor exhibit different responses if they have different signal transduction pathways and/or effector proteins; compare (a) with (b). Responses of target cells may also differ if they have different receptors for the hormone; compare (b) with (c).

Coordination of Neuroendocrine and Endocrine Signaling

In all animals but the simplest invertebrates, the endocrine and nervous systems act coordinately to control reproduction and development. As an example, we'll explore the life cycle of the butterfly, a process highlighted earlier in the chapter.

A butterfly larva grows in stages. Because its exoskeleton cannot stretch, the larva must periodically molt, shedding the old exoskeleton and secreting a new one. The signals that direct molting originate in the brain **(Figure 45.10)**. There, neurosecretory cells produce *prothoracicotropic hormone (PTTH)*, a polypeptide neurohormone. In response to PTTH, a pair of endocrine glands behind the brain release ecdysteroid. Ecdysteroid triggers each successive molt, as well as the metamorphosis of larva into butterfly during the final molt.

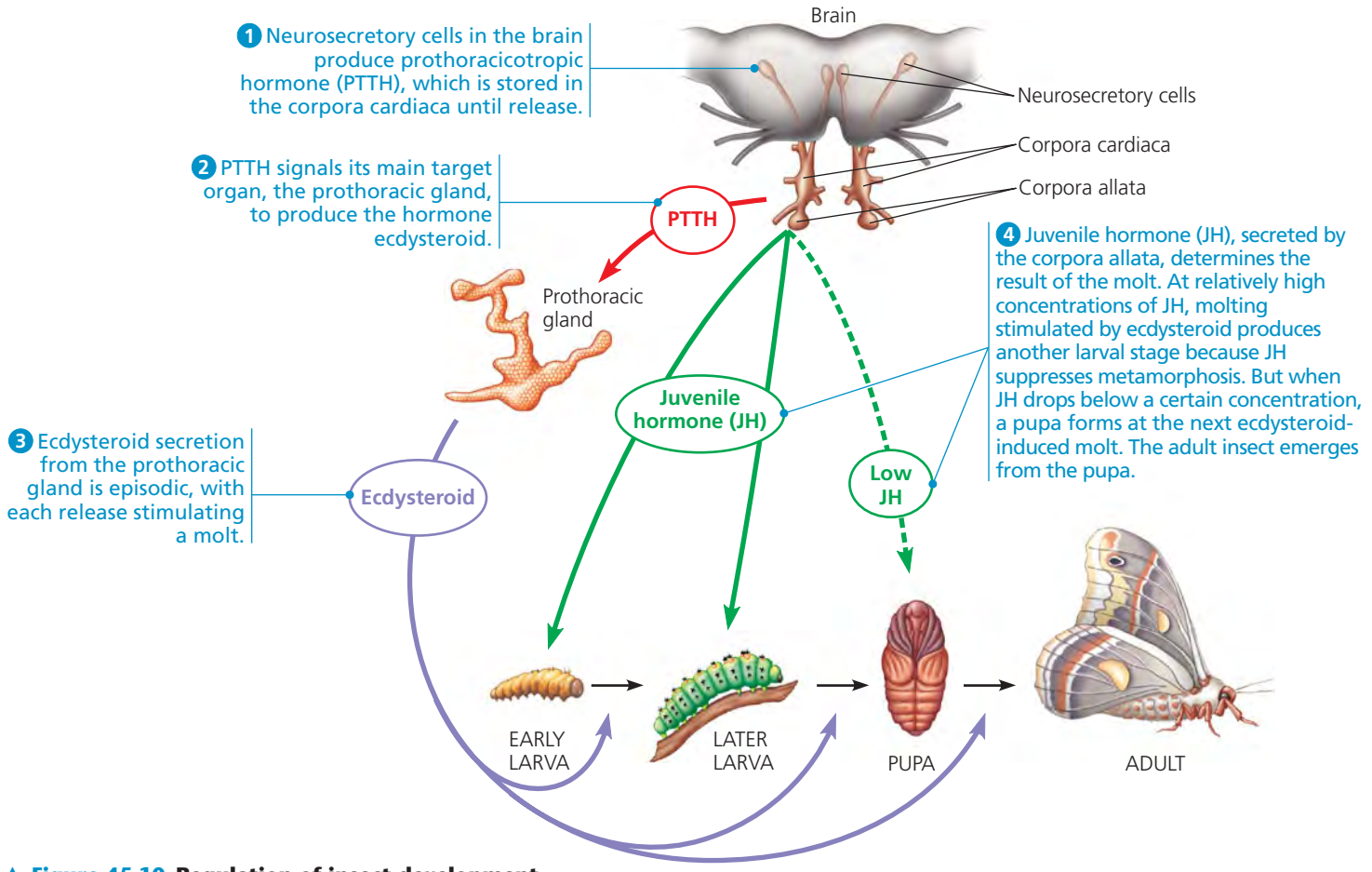
Given that ecdysteroid triggers both molting and metamorphosis, what determines when metamorphosis takes place? The answer is a third molecule, *juvenile hormone*, secreted by another pair of endocrine glands behind the brain. As its name suggests, one of the many functions of juvenile hormone is to maintain larval (juvenile) characteristics. Juvenile hormone modulates the activity of ecdysteroid. As long as the level of juvenile hormone is high, ecdysteroid stimulates larval molting. When the juvenile hormone level drops, ecdysteroid-induced molting instead produces the pupal form, within which metamorphosis occurs.

Knowledge of endocrine signaling in insects has important applications for agricultural pest control. For example, synthetic chemicals that can bind to the ecdysteroid receptor cause insect larvae to molt prematurely and die.

CONCEPT CHECK 45.1

1. How do response mechanisms in target cells differ for water-soluble and lipid-soluble hormones?
2. In what way does one activity described for prostaglandins resemble that of a pheromone?
3. **MAKE CONNECTIONS** What parallels in properties and effects can you identify between epinephrine and the plant hormone auxin (see Concept 39.2, pp. 827–829)?

For suggested answers, see Appendix A.



▲ **Figure 45.10 Regulation of insect development and metamorphosis.** As shown here for a moth, most insects go through a series of larval stages, with each molt (shedding of the old exoskeleton) leading to a larger larva. Molting of the final larval stage gives rise to a pupa, in which metamorphosis produces the adult form of the insect. Neurohormones and hormones control the progression of stages.

CONCEPT 45.2

Feedback regulation and antagonistic hormone pairs are common in endocrine systems

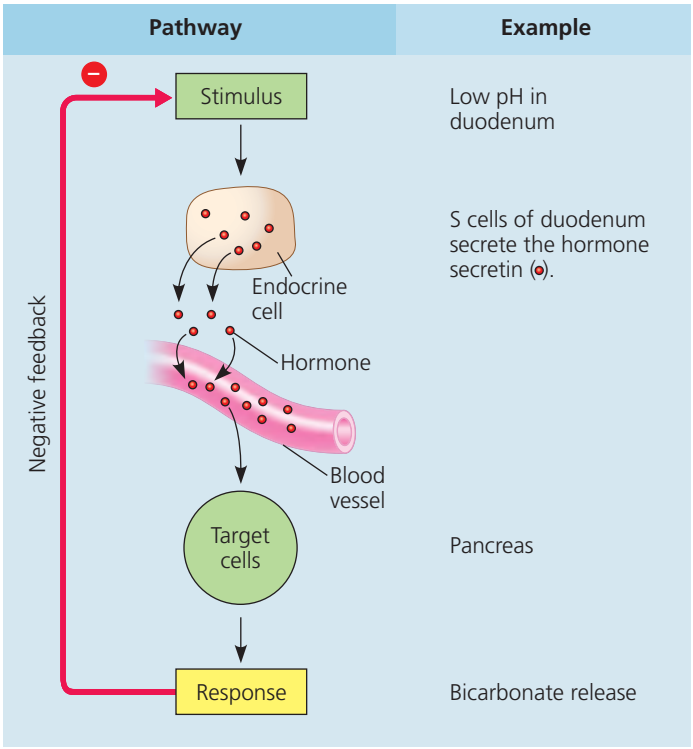
So far, we have explored forms of intercellular signaling as well as hormone structure, recognition, and response. We turn now to considering how regulatory pathways that control hormone secretion are organized.

Simple Hormone Pathways

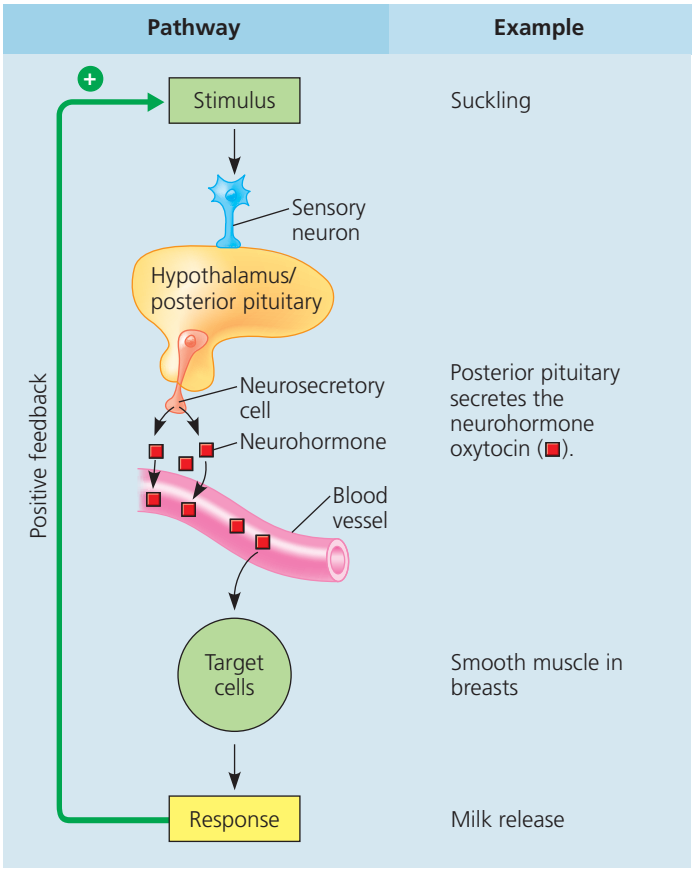
In examining the regulation of hormone secretion, we begin with two basic types of organization—simple endocrine and simple neuroendocrine pathways. In a *simple endocrine pathway*, endocrine cells respond directly to an internal or environmental stimulus by secreting a particular hormone **(Figure 45.11)**. The hormone travels in the bloodstream to target cells, where it interacts with its specific receptors. Signal transduction within target cells brings about a physiological response.

In the example of a simple endocrine pathway shown in Figure 45.11, the stimulus is the release of the acidic contents of the stomach into the duodenum (the first part of the small intestine). Low pH in the duodenum stimulates certain endocrine cells there, called S cells, to secrete the hormone *secretin*. Secretin enters the bloodstream and travels to the **pancreas**, a gland located behind the stomach (see Figure 45.4). Target cells in the pancreas then release bicarbonate into ducts leading to the duodenum, where it raises the pH.

In a *simple neuroendocrine pathway*, the stimulus is received by a sensory neuron, which stimulates a neurosecretory cell **(Figure 45.12)**. The neurosecretory cell then secretes a neurohormone, which diffuses into the bloodstream and travels to target cells. Such a pathway regulates milk release during nursing in mammals. Suckling by an infant stimulates sensory neurons in the nipples, generating signals in the nervous system that reach the hypothalamus. Nerve impulses from the hypothalamus then trigger the release of the neurohormone **oxytocin** from the posterior pituitary gland. In response to circulating oxytocin, the mammary glands secrete milk.



▲ **Figure 45.11 A simple endocrine pathway.** Endocrine cells respond to a change in some internal or external variable—the stimulus—by secreting hormone molecules that trigger a specific response by target cells. In the case of secretin signaling, the simple endocrine pathway is self-limiting because the response to secretin (bicarbonate release) reduces the stimulus (low pH) through negative feedback.



▲ **Figure 45.12 A simple neuroendocrine pathway.** Sensory neurons respond to a stimulus by sending nerve impulses to a neurosecretory cell, triggering secretion of a neurohormone. Upon reaching its target cells via the bloodstream, the neurohormone binds to its receptor, triggering signal transduction that results in a specific response. In the neuroendocrine pathway for oxytocin signaling, the response increases the stimulus, forming a positive-feedback loop that amplifies signaling in the pathway.

Feedback Regulation

A feedback loop linking the response back to the initial stimulus is characteristic of control pathways. For many hormones, the response pathway involves **negative feedback**, a loop in which the response reduces the initial stimulus. In the case of secretin signaling (see Figure 45.11), the release of bicarbonate by the pancreas increases pH in the intestine, eliminating the stimulus and thereby shutting off the pathway. By decreasing or abolishing hormone signaling, negative-feedback regulation prevents excessive pathway activity.

Whereas negative feedback dampens a stimulus, **positive feedback** reinforces a stimulus, leading to an even greater response. Consider, for instance, the oxytocin pathway outlined in Figure 45.12. In response to the circulating oxytocin, the mammary glands secrete milk. Milk released in response to the oxytocin leads to more suckling and therefore more stimulation. Activation of the pathway is sustained until the baby stops suckling.

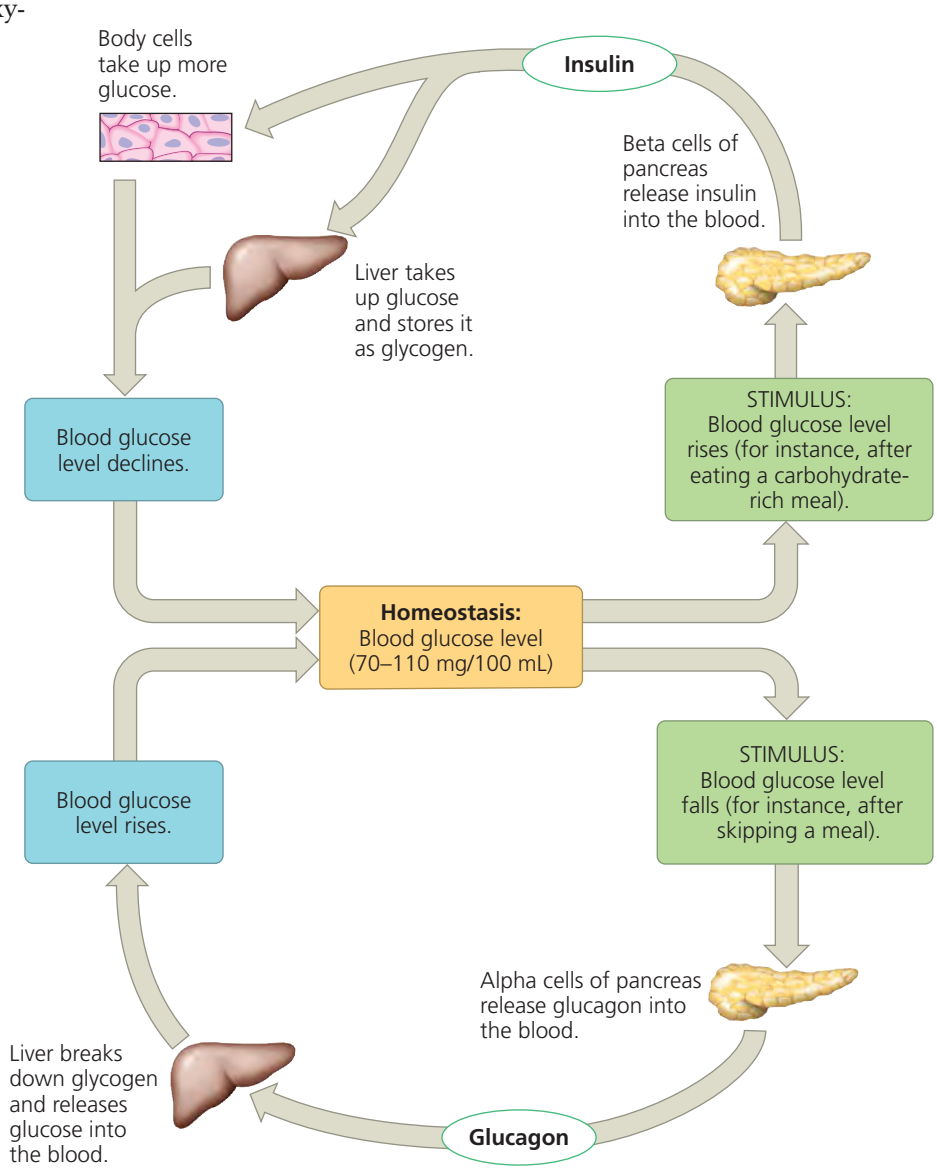
The role of oxytocin in reproduction is not limited to mammary gland regulation. When mammals give birth, oxytocin induces target cells in the uterine muscles to contract. This pathway, too, is characterized by positive-feedback regulation, such that it drives the birth process to completion.

While positive feedback amplifies both stimulus and response, negative feedback helps restore a preexisting state. It is not surprising, therefore, that hormone pathways involved in homeostasis typically involve negative rather than positive feedback. In fact, some homeostatic control systems rely on pairs of negatively regulated hormone pathways, each counterbalancing the other. To see how such control systems operate, we'll consider the regulation of blood glucose levels.

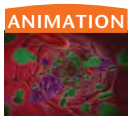
Insulin and Glucagon: Control of Blood Glucose

In humans, metabolic balance depends on a blood glucose concentration of 70–110 mg/100 mL. Because glucose is a major fuel for cellular respiration and a key source of carbon skeletons for biosynthesis, maintaining blood glucose concentrations near this normal range is critical.

Two antagonistic (opposing) hormones, insulin and glucagon, regulate the concentration of glucose in the blood **(Figure 45.13)**. Each of these hormones operates in a simple endocrine pathway regulated by negative feedback. When blood glucose rises above the normal range, release of **insulin** triggers uptake of glucose from the blood into body cells, decreasing the blood glucose concentration. When blood glucose drops below the normal range, the release of **glucagon** promotes the release of glucose into the blood from energy stores, such as liver glycogen, increasing the blood glucose concentration. Because insulin and glucagon have opposing effects, the combined activity of these two hormones tightly controls the concentration of glucose in the blood.



▲ **Figure 45.13 Maintenance of glucose homeostasis by insulin and glucagon.** The antagonistic effects of insulin and glucagon help keep blood glucose levels in the normal range.



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Glucagon and insulin are produced in the pancreas. Scattered throughout this organ are clusters of endocrine cells called pancreatic islets. Each pancreatic islet has *alpha cells*, which make glucagon, and *beta cells*, which make insulin. Like all hormones, insulin and glucagon are secreted into the interstitial fluid and enter the circulatory system.

Overall, hormone-secreting cells make up only 1–2% of the mass of the pancreas. Other cells in the pancreas produce and secrete bicarbonate ions and digestive enzymes. These exocrine secretions are released into small ducts that empty into the pancreatic duct, which leads to the small intestine. Thus, the pancreas is both an endocrine gland and an exocrine gland and has functions in both the endocrine and digestive systems.

Target Tissues for Insulin and Glucagon

Insulin lowers blood glucose levels by stimulating nearly all body cells outside the brain to take up glucose from the blood. (Brain cells can take up glucose without insulin, so the brain almost always has access to circulating fuel.) Insulin also decreases blood glucose by slowing glycogen breakdown in the liver and inhibiting the conversion of glycerol (from fats) and amino acids to glucose.

Glucagon influences blood glucose levels mainly through its effects on target cells in the liver. The liver, skeletal muscles, and adipose tissues store large amounts of fuel. The liver and muscles store sugar as glycogen, whereas cells in adipose tissue convert sugars to fats. When the blood glucose level decreases to a level at or below the normal range (70–110 mg/100 mL), a primary effect of glucagon is to signal liver cells to increase glycogen hydrolysis, convert amino acids and glycerol to glucose, and release glucose into the bloodstream. The net result is a return of the blood glucose level to the normal range.

The antagonistic effects of glucagon and insulin are vital to managing fuel storage and consumption by body cells. For both hormones, as we've mentioned, the liver is a critical target. Recall from Chapter 41 that nutrients absorbed by blood vessels of the small intestine are transported directly to the liver by the hepatic portal vein. Within the liver, glucagon and insulin regulate nutrient processing in ways that support glucose homeostasis. However, glucose homeostasis also relies on responses to glucagon and insulin elsewhere in the body as well as responses to other hormones—growth hormone and glucocorticoids—discussed later in this chapter.

In discussing the role of insulin and glucagon in glucose homeostasis, we have focused exclusively on a healthy metabolic state. However, a number of disorders can disrupt glucose homeostasis with potentially serious consequences, especially for the heart, blood vessels, eyes, and kidneys. We'll discuss the best known and most prevalent of these disorders—diabetes mellitus—next.

Diabetes Mellitus

The disease **diabetes mellitus** is caused by a deficiency of insulin or a decreased response to insulin in target tissues. Blood glucose levels rise, but cells are unable to take up enough glucose to meet metabolic needs. Instead, fat becomes the main substrate for cellular respiration. In severe cases, acidic metabolites formed during fat breakdown accumulate in the blood, threatening life by lowering blood pH and depleting sodium and potassium ions from the body.

In people with diabetes mellitus, the level of glucose in blood may exceed the capacity of the kidneys to reabsorb this nutrient. Glucose that remains in the kidney filtrate is excreted. For this reason, the presence of sugar in urine is one test for this disorder. As glucose is concentrated in the urine, more water is excreted along with it, resulting in excessive volumes of urine. *Diabetes* (from the Greek *diabainein*, to pass through) refers to this copious urination; and *mellitus* (from the Greek *meli*, honey) refers to the presence of sugar in urine. (*Diabetes insipidus*, discussed in Chapter 44, is a rare disorder of kidney function that results in large volumes of dilute urine but no major disruption in glucose metabolism.)

There are two main types of diabetes mellitus. Each is marked by high blood glucose, but with very different causes. *Type 1 diabetes*, or insulin-dependent diabetes, is an autoimmune disorder in which the immune system destroys the beta cells of the pancreas. Type 1 diabetes, which usually appears during childhood, destroys the person's ability to produce insulin. Treatment consists of insulin, typically injected several times daily. In the past, insulin was extracted from animal pancreases, but now human insulin can be obtained from genetically engineered bacteria, a relatively inexpensive source (see Figure 20.2). Stem cell research may someday provide a cure for type 1 diabetes by generating replacement beta cells that restore insulin production by the pancreas.

Type 2 diabetes, or non-insulin-dependent diabetes, is characterized by a failure of target cells to respond normally to insulin. Insulin is produced, but target cells fail to take up glucose from the blood, and blood glucose levels remain elevated. Although heredity can play a role in type 2 diabetes, excess body weight and lack of exercise significantly increase the risk. This form of diabetes generally appears after age 40, but even children who are overweight and sedentary can develop the disease. More than 90% of people with diabetes have type 2. Many can control their blood glucose levels with regular exercise and a healthy diet; some require medications. Nevertheless, type 2 diabetes is the seventh most common cause of death in the United States and a growing public health problem worldwide.

The resistance to insulin signaling in type 2 diabetes is sometimes due to a genetic defect in the insulin receptor or the insulin response pathway. In many cases, however, events in target cells suppress activity of an otherwise functional response pathway. One source of this suppression

appears to be inflammatory signals generated by the innate immune system (see Chapter 43). How obesity and inactivity relate to this suppression is being studied in both humans and laboratory animals.

CONCEPT CHECK 45.2

1. In a glucose tolerance test, periodic measurements of blood glucose level are taken after a person drinks a glucose-rich solution. In a healthy individual, blood glucose rises moderately at first but falls to near normal within 2–3 hours. Predict the results of this test in a person with diabetes mellitus. Explain your answer.
2. If a hormone pathway provides a transient response to a stimulus, how would shortening the stimulus duration affect the need for negative feedback?
3. **WHAT IF?** Consider a diabetes patient who has a family history of type 2 diabetes but is active and not obese. To identify genes that might be defective in the patient, which genes would you examine first?

For suggested answers, see Appendix A.

CONCEPT 45.3

The hypothalamus and pituitary are central to endocrine regulation

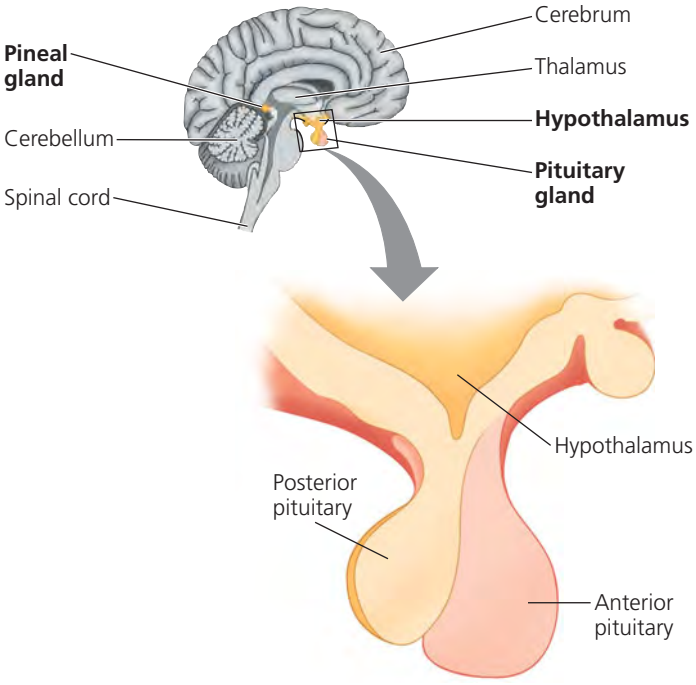
Having reviewed the organization of hormone pathways, we return to the role of the nervous system in regulating endocrine pathways. In particular, we now turn our focus to the vertebrate brain and endocrine system.

Coordination of Endocrine and Nervous Systems in Vertebrates

In vertebrates, the **hypothalamus** plays a central role in integrating the endocrine and nervous systems. One of several endocrine glands located in the brain **(Figure 45.14)**, the hypothalamus receives information from nerves throughout the body, including the brain. In response, the hypothalamus initiates endocrine signaling appropriate to environmental conditions. In many vertebrates, for example, nerve signals from the brain pass sensory information to the hypothalamus about seasonal changes. The hypothalamus, in turn, regulates the release of reproductive hormones required during the breeding season.

Signals from the hypothalamus travel to the **pituitary gland**, a gland located at its base (see Figure 45.14). Roughly the size and shape of a lima bean, the pituitary has discrete posterior and anterior parts, or lobes, that secrete different sets of hormones.

The **posterior pituitary** is an extension of the hypothalamus. Hypothalamic axons that reach into the posterior pituitary secrete neurohormones synthesized in the hypothalamus. In contrast, the **anterior pituitary** is an endocrine gland that synthesizes and secretes hormones in response to signals from the hypothalamus. Many anterior pituitary hormones act as **tropic hormones**, meaning that they regulate the function of other endocrine cells or glands.



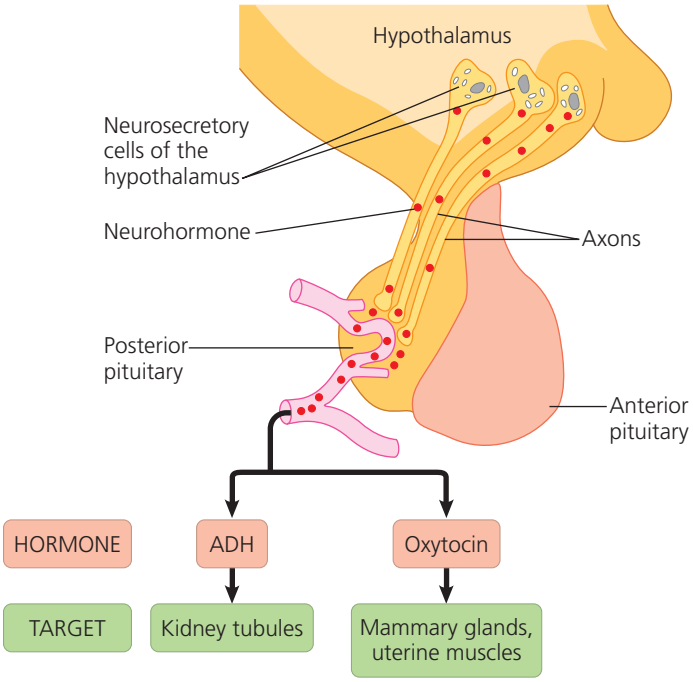
▲ **Figure 45.14 Endocrine glands in the human brain.** This side view of the brain indicates the position of the hypothalamus, the pituitary gland, and the pineal gland. (The pineal gland plays a role in regulating biorhythm.)

Posterior Pituitary Hormones

Neurosecretory cells of the hypothalamus synthesize the two posterior pituitary hormones: oxytocin and antidiuretic hormone. After traveling to the posterior pituitary within the long axons of the neurosecretory cells, the hormones are stored in pituitary cells, to be released in response to nerve impulses transmitted by the hypothalamus **(Figure 45.15)**.

As discussed in Concept 45.2 (see Figure 45.12), oxytocin regulates milk secretion by the mammary glands and also contractions of the uterus during birthing. In addition, oxytocin has targets in the brain, where it influences behaviors related to maternal care, pair bonding, and sexual activity.

Like oxytocin, **antidiuretic hormone (ADH)**, or *vasopressin*, regulates both physiology and behavior. As you read in Chapter 44, ADH is one of several hormones that regulate kidney function. In particular, ADH increases water retention in the kidneys, thus decreasing urine volume. The net result is to help maintain blood osmolarity within a normal range. ADH also plays an important role in social behavior, as detailed in Chapter 51.



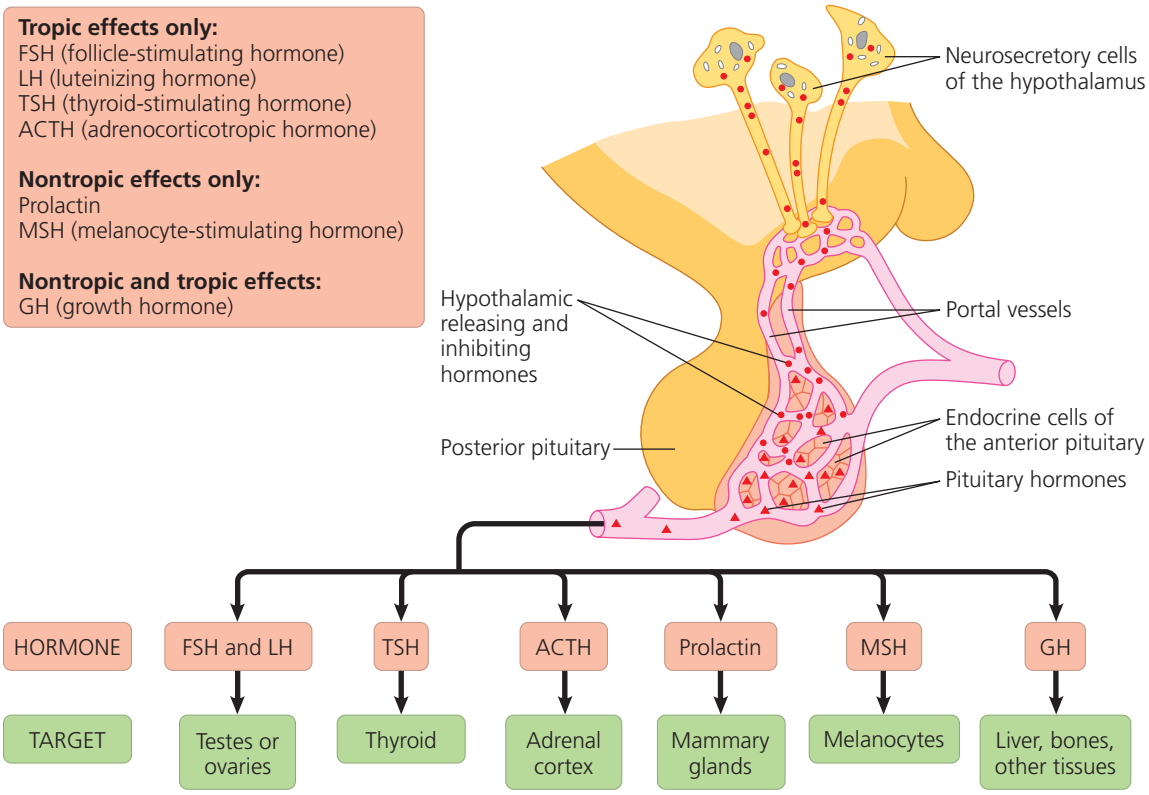
▲ **Figure 45.15 Production and release of posterior pituitary hormones.** The posterior pituitary gland is an extension of the hypothalamus. Certain neurosecretory cells in the hypothalamus make antidiuretic hormone (ADH) and oxytocin, which are transported to the posterior pituitary, where they are stored. Nerve signals from the brain trigger release of these neurohormones.

Anterior Pituitary Hormones

Endocrine signals generated by the hypothalamus regulate hormone secretion by the anterior pituitary **(Figure 45.16)**. Each hypothalamic hormone is either a *releasing hormone* or an *inhibiting hormone*, reflecting its role in promoting or inhibiting release of one or more specific hormones by the anterior pituitary. *Prolactin-releasing hormone*, for example, is a hypothalamic hormone that stimulates the anterior pituitary to secrete **prolactin**, which has activities that include stimulating milk production. Every anterior pituitary hormone is controlled by at least one releasing hormone. Some, such as prolactin, have both a releasing hormone and an inhibiting hormone.

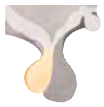
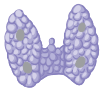
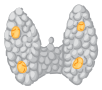
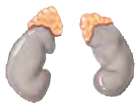
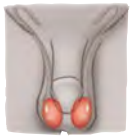
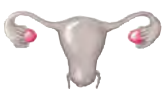
The hypothalamic releasing and inhibiting hormones are secreted near capillaries at the base of the hypothalamus. The capillaries drain into short blood vessels, called portal vessels, which subdivide into a second capillary bed within the anterior pituitary. In this way, the releasing and inhibiting hormones have direct access to the gland they control.

Hormones secreted by the anterior pituitary regulate a diverse set of processes in the human body, including metabolism, osmoregulation, and reproductive activity. We turn next to an exploration of these hormones and the processes they govern, beginning with the hormones of the thyroid gland. **Table 45.1** (on the next page), which provides an overview of the major hormones of the endocrine system and their physiological functions, will serve as a useful point of reference for this discussion.



◀ **Figure 45.16 Production and release of anterior pituitary hormones.** The release of hormones synthesized in the anterior pituitary gland is controlled by hypothalamic releasing and inhibiting hormones. The hypothalamic hormones are secreted by neurosecretory cells and enter a capillary network within the hypothalamus. These capillaries drain into portal vessels that connect with a second capillary network in the anterior pituitary.

Table 45.1 Major Human Endocrine Glands and Some of Their Hormones

Gland		Hormone	Chemical Class	Representative Actions	Regulated By
Hypothalamus		Hormones released from the posterior pituitary and hormones that regulate the anterior pituitary (see below)			
Posterior pituitary gland (releases neurohormones made in hypothalamus)		Oxytocin	Peptide	Stimulates contraction of uterus and mammary gland cells	Nervous system
		Antidiuretic hormone (ADH)	Peptide	Promotes retention of water by kidneys	Water/salt balance
Anterior pituitary gland		Growth hormone (GH)	Protein	Stimulates growth (especially bones) and metabolic functions	Hypothalamic hormones
		Prolactin	Protein	Stimulates milk production and secretion	Hypothalamic hormones
		Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates production of ova and sperm	Hypothalamic hormones
		Luteinizing hormone (LH)	Glycoprotein	Stimulates ovaries and testes	Hypothalamic hormones
		Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid gland	Hypothalamic hormones
		Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates adrenal cortex to secrete glucocorticoids	Hypothalamic hormones
Thyroid gland		Triiodothyronine (T_3) and thyroxine (T_4)	Amines	Stimulate and maintain metabolic processes	TSH
		Calcitonin	Peptide	Lowers blood calcium level	Calcium in blood
Parathyroid glands		Parathyroid hormone (PTH)	Peptide	Raises blood calcium level	Calcium in blood
Pancreas		Insulin	Protein	Lowers blood glucose level	Glucose in blood
		Glucagon	Protein	Raises blood glucose level	Glucose in blood
Adrenal glands					
Adrenal medulla		Epinephrine and norepinephrine	Amines	Raise blood glucose level; increase metabolic activities; constrict certain blood vessels	Nervous system
Adrenal cortex		Glucocorticoids	Steroids	Raise blood glucose level	ACTH
		Mineralocorticoids	Steroids	Promote reabsorption of Na^+ and excretion of K^+ in kidneys	K^+ in blood; angiotensin II
Gonads					
Testes		Androgens	Steroids	Support sperm formation; promote development and maintenance of male secondary sex characteristics	FSH and LH
Ovaries		Estrogens	Steroids	Stimulate uterine lining growth; promote development and maintenance of female secondary sex characteristics	FSH and LH
		Progestins	Steroids	Promote uterine lining growth	FSH and LH
Pineal gland		Melatonin	Amine	Involved in biological rhythms	Light/dark cycles

Thyroid Regulation: A Hormone Cascade Pathway

Sets of hormones from the hypothalamus, the anterior pituitary, and a target endocrine gland are often organized into a *hormone cascade pathway* **(Figure 45.17)**. Signals to the brain stimulate the hypothalamus to secrete a hormone that stimulates or inhibits release of a tropic anterior pituitary hormone. The anterior pituitary hormone in turn acts on a target endocrine tissue, stimulating secretion of yet another hormone that exerts systemic metabolic or developmental effects.

To learn more about how a hormone cascade pathway works, let's consider activation of the thyroid gland when an infant is exposed to cold (see Figure 45.17). When a young child's body temperature drops, the hypothalamus secretes thyrotropin-releasing hormone (TRH). The anterior pituitary responds to TRH by secreting thyroid-stimulating hormone (TSH), also known as thyrotropin. TSH stimulates release of thyroid hormone by the **thyroid gland**, an organ consisting of two lobes on the ventral surface of the trachea (see Figure 42.24). As thyroid hormone accumulates, it increases metabolic rate, resulting in the release of thermal energy, which raises body temperature.

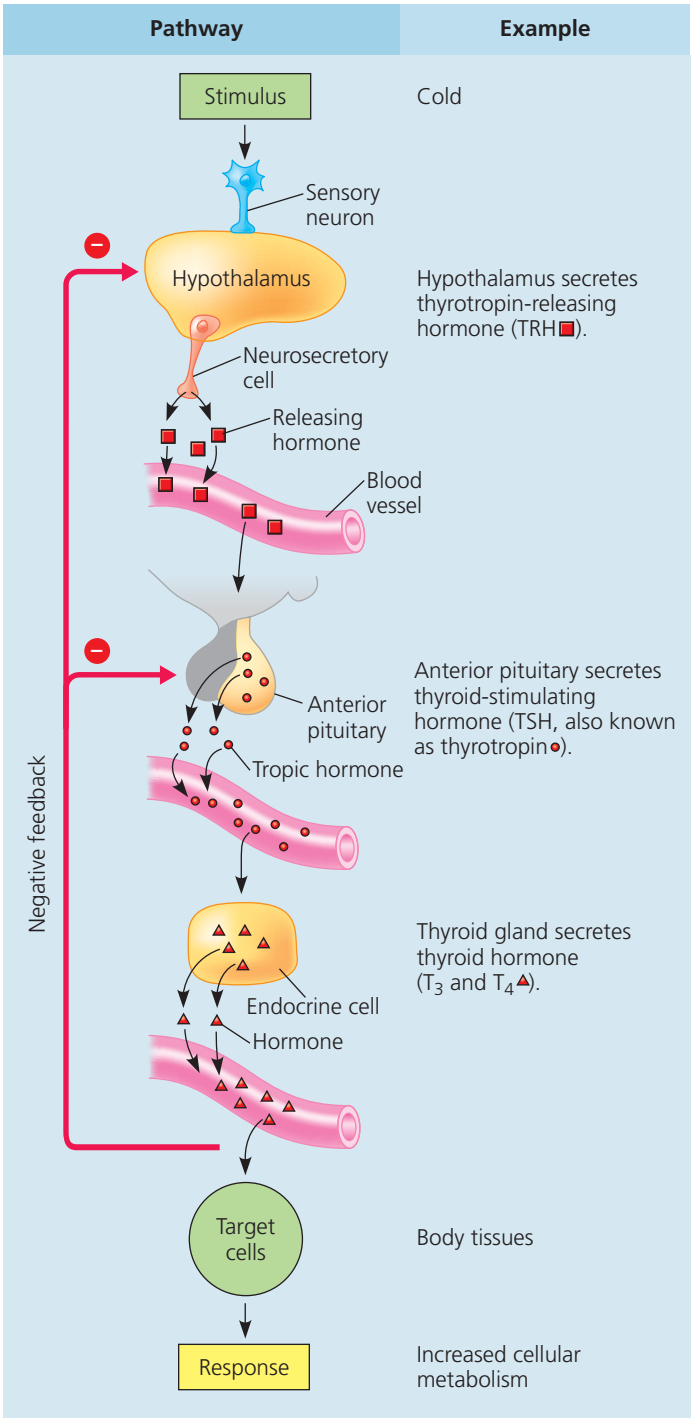
Like simple hormone pathways, hormone cascade pathways typically involve negative feedback. In the case of the thyroid hormone pathway, thyroid hormone itself carries out negative feedback. Because thyroid hormone blocks TSH release from the anterior pituitary and TRH release from the hypothalamus, the negative-feedback loop prevents overproduction of thyroid hormone. Overall, the hormone cascade pathway brings about a self-limiting response to the original stimulus in the target cells.

In humans and other mammals, thyroid hormone regulates bioenergetics; helps maintain normal blood pressure, heart rate, and muscle tone; and regulates digestive and reproductive functions. Too much or too little thyroid hormone in the blood can result in serious metabolic disorders.

Disorders of Thyroid Function and Regulation

In humans, hypothyroidism, a condition of too little thyroid function, can produce symptoms such as weight gain, lethargy, and intolerance to cold in adults. Excessive secretion of thyroid hormone, known as hyperthyroidism, can lead to high body temperature, profuse sweating, weight loss, irritability, and high blood pressure.

The most common form of hyperthyroidism is Graves' disease. Protruding eyes, caused by fluid accumulation behind the eyes, are a typical symptom. In this autoimmune disorder, the body produces antibodies that bind to and activate the receptor for TSH. The result is sustained thyroid hormone production.



▲ **Figure 45.17 A hormone cascade pathway.** In response to the stimulus, the hypothalamus secretes a releasing hormone that targets the anterior pituitary. The anterior pituitary responds by secreting a second tropic hormone, which travels through the bloodstream to an endocrine gland. In response to this tropic hormone, the endocrine gland secretes a hormone that travels to target cells, where it induces a response. In the example of thyroid hormone regulation, thyroid hormone exerts negative feedback on the hypothalamus and anterior pituitary. This feedback inhibits release of TRH and TSH, preventing overreaction to the stimulus (such as low temperature in the case of a human infant).

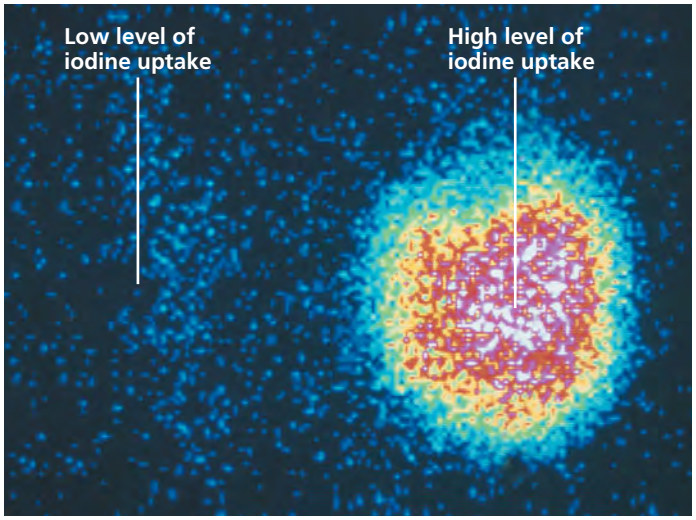
? *Suppose a lab test of two patients, each diagnosed with excessive thyroid hormone production, revealed elevated levels of TSH in one but not the other. Was the diagnosis of one patient necessarily incorrect? Explain.*

Malnutrition can also alter thyroid hormone production. The specific link between diet and thyroid hormone synthesis reflects the chemical nature of thyroid hormone. The term *thyroid hormone* actually refers to a pair of very similar hormones derived from the amino acid tyrosine. **Triiodothyronine (T_3)** contains three iodine atoms, whereas tetraiodothyronine, or **thyroxine (T_4)**, contains four iodine atoms (see Figure 45.5). In mammals, the same receptor binds both hormones. The thyroid gland secretes mainly T_4, but target cells convert most of it to T_3 by removing one iodine atom.

Although iodine is readily obtained from seafood or iodized salt, people in many parts of the world suffer from inadequate iodine in their diet. Without sufficient iodine, the thyroid gland cannot synthesize adequate amounts of T_3 and T_4, and the resulting low blood levels of T_3 and T_4 cannot exert the usual negative feedback on the hypothalamus and anterior pituitary (see Figure 45.17). As a consequence, the pituitary continues to secrete TSH. Elevated TSH levels cause an enlargement of the thyroid gland resulting in goiter, a characteristic swelling of the neck.

Humans and other vertebrates require thyroid hormones for the normal functioning of bone-forming cells, as well as for the branching of nerve cells during embryonic development of the brain. In humans, congenital hypothyroidism, an inherited condition of thyroid deficiency, results in markedly retarded skeletal growth and poor mental development. These defects can often be avoided, at least partially, if treatment with thyroid hormones begins early in life. Iodine deficiency in childhood causes the same defects, but it is fully preventable if iodized salt is used in food preparation.

The fact that iodine in the body is dedicated to the production of thyroid hormone provides a novel diagnostic tool for disorders of thyroid function: Radioactive forms of iodine enable specific imaging of the thyroid gland **(Figure 45.18)**.



▲ **Figure 45.18 Thyroid scan.** Radioactive iodine enables doctors to identify abnormal patterns of iodine uptake that could indicate a thyroid disorder.

Evolution of Hormone Function

EVOLUTION Over the course of evolution, the functions of a given hormone often diverge between species. An example is thyroid hormone, which plays a role in regulating metabolism across many evolutionary lineages. In frogs, however, thyroid hormone (thyroxine) has taken on an apparently unique function: stimulating resorption of the tadpole's tail during metamorphosis **(Figure 45.19)**.

Diverse functions have also evolved for many other vertebrate hormones. Prolactin, a product of the anterior pituitary, has an especially broad range of activities. Prolactin stimulates mammary gland growth and milk synthesis in mammals, regulates fat metabolism and reproduction in birds, delays metamorphosis in amphibians, and regulates salt and water balance in freshwater fishes. These varied roles suggest that prolactin is an ancient hormone with functions that have diversified during the evolution of vertebrate groups.

Melanocyte-stimulating hormone (MSH) is another example of an anterior pituitary hormone with distinct functions in different evolutionary lineages. In amphibians, fishes, and reptiles, MSH regulates skin color by controlling pigment distribution in skin cells called melanocytes. In mammals, MSH functions in hunger and metabolism in addition to coloration.

The specialized action of MSH that has evolved in the mammalian brain may prove to be of particular medical importance. Many patients with late-stage cancer, AIDS, tuberculosis, and certain aging disorders suffer from a devastating wasting

▲ Tadpole

▲ Adult frog

▲ **Figure 45.19 Specialized role of a hormone in frog metamorphosis.** The hormone thyroxine is responsible for the resorption of the tadpole's tail as the frog develops into its adult form.

condition called cachexia. Characterized by weight loss, muscle atrophy, and loss of appetite, cachexia is only poorly responsive to existing therapies. However, it turns out that activation of one brain receptor for MSH stimulates metabolism of fat and severely decreases appetite, changes also seen in cachexia. This fact led scientists to hypothesize that activation of this MSH receptor causes cachexia. To test this idea, they studied mice with mutations that cause cancerous tumors to develop, triggering cachexia. When the mice were treated with drugs that inhibit the brain MSH receptor, tumors occurred, but not cachexia! Whether such drugs can be used to treat cachexia in humans is an area of active study.

Tropic and Nontropic Hormones

As we have seen, thyroid-stimulating hormone (TSH) regulates the thyroid gland. This activity makes TSH an example of a tropic hormone. Although MSH and prolactin don't regulate endocrine cells or glands and are thus nontropic, three other anterior pituitary hormones act primarily or exclusively as tropic hormones: **follicle-stimulating hormone (FSH)**, **luteinizing hormone (LH)**, and **adrenocorticotropic hormone (ACTH)**.

FSH and LH stimulate the activities of both the male and female gonads, the testes and ovaries. For this reason, FSH and LH are also known as *gonadotropins*, and they are both regulated by hypothalamic *gonadotropin-releasing hormone* (*GnRH*). In Chapter 46, we will discuss how gonadotropins regulate reproductive functions.

ACTH stimulates the production and secretion of steroid hormones by the adrenal cortex. We will take a closer look at the hormone pathway involving ACTH later in this chapter.

Growth hormone (GH), which is secreted by the anterior pituitary, stimulates growth through both tropic and nontropic effects. A major target, the liver, responds to GH by releasing *insulin-like growth factors* (*IGFs*), which circulate in the blood and directly stimulate bone and cartilage growth. (IGFs also appear to play a key role in aging in many animal species.) In the absence of GH, the skeleton of an immature animal stops growing. GH also exerts diverse metabolic effects that tend to raise blood glucose levels, thus opposing the effects of insulin.

Abnormal production of GH in humans can result in several disorders, depending on when the problem occurs and whether it involves hypersecretion (too much) or hyposecretion (too little). Hypersecretion of GH during childhood can lead to gigantism, in which the person grows unusually tall—as tall as 2.4 m (8 feet)—though body proportions remain relatively normal. Excessive GH production in adulthood stimulates bony growth in the few tissues that are still responsive to the hormone. Because remaining target cells are predominantly in the face, hands, and feet, the result is an overgrowth of the extremities called acromegaly (from the Greek *acros*, extreme, and *mega*, large).

Hyposecretion of GH in childhood retards long-bone growth and can lead to pituitary dwarfism. Individuals with this disorder are for the most part properly proportioned but generally reach a height of only about 1.2 m (4 feet). If diagnosed before puberty, pituitary dwarfism can be treated successfully with human GH (also called HGH). Since the mid-1980s, scientists have used recombinant DNA technology to produce HGH in bacteria (see Chapter 20). Treatment with this genetically engineered HGH is now fairly routine for affected children.

CONCEPT CHECK 45.3

1. How do the two fused glands of the pituitary gland differ in function?
2. Why does hypothalamic control of oxytocin not require a releasing factor?
3. **WHAT IF?** Propose an explanation for why people with defects in specific endocrine pathways typically have defects in the final gland in the pathway rather than in the hypothalamus or pituitary.

For suggested answers, see Appendix A.

CONCEPT 45.4

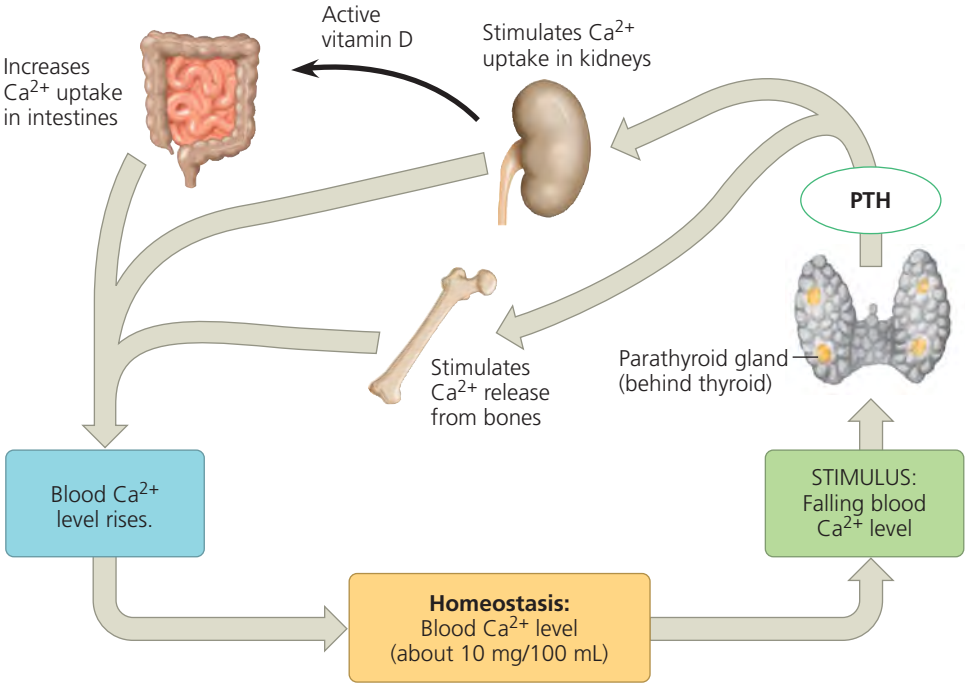
Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior

Now that we've seen how endocrine glands in the brain initiate hormone cascade pathways, we return to the broader question of how endocrine signaling regulates animal physiology. We'll focus on homeostasis, development, and behavior, leaving the topic of reproduction largely for later chapters. This section presents more examples of hormone regulation by metabolic stimuli, by nervous system input, and by hormones of the anterior pituitary. First we'll examine another simple hormone pathway, the regulation of calcium ion concentration in the circulatory system.

Parathyroid Hormone and Vitamin D: Control of Blood Calcium

Because calcium ions (Ca^{2+}) are essential to the normal functioning of all cells, homeostatic control of blood calcium level is critical. If the blood Ca^{2+} level falls substantially, skeletal muscles begin to contract convulsively, a potentially fatal condition called tetany. If the blood Ca^{2+} level rises substantially, precipitates of calcium phosphate can form in body tissues, leading to widespread organ damage.

In mammals, the **parathyroid glands**, a set of four small structures embedded in the posterior surface of the thyroid (see Figure 45.4), play a major role in blood Ca^{2+} regulation. When



▲ Figure 45.20 The roles of parathyroid hormone (PTH) in regulating blood calcium levels in mammals.

blood Ca^{2+} falls below a set point of about 10 mg/100 mL, these glands release **parathyroid hormone (PTH)**.

PTH raises the level of blood Ca^{2+} by direct and indirect effects **(Figure 45.20)**. In bone, PTH causes the mineralized matrix to decompose and release Ca^{2+} into the blood. In the kidneys, PTH directly stimulates reabsorption of Ca^{2+} through the renal tubules. PTH also has an indirect effect on the kidneys, promoting the conversion of vitamin D to an active hormone. An inactive form of vitamin D, a steroid-derived molecule, is obtained from food or synthesized in the skin when exposed to sunlight. Vitamin D activation begins in the liver and is completed in the kidneys, the process stimulated by PTH. The active form of vitamin D acts directly on the intestines, stimulating the uptake of Ca^{2+} from food and thus augmenting the effect of PTH. As blood Ca^{2+} rises, a negative-feedback loop inhibits further release of PTH from the parathyroid glands (not shown in figure).

The thyroid gland can also contribute to calcium homeostasis. If blood Ca^{2+} rises above the set point, the thyroid gland releases **calcitonin**, a hormone that inhibits bone resorption and enhances Ca^{2+} release by the kidney. In fishes, rodents, and some other animals, calcitonin is required for Ca^{2+} homeostasis. In humans, however, it is apparently needed only during the extensive bone growth of childhood.

Adrenal Hormones: Response to Stress

The **adrenal glands** of vertebrates are associated with the kidneys (the *renal* organs). In mammals, each adrenal gland is actually made up of two glands with different cell types, functions, and embryonic origins: the *adrenal cortex*, the outer portion, and the *adrenal medulla*, the central portion. The adrenal cortex consists of true endocrine cells, whereas the secretory cells of the adrenal medulla derive from neural tissue during embryonic development. Thus, like the pituitary gland, each adrenal gland is a fused endocrine and neuroendocrine gland.

Catecholamines from the Adrenal Medulla

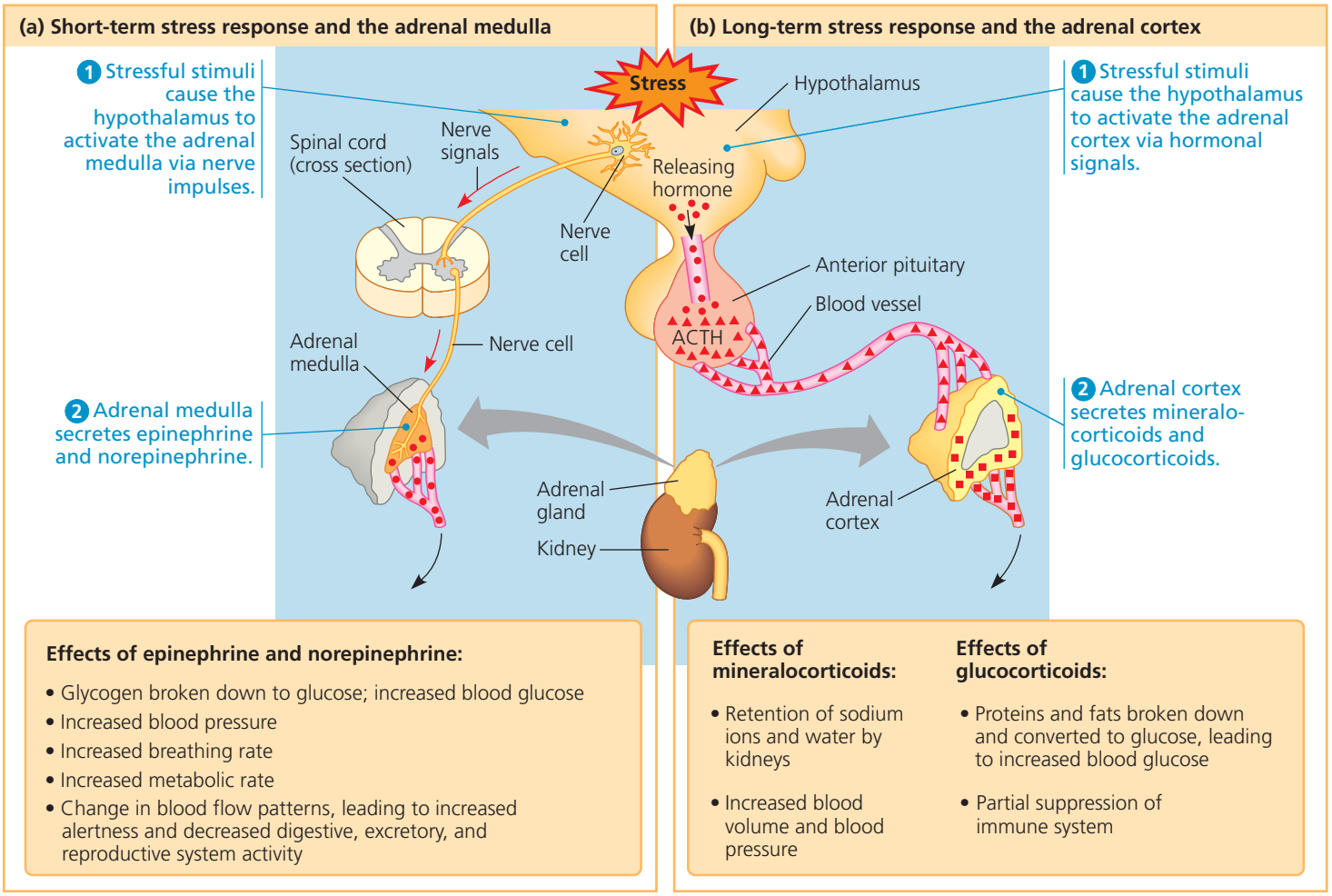
Imagine that while walking in the woods at night you hear a growling noise nearby. "A bear?" you wonder. Your heart beats faster, your breath quickens, your muscles tense, and your thoughts speed up. These and other rapid responses to perceived danger comprise the "fight-or-flight," or acute stress, response. This coordinated set of physiological changes is triggered by two hormones of the adrenal medulla, **norepinephrine** (also known as noradrenaline) and epinephrine (adrenaline). Both are **catecholamines**, a class of amine hormones synthesized from the amino acid tyrosine.

The adrenal medulla secretes epinephrine and norepinephrine in response to stress—whether extreme pleasure or life-threatening danger. A major activity of these hormones is to increase the amount of chemical energy available for immediate use. Both epinephrine and norepinephrine increase the rate of glycogen breakdown in the liver and skeletal muscles, promote glucose release by liver cells, and stimulate the release of fatty acids from fat cells. The released glucose and fatty acids circulate in the blood and can be used by body cells as fuel.

In addition to increasing the availability of energy sources, norepinephrine and epinephrine exert profound effects on the cardiovascular and respiratory systems. For example, they increase both the heart rate and stroke volume and dilate the bronchioles in the lungs, actions that raise the rate of oxygen delivery to body cells. For this reason, doctors may prescribe epinephrine as a heart stimulant or to open the airways during an asthma attack. The catecholamines also alter blood flow, causing constriction of some blood vessels and dilation of others (see Figure 45.9). The overall effect is to shunt blood away from the skin, digestive organs, and kidneys, while increasing the blood supply to the heart, brain, and skeletal muscles. Epinephrine generally has a stronger effect on heart and metabolic rates, while the primary role of norepinephrine is in modulating blood pressure.

Nerve signals carried from the brain via involuntary (autonomic) neurons regulate secretion by the adrenal medulla. In response to a stressful stimulus, nerve impulses travel to the adrenal medulla, where they trigger the

▼ Figure 45.21 Stress and the adrenal gland.



release of catecholamines from neurosecretory cells **(Figure 45.21a)**. Acting on target tissues, epinephrine and norepinephrine each function in a simple neurohormone pathway. As you will read in Chapter 48, epinephrine and norepinephrine also function as neurotransmitters.

Steroid Hormones from the Adrenal Cortex

Hormones from the adrenal cortex also function in the body's response to stress. But in contrast to the adrenal medulla, which reacts to nervous input, the adrenal cortex responds to endocrine signals. Stressful stimuli cause the hypothalamus to secrete a releasing hormone that stimulates the anterior pituitary to release the tropic hormone ACTH. When ACTH reaches the adrenal cortex via the bloodstream, it stimulates the endocrine cells to synthesize and secrete a family of steroids called **corticosteroids** **(Figure 45.21b)**. The two main types of corticosteroids in humans are glucocorticoids and mineralocorticoids.

As reflected in their name, **glucocorticoids** have a primary effect on glucose metabolism. Augmenting the fuel-mobilizing effects of glucagon from the pancreas, glucocorticoids promote glucose synthesis from noncarbohydrate sources, such as proteins, making more glucose available as fuel. Glucocorticoids, such as cortisol (see Figure 45.5), act on skeletal muscle, causing the breakdown of muscle proteins. The resulting amino acids are transported to the liver and kidneys, where they are converted to glucose and released into the blood. The synthesis of glucose from muscle proteins provides circulating fuel when the body requires more glucose than the liver can mobilize from its glycogen stores.

When glucocorticoids are introduced into the body at levels above those normally present, they suppress certain components of the body's immune system. Because of this anti-inflammatory effect, glucocorticoids are sometimes used to treat inflammatory diseases such as arthritis. However, long-term use can have serious side effects, reflecting the potent activity of glucocorticoids on metabolism. For these reasons, nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, generally are preferred for treating chronic inflammatory conditions.

Mineralocorticoids, named for their effects on mineral metabolism, act principally in maintaining salt and water balance. For example, the mineralocorticoid *aldosterone* functions in ion and water homeostasis of the blood. Low blood volume or pressure leads to production of angiotensin II, which stimulates the secretion of aldosterone (see Figure 44.22). Aldosterone, in turn, stimulates cells in the kidneys to reabsorb sodium ions and water from filtrate, raising blood pressure and volume. Aldosterone also functions in the body's response to severe stress. In these circumstances, a rise in blood ACTH levels increases the rate at which the adrenal cortex secretes aldosterone as well as glucocorticoids.

The corticosteroid products of the adrenal cortex include small amounts of steroid hormones that function as sex hormones. Small structural differences between these steroid hormones (see p. 63) are associated with major differences in effects. The sex hormones produced by the adrenal cortex are mainly "male" hormones (androgens), with small amounts of "female" hormones (estrogens and progestins). There is evidence that adrenal androgens account for the sex drive in adult females, but otherwise the physiological roles of the adrenal sex hormones are not well understood.

Gonadal Sex Hormones

Sex hormones affect growth, development, reproductive cycles, and sexual behavior. Whereas the adrenal glands secrete small quantities of these hormones, the testes of males and ovaries of females are their principal sources. The gonads produce and secrete three major categories of steroid hormones: androgens, estrogens, and progestins. All three types are found in both males and females but in significantly different proportions.

The testes primarily synthesize **androgens**, the main one being **testosterone**. Testosterone first functions before birth, as shown in the 1940s by French researcher Alfred Jost. He was interested in how hormones determine whether an individual develops as a male or female. Working with rabbits, Jost carried out a surgical study that provided a simple and unexpected answer **(Figure 45.22)**. His studies established that for mammals (but not all animals), female development is the default process in embryos.

Androgens have a major role again at human puberty, when they are responsible for the development of human male secondary sex characteristics. High concentrations of androgen lead to a low voice and male patterns of hair growth, as well as increases in muscle and bone mass. The muscle-building, or anabolic, action of testosterone and related steroids has enticed some athletes to take them as supplements, despite prohibitions against their use in nearly all sports. Use of anabolic steroids, while effective in increasing muscle mass, can cause severe acne outbreaks and liver damage, as well as significant decreases in sperm count and testicular size.

Estrogens, of which the most important is **estradiol**, are responsible for the maintenance of the female reproductive system and for the development of female secondary sex characteristics. In mammals, **progestins**, which include **progesterone**, are primarily involved in preparing and maintaining tissues of the uterus required to support the growth and development of an embryo.

Estrogens and other gonadal sex hormones are components of hormone cascade pathways. Synthesis of these hormones is controlled by gonadotropins (FSH and LH) from the anterior pituitary gland (see Figure 45.16). FSH and LH secretion is in turn controlled by GnRH (gonadotropin-releasing hormone), a releasing hormone from the hypothalamus. We will examine the feedback relationships that regulate gonadal steroid secretion in detail in Chapter 46.

Endocrine Disruptors

Between 1938 and 1971, some pregnant women at risk for complications were prescribed a synthetic estrogen called diethylstilbestrol (DES). What was not known until 1971 was that exposure to DES can alter reproductive system development in the fetus. Collectively, daughters of women who took DES are more frequently afflicted with certain reproductive abnormalities, including a form of vaginal and cervical cancer, structural changes in the reproductive organs, and

▼ Figure 45.22 **INQUIRY**

What role do hormones play in making a mammal male or female?

EXPERIMENT Alfred Jost, at the College de France in Paris, wondered whether gonadal hormones instruct an embryo to develop as male or female in accord with its chromosome set. Working with rabbit embryos still in the mother's uterus, at a stage before sex differences are observable, he surgically removed the portion of each embryo that would form the ovaries or testes. When the baby rabbits were born, Jost made note of both chromosomal sex and the sexual differentiation of the genital structures.

RESULTS

Chromosome Set	Appearance of Genitalia	
	No surgery	Embryonic gonad removed
XY (male)	Male	Female
XX (female)	Female	Female

CONCLUSION In rabbits, male development requires a hormonal signal from the male gonad. In the absence of this signal, all embryos develop as female. Jost later demonstrated that embryos developed male genitalia if the surgically removed gonad was replaced with a crystal of testosterone. The process of sex determination occurs in a highly similar manner in all mammals, including humans.

SOURCE A. Jost, Recherches sur la differenciation sexuelle de l'embryon de lapin (Studies on the sexual differentiation of the rabbit embryo), *Archives d'Anatomie Microscopique et de Morphologie Expérimentale* 36:271–316 (1947).

WHAT IF? What result would Jost have obtained if female development also required a signal from the gonad?

increased risk of miscarriage (spontaneous abortion). DES is now recognized as an *endocrine disruptor*, a foreign molecule that interrupts the normal function of a hormone pathway.

In recent years, it has been hypothesized that molecules in the environment also act as endocrine disruptors. Some estrogen-like molecules, such as those present in soybeans and other edible plant products, have been suggested to lower breast cancer risk. Others, such as bisphenol A, a chemical used in making some plastics, have been studied for potential interference with normal reproduction and development. Sorting out such effects has proved quite difficult, however, in part because enzymes in the liver change the properties of any such molecules entering the body through the digestive system.

Melatonin and Biorhythms

We conclude our discussion of the vertebrate endocrine system with the **pineal gland**, a small mass of tissue near the center of the mammalian brain (see Figure 45.14). The pineal gland is a primary source of the hormone **melatonin**, a modified amino acid.

Melatonin regulates functions related to light and to seasons marked by changes in day length. Although melatonin affects skin pigmentation in many vertebrates, its primary functions relate to biological rhythms associated with reproduction and with daily activity levels. Melatonin is secreted at night, and the amount released depends on the length of the night. In winter, for example, when days are short and nights are long, more melatonin is secreted. There is also good evidence that nightly increases in the levels of melatonin play a significant role in promoting sleep.

The release of melatonin by the pineal gland is controlled by a group of neurons in the hypothalamus called the suprachiasmatic nucleus (SCN). The SCN functions as a biological clock and receives input from specialized light-sensitive neurons in the retina of the eye. Although the SCN regulates melatonin production during the 24-hour light/dark cycle, melatonin also influences SCN activity. We will consider biological rhythms further in Chapter 49, where we analyze experiments on SCN function.

In the next chapter, we will look at reproduction in both vertebrates and invertebrates. There we will see that the endocrine system is central not only to the survival of the individual, but also to the propagation of the species.

CONCEPT CHECK 45.4

1. How does the fact that two adrenal hormones act as neurotransmitters relate to the developmental origin of the adrenal gland?
2. How would a decrease in the number of corticosteroid receptors in the hypothalamus affect levels of corticosteroids in the blood?
3. **WHAT IF?** Suppose you receive an injection of cortisone, a glucocorticoid, in an inflamed joint. What aspects of glucocorticoid activity would you be exploiting? If a glucocorticoid pill were also effective at treating the inflammation, why would it still be preferable to introduce the drug locally?

For suggested answers, see Appendix A.

45 CHAPTER REVIEW

SUMMARY OF KEY CONCEPTS

CONCEPT 45.1

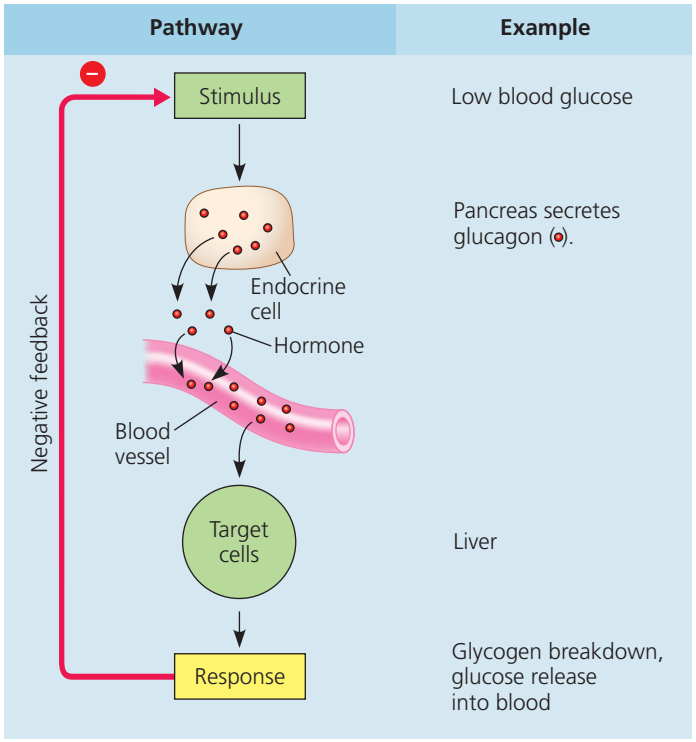
Hormones and other signaling molecules bind to target receptors, triggering specific response pathways (pp. 975–980)

- The forms of communication between animal cells differ in the type of secreting cell and the route taken by the signal to its target. **Endocrine** signals, or **hormones**, are secreted into extracellular fluids by endocrine cells or ductless glands and reach target cells via circulatory fluids. **Paracrine** signals act on neighboring cells, whereas **autocrine** signals act on the secreting cell itself. **Neurotransmitters** also act locally, but **neurohormones** can act throughout the body. **Pheromones** are released into the environment for communication between animals of the same species.
- In insects, molting and development are controlled by PTTH; **ecdysteroid**, whose release is triggered by PTTH; and juvenile hormone. Coordination of signals from the nervous and endocrine systems and modulation of one hormone activity by another bring about the precise series of developmental stages that lead to an adult form.
- Distinct cellular responses are associated with water-soluble and lipid-soluble hormones. Polypeptide hormones and most amine hormones are water-soluble and bind to receptors embedded in the plasma membrane. Binding of water-soluble hormones to cell-surface receptors triggers intracellular **signal transduction**, leading to specific responses in the cytoplasm or changes in gene expression. In contrast, steroid and thyroid hormones are lipid-soluble and readily enter target cells. There they bind to specific protein receptors in the cytosol or nucleus. These complexes of a lipid-soluble hormone and its receptor act in the nucleus to regulate transcription of specific genes. The same hormone may have different effects on target cells that have different receptors for the hormone or different signal transduction pathways.
- **Local regulators**, which carry out paracrine and autocrine signaling, include cytokines and **growth factors** (proteins/peptides), **nitric oxide** (a gas), and **prostaglandins** (modified fatty acids).

? *Predict what would happen if you injected a water-soluble hormone directly into the cytosol of a target cell.*

CONCEPT 45.2

Feedback regulation and antagonistic hormone pairs are common in endocrine systems (pp. 981–984)



- Hormone pathways may be regulated by **negative feedback**, which dampens the stimulus, or **positive feedback**, which amplifies the stimulus and drives the response to completion. Negative-feedback pathways sometimes occur in antagonistic pairs, such as the maintainance of glucose homeostasis by **glucagon** (from alpha cells of the **pancreas**) and **insulin** (from beta cells of the pancreas). Insulin reduces blood glucose levels by promoting cellular uptake of glucose, glycogen formation in the liver, protein synthesis, and fat storage. The disorder **diabetes mellitus**, which is marked by elevated blood glucose levels, results from inadequate production of insulin (type 1) or loss of responsiveness of target cells to insulin (type 2).

? *Would taking a drug that blocks the action of glucagon lessen the symptoms of diabetes or make them worse? Explain.*

CONCEPT 45.3

The hypothalamus and pituitary are central to endocrine regulation (pp. 984–989)

- Some neurosecretory cells in the **hypothalamus** produce hormones secreted by the **posterior pituitary**. Other hypothalamic cells produce hormones that are transported by portal vessels to the **anterior pituitary**, where they stimulate or inhibit the release of particular hormones.
- The two hormones released from the **posterior pituitary** act directly on nonendocrine tissues. **Oxytocin** induces uterine contractions and release of milk from mammary glands, and **antidiuretic hormone** (ADH) enhances water reabsorption in the kidneys.
- Often, anterior pituitary hormones act in a cascade. In the case of thyrotropin, or thyroid-stimulating hormone (TSH), TSH secretion is regulated by thyrotropin-releasing hormone (TRH). TSH in turn induces the **thyroid gland** to secrete **thyroid hormone**, a combination of the iodine-containing hormones $\mathbf{T_3}$ and $\mathbf{T_4}$. Thyroid hormone stimulates metabolism and influences development and maturation.
- Hormones sometimes acquire distinct roles in different species over the course of evolution. **Prolactin** stimulates milk production in mammals but has diverse effects in different vertebrates. **Melanocyte-stimulating hormone** (MSH) influences skin pigmentation in some vertebrates and fat metabolism in mammals.
- Although prolactin and MSH act on nonendocrine targets, most anterior pituitary hormones are tropic, acting on endocrine tissues or glands to regulate hormone secretion. **Tropic hormones** of the anterior pituitary include TSH, **follicle-stimulating hormone** (FSH), **luteinizing hormone** (LH), and **adrenocorticotropic hormone** (ACTH). **Growth hormone** (GH) has both tropic and nontropic effects. It promotes growth directly, has diverse metabolic effects, and stimulates the production of growth factors by other tissues.

? *Which major endocrine organs are regulated independently of the hypothalamus and pituitary? Explain.*

CONCEPT 45.4

Endocrine glands respond to diverse stimuli in regulating homeostasis, development, and behavior (pp. 989–993)

- **Parathyroid hormone** (PTH), secreted by the **parathyroid glands**, causes bone to release Ca^{2+} into the blood and stimulates reabsorption of Ca^{2+} in the kidneys. PTH also stimulates the kidneys to activate vitamin D, which promotes intestinal uptake of Ca^{2+} from food. **Calcitonin**, secreted by the thyroid, has the opposite effects in bones and kidneys as PTH. Calcitonin is important for calcium homeostasis in adults of some vertebrates, but not humans.
- In response to stress, neurosecretory cells in the adrenal medulla release **epinephrine** and **norepinephrine**, which mediate various fight-or-flight responses. The adrenal cortex releases **glucocorticoids**, such as cortisol, which influence glucose metabolism and the immune system, as well as **mineralocorticoids**, primarily aldosterone, which help regulate salt and water balance.
- Although the adrenal cortex produces small amounts of sex hormones, the gonads—testes and ovaries—produce most of the body's sex hormones. All three types—**androgens**, **estrogens**, and **progestins**—are produced in males and females, but in different proportions.
- The **pineal gland**, located within the brain, secretes **melatonin**, which functions in biological rhythms related to reproduction and sleep. Release of melatonin is controlled by the SCN, the region of the brain that functions as a biological clock.

? *ADH and epinephrine act as hormones when released into the bloodstream and as neurotransmitters when released in synapses between neurons. What is similar about the endocrine glands that produce these two molecules?*

TEST YOUR UNDERSTANDING

LEVEL 1: KNOWLEDGE/COMPREHENSION

1. Which of the following is *not* an accurate statement?
   a. Hormones are chemical messengers that travel to target cells through the circulatory system.
   b. Hormones often regulate homeostasis through antagonistic functions.
   c. Hormones of the same chemical class usually have the same function.

d. Hormones are secreted by specialized cells usually located in endocrine glands.
e. Hormones are often regulated through feedback loops.

2. An example of antagonistic hormones controlling homeostasis is
a. thyroxine and parathyroid hormone in calcium balance.
b. insulin and glucagon in glucose metabolism.
c. progestins and estrogens in sexual differentiation.
d. epinephrine and norepinephrine in fight-or-flight responses.
e. oxytocin and prolactin in milk production.

3. Growth factors are local regulators that
a. are produced by the anterior pituitary.
b. are modified fatty acids that stimulate bone and cartilage growth.
c. are found on the surface of cancer cells and stimulate abnormal cell division.
d. bind to cell-surface receptors and stimulate growth and development of target cells.
e. convey messages between nerve cells.

4. Which hormone is *incorrectly* paired with its action?
a. oxytocin—stimulates uterine contractions during childbirth
b. thyroxine—stimulates metabolic processes
c. insulin—stimulates glycogen breakdown in the liver
d. ACTH—stimulates the release of glucocorticoids by the adrenal cortex
e. melatonin—affects biological rhythms, seasonal reproduction

LEVEL 2: APPLICATION/ANALYSIS

5. Steroid and peptide hormones typically have in common
a. the building blocks from which they are synthesized.
b. their solubility in cell membranes.
c. their requirement for travel through the bloodstream.
d. the location of their receptors.
e. their reliance on signal transduction in the cell.

6. Which of the following is the most likely explanation for hypothyroidism in a patient whose iodine level is normal?
a. greater production of T_3 than of T_4
b. hyposecretion of TSH
c. hypersecretion of TSH
d. hypersecretion of MSH
e. a decrease in the thyroid secretion of calcitonin

7. Shortly after ingesting a big plate of carbohydrate-rich pasta, you measure your blood's hormone levels. What results would you expect, compared to before the meal?
a. high insulin, low glucagon
b. low insulin, low glucagon
c. high insulin, high glucagon
d. low insulin, high glucagon
e. low insulin, no change in glucagon

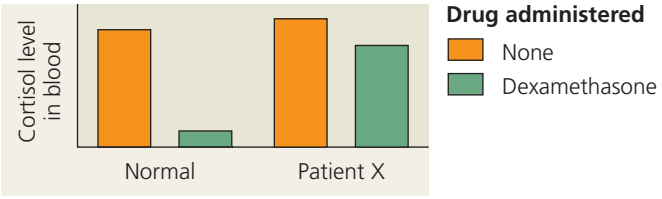
8. The relationship between the insect hormones ecdysteroid and PTTH is an example of
a. an interaction of the endocrine and nervous systems.
b. homeostasis achieved by positive feedback.
c. how peptide-derived hormones have more widespread effects than steroid hormones.
d. homeostasis maintained by antagonistic hormones.
e. competitive inhibition of a hormone receptor.

9. **DRAW IT** In mammals, milk production by mammary glands is controlled by prolactin and prolactin-releasing hormone. Draw a simple sketch of this pathway, including glands and tissues, hormones, routes for hormone movement, and effects.

LEVEL 3: SYNTHESIS/EVALUATION

10. **EVOLUTION CONNECTION** The intracellular receptors used by all the steroid and thyroid hormones are similar enough in structure that they are all considered members of one "superfamily" of proteins. Propose a hypothesis for how the genes encoding these receptors may have evolved. (*Hint*: See Figure 21.13.) How could you test your hypothesis using DNA sequence data?

11. **SCIENTIFIC INQUIRY** Chronically high levels of glucocorticoids can result in obesity, muscle weakness, and depression, a combination of symptoms called Cushing's syndrome. Excessive activity of either the pituitary or the adrenal gland can be the cause. To determine which gland has abnormal activity in a particular patient, doctors use the drug dexamethasone, a synthetic glucocorticoid that blocks ACTH release. Based on the graph, which gland is affected in patient X?



12. **WRITE ABOUT A THEME**
Environmental Interactions In a short essay (100–150 words), use specific examples to discuss the role of hormones in an animal's responses to changes in its environment.

For selected answers, see Appendix A.

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