



The northern gannet (*Sula bassanoides*). Diving into the cold waters of the North Sea precluded the development of a brood patch in this species. Rather, the females cradle their eggs in the webbing of their feet during incubation, achieving temperatures close to 37°C.

Endocrine Systems

7.1 Introduction: Principles of Endocrinology

The ability of cells to “communicate” with each other is ancient, preceding the evolution of multicellularity. Protozoan cells, for example, communicate through the release of chemical signals into the environment in order to mate. Recall that chemicals that elicit specific behavioral responses in other individuals of the same species are termed **pheromones** (p. 92). In animals, pheromones and internal signal molecules used locally within a tissue (that is, paracrine action, p. 91) appear in all phyla, as do signal molecules used by neurons at synapses except in the sponges. With the evolution of internal body cavities and circulatory systems, which provided an effective route for delivering signal molecules to distant tissues, there arose **endocrine systems**, which consist of ductless glands, often scattered throughout an animal’s body as both discrete endocrine organs and as subsets of other organs having nonendocrine functions (as shown in Figure 7-1 for a mammal). The glands secrete **hormones** (signal molecules delivered by circulatory

fluids), providing a second mechanism (in addition to nervous systems) for regulating and coordinating distant organs. The endocrine and nervous systems are specialized for controlling different types of activities. In general, the nervous system coordinates rapid, precise responses and is especially important in mediating interactions with the external environment. The endocrine system, by contrast, primarily controls activities that require duration rather than speed as well as coordinating diverse tissues (e.g. liver, muscle, and gut). In the course of animal evolution, there has been an increase in the number and complexity of processes that have come under hormonal regulation. Moreover, the two systems are often intimately linked in *neuroendocrine* interactions, in which neurons secrete neurohormones into a body fluid for transport. In vertebrates, this is reflected in a classification of glands into **central** ones linked to the central nervous system, and **peripheral** ones that are not.

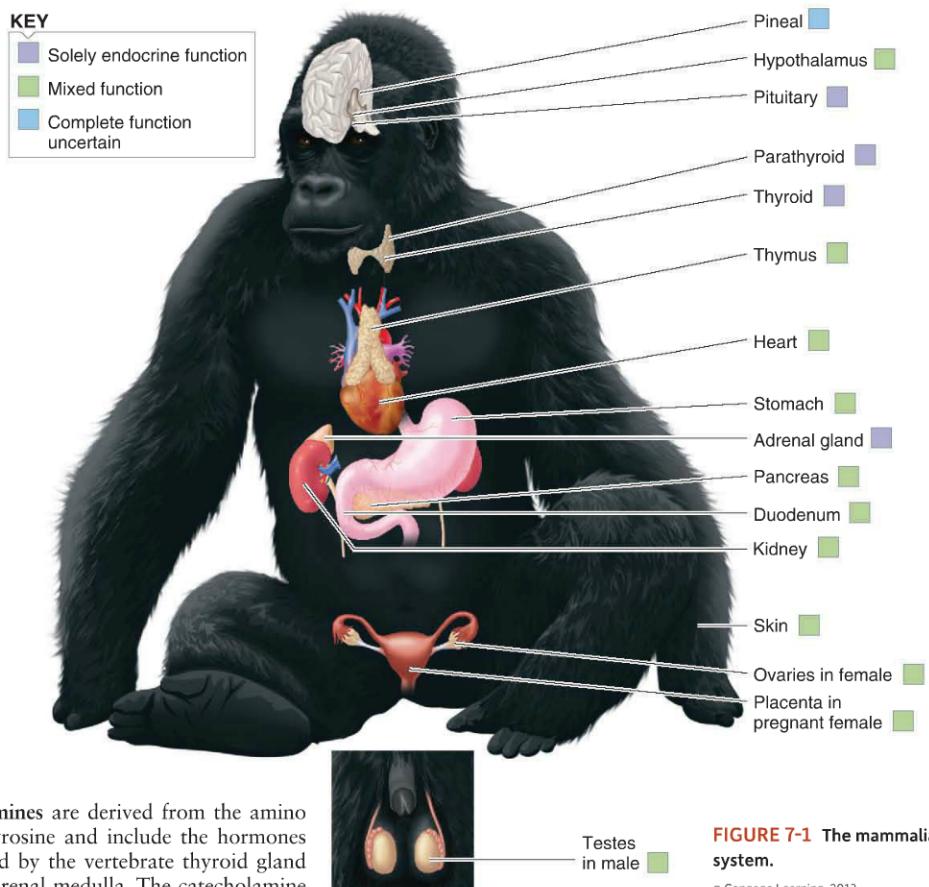
Endocrinology is the study of the evolution and physiological function of hormones. We begin this chapter by examining general principles of endocrinology,

and then we examine specific hormones in nonvertebrates (primarily insects) and vertebrates.

Hormones are chemically classified into three categories: peptides and proteins, amines, steroids

Hormones are not all similar chemically, but instead fall into three distinct classes according to their biochemical structure (Table 7-1; compare this table to the list of all chemical messengers on p. 93):

1. The peptide and protein hormones consist of specific amino acids arranged in a chain of varying length; the shorter chains are peptides and the longer ones are categorized as proteins. For convenience, we refer to this entire category as *peptides*. The majority of animal hormones fall into this class; an example is *insulin*, which regulates blood glucose in vertebrates.



- The amines are derived from the amino acid tyrosine and include the hormones secreted by the vertebrate thyroid gland and adrenal medulla. The catecholamine hormones are specifically known as **catecholamines**.
- The **steroids** are neutral lipids derived from cholesterol. These include the hormones secreted by the molting glands of arthropods and the vertebrate adrenal cortex and gonads (sex steroids such as *estradiol* and *testosterone*), as well as some mammalian placental hormones. Insects cannot synthesize the core steroid molecule and so must ingest suitable precursors in order to synthesize their primary steroid hormone *ecdysone*.

These signal types are apparently quite ancient. Several amines and peptides identical to signal molecules found in animals have been detected as pheromones in protozoa. A peptide closely related to human insulin (with a corresponding receptor) has been found in some Porifera (sponges), although its function is unclear. In recent years, all three signal types have been found in Cnidaria. For example, estradiol and testosterone have been found in some corals, in which estradiol levels surge during mass spawning events, suggesting a regulatory role in reproduction.

Minor differences in chemical structure between hormones within each category often result in profound differences in biological response. For example, note the subtle difference between testosterone, the male sex hormone responsible for inducing the development of masculine characteristics, and estradiol, a form of estrogen, which is the feminizing female sex hormone (Figure 7-2).

FIGURE 7-1 The mammalian endocrine system.

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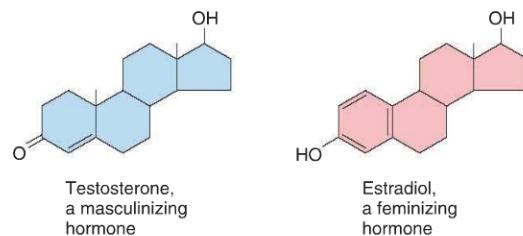


FIGURE 7-2 Comparison of two steroid hormones, testosterone and estradiol.

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Solubility Characteristics of Hormone Classes The structural classification of hormones is of more than biochemical interest. The chemical properties of a hormone, most notably its solubility, determine the means by which the hormone is synthesized, stored, and secreted; the way it is transported in the blood; and the mechanism by which it exerts its effects at the target cell, and typically, the type of processes regulated (rapid versus long-term) and their half-lives (turnover) in the circulation. The following differences

TABLE 7-1 Chemical Classification of Vertebrate Hormones

| Amines | | | | |
|------------------------------|--|---|---|--|
| Properties | Peptides | Catecholamines | Thyroid Hormone | Steroids |
| Structure | Chains of specific amino acids, for example: <chem>Cys^1-s-s-Cys^6-Pro^7-Arg^8-Gly^9NH2</chem> Tyr ² Asn ⁵ Phe ³ — Gln ⁴ (Vasopressin) | Tyrosine derivative, for example: (Epinephrine) | Iodinated tyrosine derivative, for example: (Thyroxine, T ₄) | Cholesterol derivative, for example: |
| Solubility | Hydrophilic (lipophobic) | Hydrophilic (lipophobic) | Lipophilic (hydrophobic) | Lipophilic (hydrophobic) |
| Synthesis | In rough endoplasmic reticulum; packaged in Golgi complex | In cytosol | In colloid, an inland extra-cellular site | Stepwise modification of cholesterol molecule in various intracellular compartments |
| Storage | Large amounts in secretory granules | In chromaffin granules | In colloid | Not stored; cholesterol precursor stored in lipid droplets |
| Secretion | Exocytosis of granules | Exocytosis of granules | Endocytosis of colloid | Simple diffusion |
| Transport in Blood | As free hormone | Half bound to plasma proteins | Mostly bound to plasma proteins | Mostly bound to plasma proteins |
| Receptor Site | Surface of target cell | Surface of target cell | Inside target cell | Inside target cell |
| Mechanism of Action | Channel changes or activation of second-messenger system to alter activity of preexisting proteins that produce the effect | Activation of second messenger system to alter activity of preexisting proteins that produce the effect | Activation of specific genes to produce new proteins that produce the effect | Activation of specific genes to produce new proteins that produce the effect |
| Hormones of This Type | All hormones from the hypothalamus, anterior pituitary, posterior pituitary, pineal gland, pancreas, parathyroid gland, gastrointestinal tract, kidneys, liver, thyroid C cells, heart | Only hormones from the adrenal medulla | Only hormones from the thyroid follicular cells | Hormones from the adrenal cortex and gonads plus most placental hormones (vitamin D is steroid-like) |

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in the solubility of the various types of hormones are critical to their function (Table 7-1):

- All peptides and catecholamines are *hydrophilic* (water loving); that is, they are highly H₂O soluble and have low lipid solubility.
- All steroid and thyroid hormones are *lipophilic* (lipid loving); that is, they have high lipid solubility and are poorly soluble in H₂O.

We are first going to consider the different ways in which these hormone types are processed at their site of origin, the endocrine cell, before comparing their means of transport and mechanisms of action.

The mechanisms of hormone synthesis, storage, and secretion vary according to the class of hormone

Because of their chemical differences, the means by which the various classes of hormones are synthesized, stored, and secreted differ as follows.

Peptide Hormones Peptide hormones are synthesized by the same method used for the manufacture of any protein that is to be exported (see Figure 2-10, p. 40). Because they are destined to be released from the endocrine cell, the synthesized hormones must be segregated from intracellular proteins by being sequestered in a membrane-enclosed compart-

ment until they are secreted. Briefly, synthesis of peptide hormones requires the following steps:

1. Large precursor proteins, or **preprohormones**, are synthesized by ribosomes on the rough endoplasmic reticulum. The preprohormones then migrate to the Golgi complex in membrane-enclosed vesicles that pinch off from the smooth endoplasmic reticulum.
2. During their journey through the endoplasmic reticulum and Golgi complex, the large preprohormone precursor molecules are pruned first to **prohormones** and finally to **active hormones**. The peptide “scraps” that remain after the large preprohormone molecule is cleaved to form the classic hormone are often stored and cosecreted along with the hormone. This raises the possibility that these other peptides may also exert biological effects that differ from the traditional hormonal product; that is, the cell may actually be secreting multiple hormones, but the functions of the other peptide products are for the most part unknown. A known example involves the large precursor molecule **pro-opiomelanocortin (POMC)** in vertebrates. Before secretion, several diverse cell types produce POMC and slice it in unique ways, depending on the processing enzymes they possess, to yield different active products. In particular, POMC can be cleaved into **adrenocorticotropic hormone (ACTH)**, **melanocyte-stimulating hormones (MSH)**, and a morphinelike substance, **β -endorphin**, along with peptide “scraps” that have no known function. We’ll examine the roles of each active product later.
3. The Golgi complex concentrates the finished hormones, then packages them into secretory vesicles that are pinched off and stored in the cytoplasm until an appropriate signal triggers their secretion. By storing peptide hormones in a readily releasable form, the gland can respond rapidly to any demands for increased secretion without first needing to increase hormone synthesis.
4. On appropriate stimulation, the secretory vesicles fuse with the plasma membrane and release their contents to the outside by the process of exocytosis (see p. 42). Such secretion usually does not go on continuously; it is triggered only by specific stimuli. The blood subsequently picks up the secreted hormone for distribution.

Steroid Hormones All steroidogenic (steroid-producing) cells perform the following steps to produce and release their hormonal product:

1. Cholesterol is the common precursor for all steroid hormones; however, numerous species cannot synthesize cholesterol and must obtain it from their diet. Vertebrate steroidogenic cells can synthesize some cholesterol on their own, although most is derived from low-density lipoproteins (LDLs) from the blood (see p. 389). Unused cholesterol may be chemically modified and stored in large amounts as lipid droplets within steroidogenic cells. Utilization of LDLs and conversion of stored cholesterol into free cholesterol for use in steroid hormone production can be closely coordinated with the animal’s overall need for the hormone product.
2. Synthesis of the various steroid hormones from cholesterol requires a series of enzymatic reactions that modify the type and position of side groups attached to the

cholesterol framework or the degree of saturation within the rings (Figure 7-3). Each conversion from cholesterol to a specific steroid hormone requires enzymes found in the mitochondria or endoplasmic reticulum. Accordingly, each steroidogenic organ can produce only the steroid hormones for which it has a complete set of appropriate enzymes. For example, a key enzyme necessary for the production of **cortisol** is found only in the adrenal cortex. The steroid molecule is therefore shuttled back and forth between different compartments within the steroidogenic cell for step-by-step modification until the final secretory product is formed.

3. Unlike peptide hormones, steroid hormones cannot be stored after their formation. Once formed, the lipid-soluble steroid hormones immediately diffuse through the steroidogenic cell’s lipid plasma membrane to enter the circulatory system. Only the hormone precursor cholesterol is stored in significant quantities within steroidogenic cells. Accordingly, the rate of steroid hormone secretion is controlled entirely by the rate of hormone synthesis. In contrast, peptide hormone secretion is controlled primarily by regulating the release of presynthesized, stored hormone.

4. After their secretion into the circulation, some steroid hormones undergo further interconversions within the blood or other organs, where they are converted into more potent or different hormones.

Amines The amine hormones of vertebrates—thyroid hormone and catecholamine hormone—have unique synthetic and secretory pathways that are thoroughly described when each of these hormones is specifically addressed. However, in brief, the amines share the following features:

- They are derived from the naturally occurring amino acid tyrosine.
- Both types of amines are stored until they are secreted.
- Thyroid hormone also undergoes further processing once in the peripheral circulation.

Hydrophilic hormones are transported dissolved in the plasma, whereas lipid-soluble hormones are almost always transported bound to plasma proteins

All hormones are carried by the blood, but they are not all transported in the same manner:

1. The hydrophilic peptide hormones are transported simply dissolved in the plasma or, in some cases, bound to a specific carrier protein.
2. Lipophilic steroids and thyroid hormone (in vertebrates), which are poorly soluble in water, cannot dissolve in the aqueous plasma in sufficient quantities to account for their known plasma concentrations. Instead, most of these hormones circulate to their target cells reversibly bound to plasma proteins. Some plasma proteins are designed to carry only one type of hormone, whereas other plasma proteins, such as albumin, indiscriminately pick up any “hitchhiking” hormone.

Only the small, unbound, freely dissolved fraction of a lipophilic hormone is biologically active (that is, free to

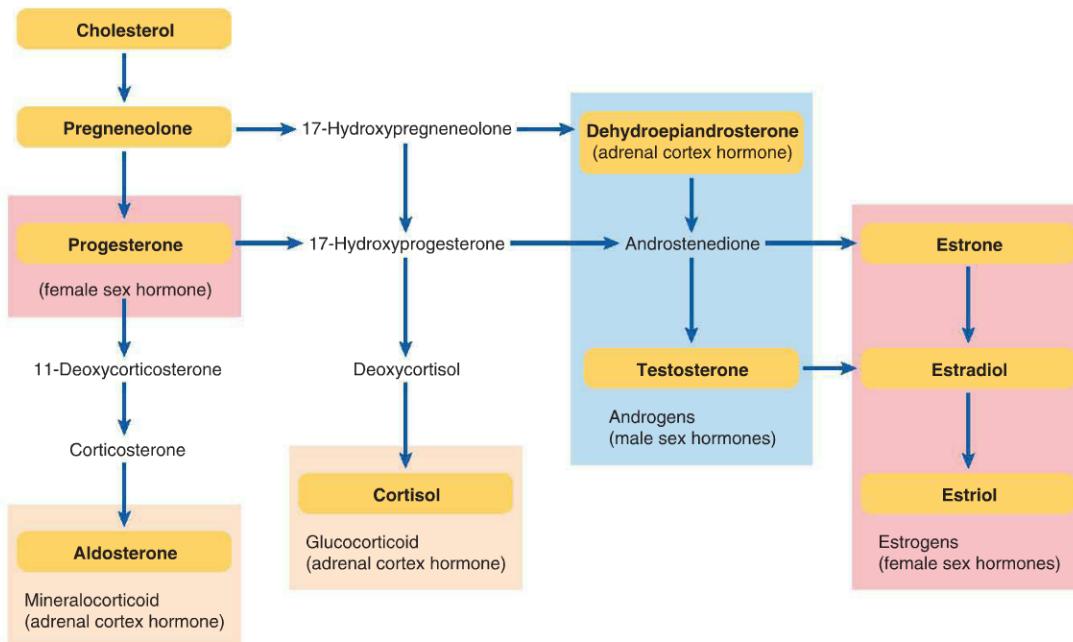


FIGURE 7-3 Steroidogenic pathways for the major steroid hormones. All steroid hormones are produced through a series of enzymatic reactions that modify cholesterol molecules, such as by varying the side groups attached to them. Each steroidogenic organ can produce only those steroid hormones for which it has a complete set of the enzymes needed to appropriately modify cholesterol. For example, the testes have the enzymes necessary to convert cholesterol into testosterone (male sex hormone), whereas the ovaries have the enzymes needed to yield progesterone and the various estrogens (female sex hormones).

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diffuse and bind with target cell receptors to exert an effect. Once a hormone has interacted with a target cell, it is rapidly inactivated and excreted so that it is no longer available to interact with another target cell. Because the *carrier-bound* hormone is in dynamic equilibrium with the *free hormone* pool, the bound form of lipophilic hormone provides a large reserve that can be called on to replenish the active free pool. To maintain normal endocrine function, the magnitude of the small, free, effective pool, rather than the total plasma concentration of a particular lipophilic hormone, is monitored and adjusted through feedback mechanisms.

Catecholamines in vertebrates are unusual in that only about 50% of these hydrophilic hormones circulate as free hormone, whereas the other 50% are loosely bound to the plasma protein albumin. Because catecholamines are water soluble, the importance of this protein binding is unclear.

Hormones exert a variety of regulatory effects throughout the body

Endocrine systems have regulatory designs similar to that of nervous systems. These are cells that sense (usually with receptor proteins) some state in the body that is being regulated, integrator cells (which may be neurons or glands), and effector organs and behaviors that carry out responses. Hormones are the messengers that transmit commands, similar to the roles of action potentials and neurotransmitters in nervous systems.

Even though hormones are distributed throughout an animal body by blood or hemolymph, only specific target cells can respond to each hormone because only the target cells have receptors (intracellular or integral plasma membrane proteins) for binding with the particular hormone. Binding of a hormone with its specific target cell receptors initiates a chain of events within the target cells to bring about the hormone's final effect. Some hormones have a single target cell type; others have many.

Tropic Hormones The sole function of some hormones is regulating the production and secretion of another hormone. A hormone that has as its primary function the regulation of hormone secretion by another endocrine gland is classified functionally as a **tropic hormone** (*tropic* means “causing to turn” or “attracting,” here meaning “stimulating”). (Do not confuse these with *trophic hormones*, because “trophic” means “nourishing.” Tropic hormones are involved in triggering cell growth and development, and are usually nontropic!) Tropic hormones stimulate and maintain their endocrine target tissues. For example, the tropic hormone thyroid-stimulating hormone (TSH) from the anterior pituitary stimulates thyroid hormone secretion by the thyroid gland and also maintains the structural integrity of this gland. In the absence of TSH, the thyroid gland atrophies (shrinks) and produces very low levels of its hormone. A **nontropic hormone**, in contrast, primarily exerts its effects on nonendocrine target tissues. Thyroid hor-

mone, which increases the rate of O_2 consumption and the metabolic activity of almost every cell of mammals and birds, is an example of a nontropic hormone.

Complexity of Endocrine Function The following factors add to the complexity of an endocrine system:

- A single endocrine gland may produce multiple hormones. The mammalian anterior pituitary, for example, secretes six different hormones, usually made by different specialized cells in that gland; each hormone is under different control mechanisms and has different functions, some being tropic and others nontropic.
- A single hormone may be secreted by more than one endocrine gland. For example, the vertebrate hypothalamus and pancreas both secrete the hormone *somatostatin*. In amphibians *thyrotropin-releasing hormone* is synthesized in the hypothalamus and the skin as well as other organs. The functional significance of this arrangement has not been established.
- Frequently, a single hormone has more than one type of target cell and therefore can induce more than one type of effect. This is the “same key, different locks” concept that we discussed in Chapter 3 (p. 93). As an example, *vasopressin* from the posterior pituitary promotes H_2O reabsorption by mammalian kidney tubules by binding with V_2 receptors on the distal and collecting tubular cells and vasoconstriction of arterioles throughout the body by binding with V_1 receptors on arteriolar smooth muscle. Sometimes hormones that have multiple target-cell types can coordinate and integrate the activities of various tissues toward a common end. For example, the effects of *insulin* from the pancreas on muscle, liver, and fat all act in concert to store nutrients after absorption of a meal.
- The secretion rate of some hormones varies considerably over the course of time in a cyclic pattern. Therefore, endocrine systems also provide temporal (time) coordination of function. This is particularly evident in the endocrine control of reproductive cycles, such as the estrous cycle, in which normal function requires highly specific patterns of change in the secretion of various hormones.
- A single target cell may be influenced by more than one hormone. Some cells contain an array of receptors for responding in different ways to different hormones. To illustrate, *insulin* promotes the conversion of glucose into *glycogen* (a storage polymer) within vertebrate liver cells by stimulating one particular hepatic enzyme, whereas another hormone, *glucagon*, by activating a different set of hepatic enzymes, enhances the degradation of glycogen into glucose within liver cells.
- The same chemical messenger may be either a hormone or a neurotransmitter, depending on its source and mode of delivery to the target cell. A prime example is norepinephrine, which is secreted as a hormone by the vertebrate adrenal medulla and released as a neurotransmitter from sympathetic postganglionic nerve fibers. The effects of the identical hormone and neurotransmitter are generally different, again illustrating the “same key, different locks” principle (p. 93).
- Some organs are exclusively endocrine in function (they specialize in hormonal secretion alone, the anterior pituitary and thyroid glands being examples), whereas other organs of the endocrine system perform nonendocrine

functions in addition to secreting hormones. For example, vertebrate testes produce sperm and also secrete the male sex-hormone *testosterone*.

- Nonnative or hormonelike substances termed **endocrine-disrupting chemicals** (EDCs), whose structures are similar to hormones, can sometimes disrupt endocrine communication by altering hormone secretion, transport or action. These compounds are derived from the by-products of manufactured organic compounds.

This has been a brief overview of the general functions of the endocrine system. Certain hormones are introduced elsewhere and are not discussed in this chapter; these (in vertebrates) are the *gastrointestinal hormones* (Chapter 14), the renal hormones (*erythropoietin* in Chapter 9, and *renin* in Chapter 13), *atrial natriuretic peptide* from the heart (Chapter 12), and *thymosin* (Chapter 10). Most of the remainder of the major hormones are described in greater detail in this chapter.

Hormones produce their effects by altering intracellular proteins through ion fluxes, second messengers, and transcription factors

To induce their effects, hormones must bind with target cell receptors specific for them. Each interaction between a particular hormone and a target-cell receptor produces a highly characteristic response that differs among hormones and among different target cells influenced by the same hormone.

General Mechanisms of Hydrophilic and Lipophilic Hormone Action The location of the receptors within the target cell, and the mechanism by which binding of the hormone with the receptors induces a response, both vary, depending on the hormone’s solubility characteristics. Receptor–hormone interactions can be grouped into two broad categories based on the location of their receptors (Table 7-1):

1. **Membrane receptors.** The hydrophilic peptides and catecholamines, which are poorly soluble in lipid, cannot pass through the lipid membrane barriers of their target cells. Instead, they bind with specific receptors located on the outer plasma membrane surface of the target cell. In turn, these receptors either alter the conformation (shape) of adjacent ion channels already present in the membrane (p. 94), or activate second-messenger systems within the target cell. Second messengers directly alter the activity of preexisting intracellular proteins, usually enzymes, to produce the desired effect.
2. **Internal receptors.** The lipophilic steroids and thyroid hormone (in the free form, not bound with a plasma protein carrier) easily pass through the surface membrane to bind with specific receptors located *inside* the target cell. The receptors inside the cell are typically *transcription factors* that regulate specific genes in the target cell that code for the formation of new intracellular proteins (pp. 31 and 94). Some lipophilic hormones also have specific receptors in the plasma membrane and cytosol of target tissues.

Membrane receptors were covered in Chapters 2 and 3; however, the lipophilic mechanism of hormonal action warrants further examination.

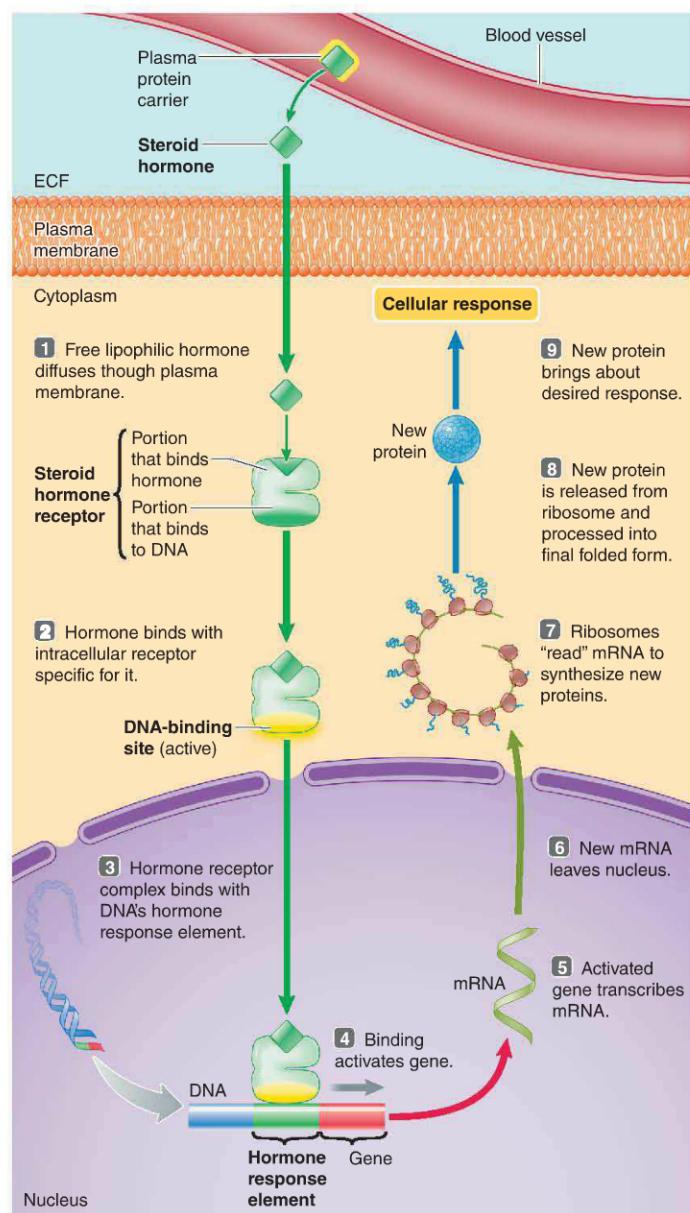


FIGURE 7-4 Mechanism of action of lipophilic hormones.

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By stimulating genes, lipophilic hormones promote synthesis of new proteins

All lipophilic hormones (steroids and thyroid hormone) bind with intracellular receptors in their target cells by activating specific genes that cause the synthesis of new proteins, as summarized in Figure 7-4.

Free lipophilic hormone (hormone not bound with its plasma-protein carrier) diffuses through the plasma mem-

brane of the target cell (step 1 in Figure 7-4) and binds with its specific receptor inside the cell, either in the cytoplasm or in the nucleus (step 2). Each receptor has a specific region for binding with its hormone and another region for binding with DNA. The receptor cannot bind with DNA unless it first binds with the hormone. Once the hormone is bound to the receptor, the hormone receptor complex binds with DNA at a specific attachment site on the DNA known as the **hormone response element (HRE)** (step 3). Different steroid hormones and thyroid hormone, once bound with their respective receptors, attach at different HREs on DNA. For example, the estrogen receptor complex binds at DNA's estrogen response element.

Binding of the hormone receptor complex with DNA "turns on" or activates a specific gene within the target cell (step 4). This gene contains a code for synthesizing a given protein. The code of the activated gene is transcribed into complementary messenger RNA (mRNA) (step 5). The new mRNA leaves the nucleus and enters the cytoplasm (step 6), where it binds to a ribosome, the "workbench" that mediates the assembly of new proteins. Here, mRNA directs the synthesis of the designated new proteins according to the DNA code in the activated genes (step 7). The newly synthesized protein, either enzymatic or structural, is released from the ribosome (step 8) and produces the target cell's ultimate response to the hormone (step 9). By means of this mechanism, different genes are activated by different lipophilic hormones, resulting in different biological effects.

By means of this mechanism of nuclear receptors, different lipophilic hormones activate different genes, resulting in hormone-specific biological effects. Genomic and evolutionary analysis of nuclear receptors has revealed that they share an extensive homology and so are grouped into a large superfamily divided into six subfamilies. For example, one subfamily places the vertebrate thyroid-hormone receptor in the same class as the vertebrate vitamin D receptor and the arthropod ecdysone receptor. Another subfamily contains the vertebrate steroid receptors; vertebrate genomes have six nuclear steroid receptors: two for estrogens, and one each for testosterone/androgens, glucocorticoids, mineralocorticoids (such as aldosterone), and progesterone (hormones we discuss later). Recently, researchers have found that the genome of a mollusk, the seashell *Aplysia* (p. 198), has an estrogen-type receptor. Although this receptor is not activated by steroids, its existence suggests that steroid receptors evolved before chordates arose.

Even though most steroid actions are accomplished by hormonal binding with intracellular receptors that leads to gene activation, recent studies have unveiled another mechanism by which steroid hormones induce effects that occur too rapidly to be mediated by gene transcription. Some ste-

roid hormones, most notably some of the sex hormones, bind with unique steroid receptors in the plasma membrane, in addition to binding with the traditional steroid receptors in the nucleus. This membrane binding leads to *nongenomic steroid receptor actions*, that is, actions accomplished by something other than altering gene activity, such as by inducing changes in ionic flux across the membrane or by altering activity of cellular enzymes.

Onset and Duration of Hormonal Responses Compared to neural responses that are brought about within milliseconds, hormone action is relatively slow and prolonged, taking minutes to hours for the response to take place after the hormone binds to its receptor. The variability in time of onset for hormonal responses depends on the mechanism employed. Hormones that act through a second-messenger system to alter a preexisting enzyme's activity elicit full action within a few minutes. In contrast, hormonal responses that require the synthesis of new protein may take up to several hours before any response can be measured.

Also, in contrast to neural responses that are quickly terminated once the triggering signal ceases, hormonal responses persist for a period of time after the hormone is no longer bound to its receptor. Once an enzyme is activated in response to hydrophilic hormonal input, it no longer depends on the presence of the hormone. Thus, the response lasts until the enzyme is inactivated. As a result, a hormone's effect usually lasts for some time after its withdrawal. Predictably, the responses that depend on protein synthesis last longer than do those stemming from enzyme activation.

Furthermore, as we explain shortly, compared to hydrophilic hormones, lipophilic hormones usually persist longer after secretion before being inactivated.

Hormone actions are greatly amplified at the target cell

The actions of hormones are greatly amplified at the target cell. As we noted earlier, hormones exert their effect at incredibly low concentrations—as low as 1 picogram (10^{-12} gram; 1 millionth of a millionth of a gram) per mL—as opposed to the much higher localized concentration of neurotransmitter at the target cell during neural communication. Interaction of one hormonal molecule with its receptor can result in the formation of many active protein products that ultimately carry out the physiological effect. For example, one peptide hormone results in the production of many cAMP messengers, each in turn activating many latent enzymes (see p. 97). Similarly, one steroid-hormone-activated gene induces formation of many messenger RNA molecules, each of which is used to make numerous new proteins.

Endocrine-disrupting chemicals can mimic the effects of native hormones

As we noted earlier, endocrine-disrupting chemicals (EDCs) are human-made substances that are released into the environment and interfere with the endocrine modulation of neural and behavioral maturation of animals. EDCs range across all continents and oceans, are found in animal populations from the poles to the tropics, and can be passed from generation to generation. The discovery of hormonally me-

diated toxic effects in fish downstream of sewage discharge points led to the realization that wastewater contains EDCs. Even so, some scientists have suggested that environmental EDCs, except in extreme cases of a discrete spill or a point source, rarely occur in high enough concentrations to impact endocrine function. Further, natural endocrine disruption has been happening for millions of years as exemplified by some plants, which evolved these secondary products to serve as plant regulators or as endocrine-disrupting defenses against herbivores, especially insects.

Sexual development of the vertebrate brain is influenced by estrogenic (female) and androgenic (male) hormones. Researchers have found that many EDCs either mimic (as agonists) the actions of estrogens or oppose (as antagonists) their actions (anti-estrogenic); in some situations EDCs may even function as anti-androgens. For example, DDE (dichlorodiphenyldichloroethylene), a breakdown product of the pesticide DDT (dichlorodiphenyltrichloroethane), which was used globally from the 1940s to 1960s to kill mosquitoes and other insect pests, can be found in almost all living tissue on Earth and acts as an anti-androgen in mammals. More recent discoveries have demonstrated that common household products (for example, heavy-duty laundry powders and liquid detergents, personal care products, and household cleaners) contain nonionic surfactants that break down in the environment to form estrogen agonists (which interact with estrogen receptors). EDCs that interfere with sex hormone activity and production have the potential to disturb normal brain sexual development, as has been demonstrated in wildlife studies of birds, fishes, whales, porpoises, alligators, and turtles. These effects have been linked with direct exposure to sewage and industrial effluents and pesticides, and indirectly to accumulation through aquatic food webs. Similarly, EDCs that impair thyroid function are believed to contribute to learning difficulties in animals, in addition to other neurological abnormalities.

The effective plasma concentration of a hormone is normally regulated by changes in its rate of secretion

The primary function of most hormones is the regulation of various homeostatic activities. Because hormones' effects are proportional to their concentrations in the blood, it follows that these concentrations must be subject to control according to homeostatic need (Figure 7-5). The plasma concentration of free, biologically active hormone—and thus the hormone's availability to its receptors—depends on several factors: (1) the hormone's rate of secretion into the blood by the endocrine gland; (2) for a few hormones, rate of metabolic activation; (3) for lipophilic hormones, extent of binding to plasma proteins; and (4) rate of removal from the circulation by metabolic inactivation and excretion in urine. Furthermore, the magnitude of the hormonal response depends on the availability and sensitivity of the target cell's receptors for the hormone. Let's first examine the factors that influence the plasma concentration of the hormone before turning our attention to the target cells' responsiveness to the hormone.

Normally, the effective plasma concentration of a hormone is regulated by appropriate adjustments in the rate of its secretion. Secretion rates of all hormones are subject to

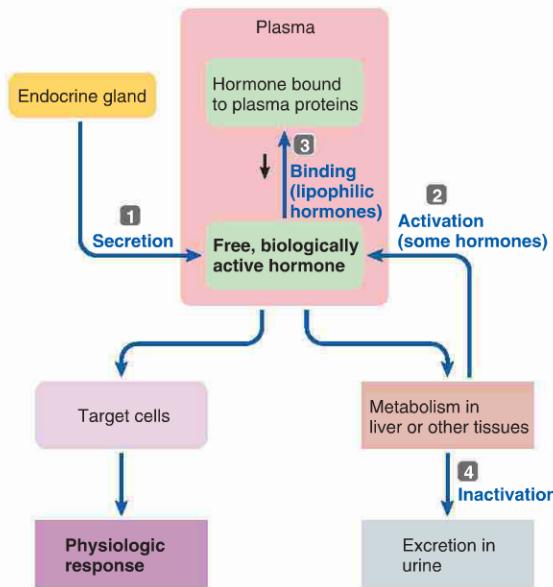


FIGURE 7-5 Factors affecting the plasma concentration of free, biologically active hormone. The plasma concentration of free, biologically active hormone, which can interact with its target cells to produce a physiological response, depends on (1) the hormone's rate of secretion by the endocrine gland, (2) its rate of metabolic activation (for a few hormones), (3) its extent of binding to plasma proteins (for lipophilic hormones), and (4) its rate of metabolic inactivation and excretion.

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control, often by a combination of several complex mechanisms. The regulatory system for each hormone is considered in detail in later sections. For now, we address these general mechanisms, which are common to many different hormones: negative-feedback control, neuroendocrine reflexes, and diurnal (circadian) rhythms.

Negative-Feedback Control Negative feedback is a prominent feature of most biological control systems (see p. 13), including hormonal. Recall that *negative feedback exists when the output of a system counteracts a change in input*, thus maintaining a controlled variable within a narrow range around a set level. Control of hormonal secretion to maintain a hormone's plasma concentration provides some classic physiological examples of negative feedback. For example, when the plasma concentration (in a mammal) of free circulating thyroid hormone falls below a given "set point," the anterior pituitary secretes thyroid-stimulating hormone (TSH), which stimulates the thyroid to increase its secretion of thyroid hormone. Thyroid hormone in turn inhibits further secretion of TSH by the anterior pituitary. Negative feedback ensures that once thyroid gland secretion has been "turned on" by TSH, it will not continue unabated but instead will be "turned off" when the appropriate level of free circulating thyroid hormone has been achieved. Thus, the effect of a particular hormone's actions can inhibit its own secretion.

Neuroendocrine Reflexes Many endocrine control systems involve **neuroendocrine reflexes**, which include neural as well as hormonal components. The purpose of such reflexes is to produce a sudden increase in hormone secretion (that is, a *reset* mechanism, p. 18, that "turns up the thermostat setting") in response to a specific stimulus, frequently a stimulus external to the body. In some instances, neural input to the endocrine gland is the only factor regulating secretion of the hormone. For example, secretion of epinephrine by the adrenal medulla is solely controlled by the sympathetic nervous system. Some endocrine control systems, in contrast, include both feedback control, which maintains a constant basal level of the hormone, and neuroendocrine resetting reflexes (which cause sudden bursts in secretion in response to a sudden increased need for the hormone). An example is the increased secretion of cortisol by the adrenal cortex during a stress response (see p. 305).

Diurnal (Circadian) and Other Biological Rhythms Although some form of negative feedback usually regulates hormone secretion rates, this does not imply that hormones are always maintained at a constant level. Instead, the secretion rates of most hormones rhythmically fluctuate up and down as a function of time. The most common endocrine rhythm is the **diurnal** ("day-night"), or **circadian** ("around a day"), **rhythm**, which is characterized by repetitive oscillations in gene expression that correspond with changes in the physiology, metabolism, and behavior in nearly all organisms on Earth, from bacteria to mammals. As we'll see, fluctuations in certain hormone levels are very regular and have a frequency of one cycle every 24 hours. This rhythmicity is caused by endogenous oscillators, called **biological clocks**, similar to the self-paced respiratory neurons in the brainstem that govern the rhythmic motions of breathing, except the time-keeping oscillators cycle on a much longer time scale. Furthermore, unlike the rhythmicity of breathing, endocrine rhythms are locked on, or **entrained**, to external cues, called **zeitgebers** ("time givers"), such as the light-dark cycle; that is, the inherent 24-hour cycles of peak and ebb of hormone secretion are set to "march in step" with cycles of light and dark. Such biological rhythms are a classic example of **anticipatory regulation** (Chapter 1): Once synchronized with a regular environmental cycle such as day-night or summer-winter, clocks allow organisms to prepare for these cyclical changes in advance of their actual occurrence. For example, *cortisol* secretion (p. 286) in a diurnal mammal rises during the late night, reaching its peak secretion in the early morning just before waking time, and then falls throughout the day to its lowest level at dusk (Figure 7-6). This prepares the animal for the stresses associated with waking up and initiating activity such as finding food.

Inherent hormonal rhythmicity and the entrainment of zeitgebers are not accomplished by the endocrine organs themselves but instead result from the central nervous system changing the set point of these organs. Indeed, neural clocks regulate many neuromuscular functions such as feeding and other behaviors, as well as hormonal secretion. In turn, the neurons themselves exhibit clock cycles due to **clock genes**, which are found in all organisms. (We examine these neural and molecular biological mechanisms in detail later; p. 284) Negative-feedback control mechanisms maintain whatever set point is established for that time of day.

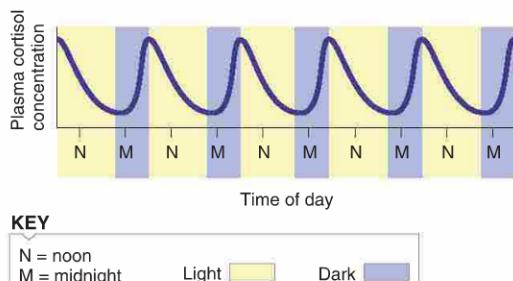


FIGURE 7-6 Diurnal rhythm of cortisol secretion.

Source: Adapted from George A. Hedge, Howard D. Colby, & Robert L. Goodman. (1987). *Clinical Endocrine Physiology*. Philadelphia: W. B. Saunders Company, Figure 1-13, p. 28.

Some endocrine cycles operate on time scales other than a circadian rhythm—some much shorter than a day and some much longer. A well-known example of the latter is the monthly menstrual cycle in humans, and a tidal rhythm called *circalunadian* (“about a lunar day”) in many shoreline animals. Another common cycle is the *circannual* (yearly) rhythm in seasonally reproducing organisms and hibernating animals.

The effective plasma concentration of a hormone can be influenced by the hormone’s transport, metabolism, and excretion

Even though the effective plasma concentration of a hormone is normally regulated by appropriate adjustments in the rate of secretion, alterations in the transport, metabolism, or excretion of a hormone can also influence the size of its effective pool, sometimes inappropriately. For example, the vertebrate liver synthesizes plasma proteins, so liver disease may result in abnormal endocrine activity because of a change in the balance between free and bound pools of certain hormones.

Eventually, all hormones are metabolized by enzyme-mediated reactions that modify the hormonal structure in some way. In most cases, this inactivates the hormone. Hormone metabolism is not always a mechanism for removal of used hormones, however. In some cases, a hormone is activated by metabolism; that is, the hormone’s product has greater activity than the original hormone. For example, after the thyroid hormone thyroxine is secreted, it is converted to a more powerful hormone by enzymatic removal of one of the iodine atoms it contains. Usually the rate of such hormone activation is itself under hormonal or metabolic control.

Metabolic Inactivation and Urinary Excretion of Hormones

The liver is the most common site for metabolic hormonal inactivation in vertebrates, but some hormones are also metabolized in the kidneys, blood, or target cells. In contrast to hormone activation, which is typically regulated, hormonal inactivation and excretion are not subject to control. The primary means of eliminating hormones and their metabolites from vertebrate blood is by urinary excretion. When liver and kidney function are normal, measuring urinary

concentrations of hormones and their metabolites provides a useful, noninvasive way to assess endocrine function because the rate of excretion of these products in urine directly reflects their rate of secretion by the endocrine glands. This type of information may provide the only clue that an animal has come into breeding condition and can participate in a captive breeding program. Because the liver and kidney are important in removing hormones from the blood by means of metabolic inactivation and urinary excretion, animals with liver or kidney disease may suffer from excess activity of certain hormones solely as a result of reduced hormone elimination.

The amount of time after a hormone is secreted before it is inactivated and the means by which this is accomplished differ for different classes of hormones. In general, the hydrophilic peptides and catecholamines are easy targets for blood and tissue enzymes, so they remain in the blood only briefly (a few minutes to a few hours) before being enzymatically inactivated. In the case of some peptide hormones, the target cell actually engulfs the bound hormone by endocytosis and degrades it intracellularly. In contrast, binding of lipophilic hormones to plasma proteins renders them less vulnerable to metabolic inactivation and prevents them from escaping into the urine. Therefore, lipophilic hormones are removed from the plasma much more slowly. They may persist in the blood for hours (steroids) or up to a week in humans (thyroid hormone). In general, lipophilic hormones must undergo a series of reactions to reduce their biological activity and enhance their H_2O solubility so that they can be freed of their plasma protein carriers and be eliminated in the urine.

The responsiveness of a target cell to its hormone can be varied by regulating the number of its hormone-specific receptors

A target cell’s response to a hormone is correlated with the number of the cell’s receptors occupied by molecules of that hormone, which in turn depends on the number of receptors present in the target cell and on the plasma concentration of the hormone. Thus, the response of a target cell to a given plasma concentration can be fine-tuned up or down by varying the number of receptors available for hormone binding.

Down-Regulation As an illustration, when the plasma concentration of insulin is chronically elevated, the total number of target cell receptors for insulin is reduced as a direct result of the effect that an elevated level of insulin has on the insulin receptors. This phenomenon, known as *down-regulation*, constitutes an important locally acting negative-feedback mechanism that prevents the target cells from overreacting to the high concentration of insulin; that is, the target cells are desensitized to insulin, helping blunt the effect of insulin hypersecretion. This is a form of *acclimatization*, one of the key regulatory mechanisms we discussed in Chapter 1 (p. 17). Down-regulation of insulin is accomplished by the following mechanism. The binding of insulin to its surface receptors induces endocytosis of the hormone–receptor complex, which is subsequently attacked by intracellular lysosomal enzymes. This internalization serves a twofold purpose: It provides a pathway for degradation of the hormone, and it also plays a role in regulating the number of receptors available for

binding on the target cell's surface. At high plasma-insulin concentrations, the number of surface receptors for insulin is gradually reduced as a result of the accelerated rate of receptor internalization and degradation brought about by increased hormonal binding. The rate of synthesis of new receptors within the endoplasmic reticulum and their insertion in the plasma membrane do not keep pace with their rate of destruction. Over time, this self-induced loss of target cell receptors for insulin reduces the target cell's sensitivity to the elevated hormone concentration.

Permissiveness, Synergism, and Antagonism A given hormone's effects are influenced not only by the concentration of the hormone itself but also by the concentrations of other hormones that interact with it. Because hormones are widely distributed through the blood, target cells may be exposed simultaneously to many different hormones, giving rise to numerous complex hormonal interactions on target cells. Hormones frequently alter the receptors for other kinds of hormones as part of their normal physiological activity. A hormone can influence the activity of another hormone at a given target cell in one of three ways: permissiveness, synergism, and antagonism.

- With **permissiveness**, one hormone must be present in adequate amounts for the full exertion of another hormone's effect. In essence, the first hormone, by enhancing a target cell's responsiveness to another hormone, "permits" this other hormone to exert its full effect. For example, thyroid hormone increases the number of receptors for epinephrine in epinephrine's target cells, increasing the effectiveness of epinephrine. Epinephrine is only marginally effective in the absence of thyroid hormone.
- Synergism** occurs when the actions of several hormones are complementary and their combined effect is greater than the sum of their separate effects. An example is the synergistic action of follicle-stimulating hormone and testosterone, both of which are required to maintain the normal rate of sperm production. Synergism probably results from each hormone's influence on the number or affinity of receptors for the other hormone.
- Antagonism** occurs when one hormone causes the loss of another hormone's receptors, reducing the effectiveness of the second hormone. To illustrate, progesterone (a mammalian hormone secreted during pregnancy that decreases contractions of the uterus) inhibits uterine responsiveness to estrogen (another hormone secreted during pregnancy that increases uterine contractions). By causing loss of estrogen receptors on uterine smooth muscle, progesterone prevents estrogen from exerting its excitatory effects during pregnancy and thus keeps the uterus in a quiet (noncontracting) environment suitable for the developing fetus.

Endocrine disorders are attributable to hormonal excess, hormonal deficiency, or decreased responsiveness of the target cells

From the preceding discussion, you can see that abnormalities in a hormone's effective plasma concentration can arise from a variety of factors. Endocrine disorders most commonly result from abnormal plasma concentrations of a

hormone caused by inappropriate rates of secretion—that is, too little hormone secreted (**hyposecretion**) or too much hormone secreted (**hypersecretion**). Occasionally endocrine dysfunction arises because target cell responsiveness to the hormone is abnormally low, even though the plasma concentration of the hormone is normal.

Hyposecretion If an endocrine gland (such as the adrenal gland) is secreting too little of its hormone because of an abnormality within that gland, the condition is referred to as *primary hyposecretion*. If, in contrast, the endocrine gland is normal but is secreting too little hormone because of a deficiency of its tropic hormone, the condition is known as *secondary hyposecretion*. The following are among the many different factors (each listed with an example) that may be responsible for hormone deficiency: (1) *genetic* (inborn absence of an enzyme that catalyzes synthesis of the hormone); (2) *dietary* (lack of iodine, which is necessary for synthesis of thyroid hormone); (3) *chemical or toxic* (certain insecticide residues may destroy the adrenal cortex); (4) *immunologic* (auto-immune antibodies may cause self-destruction of the animal's own thyroid tissue); (5) *other disease processes* (cancer or tuberculosis may coincidentally destroy endocrine glands); (6) *iatrogenic* (physician or veterinarian-induced, such as surgical removal of a cancerous thyroid gland); and (7) *idiopathic* (meaning the cause is not known).

The most common method of treating hormone hyposecretion is to administer a hormone that is the same as (or similar to, such as from another species) the one that is deficient or missing. The sources of hormone preparation for clinical use include (1) endocrine tissues from domestic livestock; (2) placental tissue and urine of pregnant women; (3) laboratory synthesis of hormones; and (4) genetically engineered "hormone factories": bacteria into which genes coding for the production of mammalian hormones have been introduced. The method of choice for a given hormone is determined largely by its structural complexity and degree of species specificity.

Hypersecretion Like hyposecretion, hypersecretion by a particular endocrine gland is designated as primary or secondary depending on whether the defect lies in that gland or is due to excessive stimulation from the outside, respectively. Hypersecretion may be caused by (1) tumors that ignore the normal regulatory input and continuously secrete excess hormone and (2) immunologic factors, such as excessive stimulation of the thyroid gland by an abnormal antibody that mimics the action of TSH, the thyroid tropic hormone. Excessive levels of a particular hormone may also arise from substance abuse, such as the banned practice among athletes of using certain steroids that increase muscle mass by promoting protein synthesis in muscle cells, and the injections of these and other hormones into livestock to enhance production (such as GH, p. 291). Note however that such injections lead to feedback inhibition of natural hormone production (see p. 296).

There are several ways of treating hormonal hypersecretion. If a tumor is the culprit, it may be surgically removed or destroyed with radiation treatment. In some instances, drugs that block hormone synthesis or inhibit hormone secretion can limit hypersecretion. Sometimes giving drugs that inhibit the action of the hormone without actually reducing the excess hormone secretion may treat the condition.

Having completed our discussion of the general principles of endocrinology, we now look at the function of selected nonvertebrate and vertebrate endocrine glands.

check your understanding 7.1

List the three chemical classifications of vertebrate hormones and the properties that describe them.

How do hormones produce their effects on a target cell?

What factors determine the plasma concentration of a hormone?

7.2 Nonvertebrate Endocrinology

Considerable diversity is evident in the function of endocrine systems in nonvertebrates, not surprising since the term “nonvertebrate” includes over 30 phyla and is not a true evolutionary grouping. Currently researchers are seeking to determine how homologous these systems are among different animal groups. Earlier we noted evidence that sponges and Cnidaria have signal molecules similar or identical to those of more complex animals, but these would likely act locally (paracrine fashion), slowly by diffusion to distant cells, or through external fluids. True hormone (endocrine) systems arose along with internal body fluids that provided a route for transport, and may have started first with neuroendocrine systems. Nonvertebrate hormones are produced either by neuroendocrine cells or distinct glands in **neural haemal organs** where the axonal endings secrete the hormone into the coelom (body cavity), hemolymph, or blood, which then can bind to specific receptors on peripheral organs. Nonvertebrate hormonal systems that have been documented include the following.

Mollusks Gastropods produce hormones that regulate such functions as egg laying and growth. For example, the **juxtaganglionar organ (JO)** consists of scattered cells in the connective tissue around the cerebral ganglion; the cells release peptides of uncertain function into the hemolymph during egg laying. Also, **bag cells** (two clusters in connective tissue above the abdominal ganglion) produce a peptide called **egg-laying hormone (ELH)**. When injected into the seashell *Aplysia* (p. 198), ELH elicits ovulation and egg-laying behaviors such as head tamping on the sand to cover eggs.

In addition, the intestines of some bivalves have been found to produce insulin, which may have a carbohydrate-regulating role similar to that in vertebrates. Moreover, steroid (estrogen) receptors have been found in *Aplysia* and an octopus, though they do not respond to vertebrate estrogen, so their functions are uncertain.

Annelids Earthworms and leeches have ganglionic tissues that have been found to contain molecules closely related to vertebrate hormones. These molecules are also in the circulatory fluid. One of these, **annetocin** (related to vertebrate *oxytocin*, p. 286), elicits egg-laying behavior when injected into a leech or earthworm.



Photo: Hilari Klandorf

Consider the striking changes associated with the metamorphosis of this caterpillar into an imperial moth (*Eacles imperialis*).

Crustaceans Decapods (crabs, shrimp, and so on) have a number of endocrine glands. The best studied are the Y- and X-organs:

- Y-organs in the head make **crustecdysone** to promote molting. This hormone is identical to ecdysone in insects, which we discuss shortly
- **Neurosecretory** (p. 91) X-organs (in the eyestalks) send their axons into **sinus glands** (also in eyestalks) to release several neurohormones, including (an incomplete list):
 (1) **chromatophorotropins** that activate **chromatophores** (p. 154) for changing color of the cuticle; (2) **crustacean hyperglycemic hormone** that triggers release of glucose from glycogen in the hepatopancreas (similar to vertebrate *glucagon*, p. 316); and (3) **vitellogenesis-inhibiting hormone**, which inhibits egg development.

Insects The most intensely studied of nonvertebrate endocrine systems is that of insects, which we discuss in detail. Several tissues in insects produce hormones, including (Figure 7-7a):

- The paired **corpora allata**, located behind the brain, with one lying on either side of the esophagus or fused

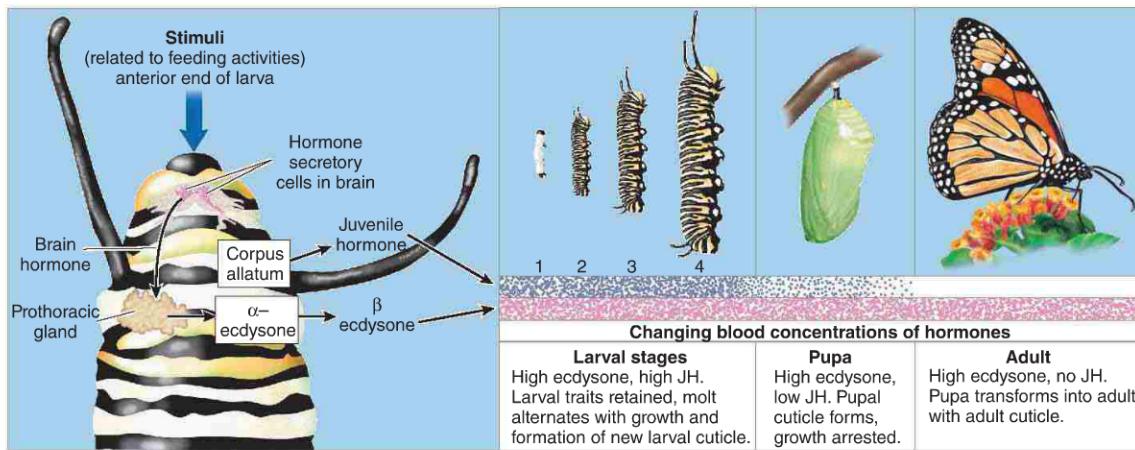


FIGURE 7-7 Developmental hormones in insects. (a) Hormone-producing tissues of an insect. (b) Ecdysone and juvenile hormone (JH) are two of the hormones involved in larval development and metamorphosis.

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into a single organ (as in higher Diptera), which secrete hormones, including **juvenile hormone (JH)**.

- The prothoracic glands, a pair of diffuse glands that are usually located at the back of the head or in the thorax, and that secrete **ecdysone** into the circulatory system.
- Neurosecretory cells in the brain that produce one or more neurohormones, including **prothoracitropic hormone (PTTH)**.
- The paired **corpora cardiaca**, which form a part of the wall of the dorsal longitudinal circulatory vessel (aorta).

The function of insect hormones has been studied with regard to their role in molting, osmoregulation, and reproduction, with molting processes receiving the most study. It is that process that we now examine.

Molting is the process of replacing one exoskeleton with another

To develop from larvae to adult, arthropods must periodically shed their chitin exoskeleton and replace it with a larger one. This cyclical pattern of replacement of the exoskeleton is essential for increasing body size as well as for any changes in body form (such as the acquisition of wings in adults). **Molting** is the process of replacing the exoskeleton with another, whereas the shedding of the old exoskeleton is termed **ecdysis**. Ecdysis is controlled by at least two neuropeptides including **ecdysis-triggering hormone** and **eclosion hormone**. Ecdysis-triggering hormone triggers the molting of the cuticle, while eclosion hormone initiates a sequence of behaviors that must occur in a stereotyped sequence for the insect to successfully molt. These behaviors include:

- Abdominal movements that loosen the connections between the old and new cuticle.
- Waves of peristalsis that move from posterior to anterior up the abdomen, which culminates in the shedding of the old cuticle.

- Tonic abdominal contractions to promote the movement of blood into the thorax and wings, followed by a stereotyped series of wing movements.

Eclosion hormone also regulates the release of **bursicon**, the hormone that orchestrates the final steps of adult ecdisis by increasing the plasticity of wing cuticle (wing expansion) and mediates tanning in the cuticle. Bursicon is released from neurons in the abdominal ganglia into the haemolymph. In most insects, a final molt occurs when the adult characteristics are expressed and the juvenile characteristics are lost. **Ecdysone** and **juvenile hormone (JH)** are two of the regulatory hormones involved in larval development and **metamorphosis**, the change from the juvenile form to the adult stage (Figure 7-7b). Ecdysone, a member of the steroid family of **ecdysteroids**, is secreted by the prothoracic glands or their equivalent homologs, and governs the initiation of the molting process. Ecdysteroid hormones (as with other steroid hormones) bind to a receptor in the nucleus, in this case the **ecdysone receptor (EcR)**, which activates gene transcription. All arthropods use ecdysteroids as a type of growth hormone.

The secretion of ecdysteroids in insects is principally regulated by a tropic neurohormone, **prothoracitropic hormone (PTTH)**. PTTH is synthesized by neurosecretory cells in the brain and travels along axons to peripheral neurohemal organs, the corpora cardiaca and corpora allata, where it is released into the circulation. At the time of molt, neural signals trigger the release of PTTH, which then is transported by the haemolymph to the prothoracic glands, where it stimulates the release of ecdysone, the molt-inducing hormone. In most species the prothoracic glands break down after the final molt to the adult stage. Ecdysone is later peripherally converted into another ecdysteroid, **20-OH-ecdysone**, in various tissues, and this form is recognized as the molt-inducer.

The quantity of JH released determines the quality of the molt

JH, secreted from the corpora allata, partners the release of ecdysone and ultimately determines the “quality” of the molt. JH has two broad actions in insects: It has a “priming” or activating action whereby it prepares a tissue for hormonal response by directing the synthesis and assembly of the cell machinery necessary to carry out the responses elicited by the binding of JH to its receptor. It also performs a regulatory role by controlling the rate of functioning of the primed tissue. For example, the fat body of virtually all insects cannot synthesize the protein **vitellogenin** (protein taken up by the developing oocyte as **vitellin**, the principal yolk protein) until it has been primed by exposure to JH. Thus, in addition to controlling metamorphosis, JH regulates many aspects of reproduction as well. The fat body is most highly developed during the larval instars and normally regresses at the end of metamorphosis, except in some adult species of insects that do not actively feed.

The quantity of JH released at each molt determines whether molting will ultimately produce a larva or an adult, because when released, JH ensures that larval characteristics are retained. For example, in insects such as moths and beetles JH is released at progressively decreasing concentrations during each larval stage (or instar) until the final stage, when its release is inhibited and negligible concentrations of JH are detectable. JH release is regulated by the cerebral neuropeptide **allostatin**, which suppresses the release of JH, as well as by **allotropin**, which stimulates the release of JH. During the time of molt the tissues are exposed to a pulse of ecdysteroids in the absence of JH, which enables metamorphosis of the tissues into the adult form. However, if the corpora allata are prematurely removed from an insect, metamorphosis occurs, producing a small adult. Conversely, if JH is administered at each molt the juvenile fails to develop into the adult form.

There is also evidence that JH induces the production and release of pheromones in several species of insects (such as cockroaches, some coleopterans, and lepidopterans) and in the boll weevil. JH enhances the production of sex pheromone in the male fat body. Concentrations of JH are regulated by the proteins **juvenile hormone-binding protein (JHBP)** and **juvenile hormone esterase (JHE)**. JHBP is produced by the fat body and released into the hemolymph, where it binds JH for transport and protection from degrading enzymes, including JHE. Fat bodies make JHE at increasing levels before the final larval molt to degrade JH; at high concentrations, JHE can degrade the JH bound to the transporter JHBP.

With the prevalence of insects in terrestrial ecosystems, their endocrine system is a prominent target of evolutionary adaptation in plants that are eaten by insects. Substances closely related to ecdysone occur in certain varieties of plants and are believed to protect the plants from feeding by insects. Plant substances called **precocenes** block JH production by the corpora allata, triggering a premature metamorphosis in species in which the larval stage (such as caterpillars) and not the adult is the herbivore. Similarly, to protect crops humans have targeted insect endocrine and pheromone systems. EcR, for example, is now an important target in the design of novel, environmentally safe insecticides. Also, the genes for JHBP and JHE have recently been cloned

and are being studied as a mechanism for controlling development of insect pests.

Pheromones are used in mating and colonial interactions

Let's end our examination of insect endocrinology with a brief look at pheromones. Although, strictly speaking, pheromones are neither hormones nor endocrine in origin, they are used in very similar ways, traveling from one body to another and binding to receptors to stimulate specific behaviors. The most widespread use of pheromones in all animals including insects is in mating. This was first discovered in the 1870s by the French naturalist Jean-Henri Fabré. A female great peacock moth that hatched from a cocoon in his laboratory was soon surrounded by dozens of male great peacocks coming in through the windows. He postulated the existence of an attractive odorant, which we now know is the case. Males, using receptors on their antennae, are incredibly sensitive to these female sex **pheromones**, and some species can detect just a single molecule that has traveled a great distance from the female. Pheromone synthesis in insects is regulated by the neurohormone **pheromone biosynthesis activation peptide (PBAN)**, which controls the enzymes involved in pheromone synthesis via G-protein coupled receptors. The release of PBAN is regulated by environmental factors such as day length and host-plant odors.

Pheromone use beyond reproduction has probably diversified more in insects than in any other animal group. Social insects, such as ants, termites, and bees, rely heavily on pheromones to control and coordinate colony functions and development of castes such as workers and soldiers. For example, **alarm pheromones** are released when a colony is attacked; these signal molecules trigger rapid and violent defense behaviors. Many biologists consider insect colonies “superorganisms,” with individual insects acting like cells and organs and with pheromones acting like true hormones.

check your understanding 7.2

Describe the process of molting in insects. What factor(s) determine the onset of metamorphosis?

7.3 Vertebrate Endocrinology: Central Endocrine Glands

The central endocrine glands of vertebrates include the **hypothalamus**, the **pituitary gland**, and **pineal gland**. The hypothalamus, a part of the brain, and the posterior pituitary gland act as a unit to release hormones essential for maintaining water balance and reproduction. The hypothalamus also secretes regulatory hormones that control the hormonal output of the anterior pituitary gland, which secretes seven hormones that in turn largely control the hormonal output of several peripheral endocrine glands.

Earlier, we discussed the concept of biological clocks, zeitgebers, and rhythmicity in hormone production. The pineal gland is a part of the brain that secretes a hormone

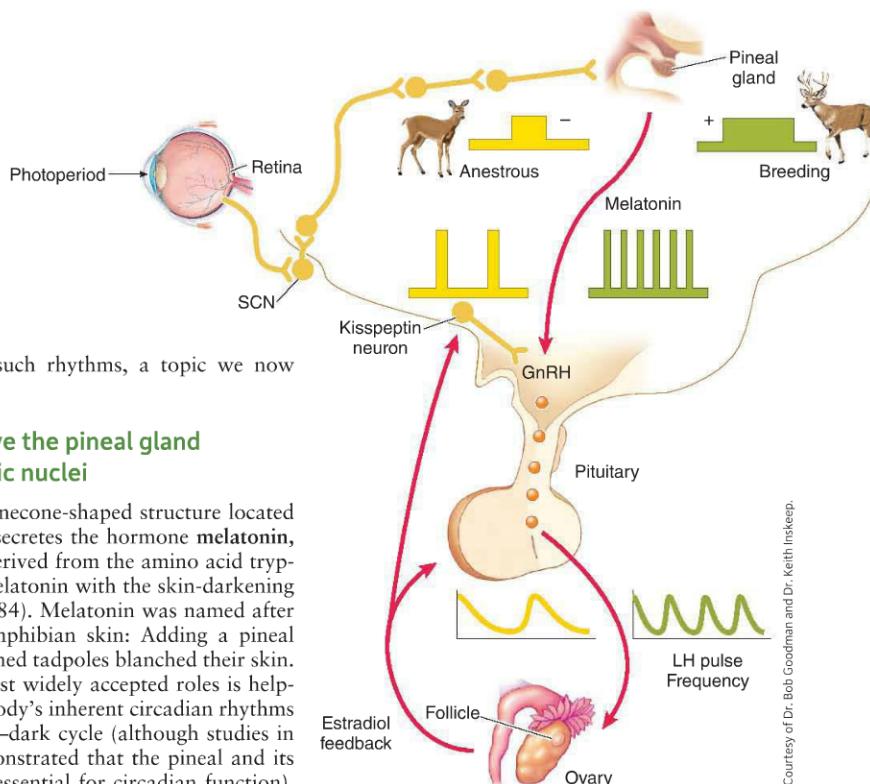
important in establishing such rhythms, a topic we now discuss in detail.

Biological clocks involve the pineal gland and the suprachiasmatic nuclei

The pineal gland, a tiny, pinecone-shaped structure located in the center of the brain, secretes the hormone melatonin, an indoleamine hormone derived from the amino acid tryptophan. (Do not confuse melatonin with the skin-darkening pigment, melanin—see p. 284). Melatonin was named after its lightening action on amphibian skin: Adding a pineal extract to water that contained tadpoles blanched their skin.

One of melatonin's most widely accepted roles is helping to keep the vertebrate body's inherent circadian rhythms in synchrony with the light–dark cycle (although studies in the quail and chicken demonstrated that the pineal and its melatonin rhythm are not essential for circadian function). Melatonin is the hormone of darkness: Its secretion increases up to 10-fold during the darkness of night and then falls to low levels during the light of day. Short-day breeders (such as sheep and deer) rely on steadily increasing concentrations of melatonin (Figure 7-8), whereas long-day breeders (such as many birds) rely on the progressively decreasing concentrations of melatonin to trigger reproduction. In fish, reptiles, birds, and amphibians, the pineal is photosensitive and is not directly controlled by nervous input, but rather by sunlight penetrating the skull. Pineal cells in these vertebrates are modified rod cells with reduced outer segments, containing photosensitive pigments structurally related to rhodopsin. As in mammals, there is a diurnal rhythm of melatonin, which is independent of cues from the eye. Some studies also show that melatonin controls color changes in certain ectothermic vertebrates independently of the control pathway of *melanocyte-stimulating hormone* regulation, which we will discuss later.

The master biological clock that serves as the pacemaker for circadian rhythms in mammals is the **suprachiasmatic nucleus (SCN)** (*mediobasal hypothalamus* in birds) a cluster of nerve cell bodies in the hypothalamus above the optic chiasm (the point at which part of the nerve fibers from each eye cross to the opposite half of the brain; see p. 255) (*supra*, “above”; *chiasm*, “cross”). The SCN is strategically located to receive light–dark information from the eyes. The release of glutamate by the neural input to the SCN acts to entrain the individual cells to the SCN to produce a coordinated 24-hour signal that is conveyed to multiple sites in the brain to control rhythmic patterns of body temp, feeding behavior, and so forth.



Courtesy of Dr. Bob Goodman and Dr. Keith Inskeep.

FIGURE 7-8 Pineal synchronization of reproductive activity in a seasonally breeding animal. In this example, a short-day breeder responds to a declining photoperiod by increasing melatonin secretion. In turn, GnRH pulse frequency is increased, which increases LH pulse frequency and stimulates gonadal development. Low concentrations of gonadal estrogen inhibit GnRH release during anestrus by binding to estrogen receptors on neurons in the periventricular and arcuate nuclei, limiting the release of kisspeptin. During the breeding season, this estrogen negative feedback decreases and kisspeptin stimulates GnRH pulse frequency, increasing follicular development and estrogen secretion and leading to positive feedback of estrogen, triggering an LH surge to cause ovulation.

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In mammals, pineal and melatonin output are under the control of the SCN. Daily changes in light intensity become the major environmental cue used to adjust this master clock. Special photoreceptors in the retina pick up light signals and transmit them directly to the SCN. Intermingled among the visually oriented retinal ganglion cells, about 1 to 2% of the retinal ganglion cells form an entirely independent light-detection system that responds to levels of illumination, like a light meter on a camera, rather than the contrasts, colors, and contours detected by the image-forming visual system. These photoreceptors are distinct from the rods and cones used to perceive, or see, light (see p. 248) and are located in the preganglionic region of the retina. These cells express **melanopsin**, a photoreceptor protein originally isolated in frogs and act to entrain the circadian clock (see *Molecular Biology and Genomics: Clocks*

(*Clocks and Genes*). The melanopsin-containing, illumination-detecting retinal ganglion cells cue the pineal gland about the absence or presence of light by sending their signals along the **retino-hypothalamic tract** to the SCN. This pathway is distinct from the neural systems that result in vision perception. This is the major way the internal clock is coordinated to a 24-hour day. In rodent models in which the rods and cones of the retina are absent due to genetic modification and the animals are visually blind, they are still able to adjust their circadian system normally to light due to persistent regulation by the melanopsin cells. In many blind people it is the melanopsin cells that allow a relatively normal lifestyle in spite of the lack of normal visual input. However, in a few individuals that totally lack a retina or have no eyes, the circadian system free-runs and these individuals suffer severely due to the lack of synchrony to the natural environment. These subjects can be treated successfully by the administration of melatonin at the normal sleep time to restore normal timing.

Moreover the SCN signals the adrenal gland through the sympathetic nervous system to control the production of adrenal hormones including *cortisol* or *corticosterone*. The consequent adrenal steroid hormone rhythm also plays a role in coordinating the daily biological rhythmicity. These peripheral mechanisms are particularly important in synchronizing the different body organs, which have their own biological rhythms to ensure optimal timing.

All eukaryotic cells, including all those within an animal, express clock genes

The molecular biology of the circadian clock was first elucidated in *Drosophila* and other simple models. These studies determined that clock function is generated by the interplay of a small number of genes called **clock genes**, which have now been found in all eukaryotes examined (as well as some bacteria and archaea). Clock genes interact with each other through both transcription and negative-feedback loops to produce a cycle that lasts approximately a day, that is, a circadian rhythm. Remarkably the clock genes expressed in insects and vertebrates have a major degree of homology (see *Molecular Biology and Genomics: Clocks and Genes*), which allowed the rapid discovery of the clock gene mechanisms in birds and mammals. Initially the expectation was that the clock genes would be expressed solely in the SCN, which was recognized as the central pacemaker for the circadian system. However, it was discovered that clock genes were expressed in virtually all cells in the body, consistent with their early evolution, and which endows all organ systems their own circadian rhythms. Thus, the SCN acts as the conductor, which synchronizes all the multiple organs in the body to have the appropriate timing across the day. For example, the liver produces enzymes in anticipation of meal-times. If these rhythms are disrupted, such as travel across time zones as occurs when horses are transferred between Europe and Asia for horseracing, these internal rhythms become desynchronized. It has been demonstrated in rodents that it takes about three days for the brain to readjust to an eight-hour phase (time zone) shift. However it takes as long as seven days for the gut and liver to adjust to such a phase change.

The biological clock must be synchronized with environmental cues

On its own, the circadian biological clock generally cycles a bit slower or faster than the 24-hour environmental cycle. In many insects and vertebrates (including humans), this rhythm is slightly longer than 24 hours and so must be adjusted each day by light from the environment to reset the natural daylight cycle to a period of 24 hours. (Blind cave fish and salamanders may exhibit rhythmic behaviors, but they generally do not follow a 24-hour cycle.) If this master clock were not continuously adjusted to keep pace with the world outside, the body's circadian rhythm would lag progressively out of synchrony with the daily cycles of light and dark. The existence of internal clocks was revealed by the discovery that circadian rhythms persist even if the light-dark cycle is artificially reverted to constant light (LL) or constant dark (DD). Under these conditions the rhythm is allowed to free-run, and animals may entrain on other zeitgebers, including environmental temperature, or the noises associated with individuals providing food at particular time in the day. Thus, the SCN must be reset daily by external cues so that the body's biological rhythms synchronize with the activity levels driven by the surrounding environment. The SCN works in conjunction with the pineal gland and its hormonal product melatonin to synchronize the various circadian rhythms with the 24-hour day-night cycle.

Biological clocks are ultimately regulated by genes and proteins that must somehow respond to sunlight, but until recently these were almost completely unknown. See *Molecular Biology and Genomics: Clocks and Genes* for these findings.

The pituitary gland descends from the hypothalamus and consists of two or three lobes

The **pituitary gland**, or **hypophysis**, is a small endocrine gland in a bony cavity at the base of the vertebrate brain just below the hypothalamus (Figure 7-9). The pituitary is connected to the hypothalamus by a thin stalk, the **infundibulum**, which contains nerve fibers and small blood vessels.

The pituitary has two anatomically and functionally distinct lobes, the **posterior pituitary** and the **anterior pituitary**. The posterior pituitary, being derived embryonically from an outgrowth of the brain, consists of nervous tissue from the hypothalamus and thus is also termed the **neurohypophysis**. The anterior pituitary, in contrast, consists of glandular epithelial tissue derived embryonically from an outpouching of ectoderm that buds off from the roof of the mouth. Accordingly, the anterior pituitary is also known as the **adenohypophysis** (*adeno*, “glandular”). The anterior pituitary consists of the **pars distalis** (PD) (main body of the pituitary gland) and the **pars tuberalis** (PT), which forms the stalk of the pituitary gland immediately adjacent to the base of the brain. The posterior pituitary is connected to the hypothalamus by a neural pathway, whereas the anterior pituitary is connected to the hypothalamus by a vascular link.

The Intermediate Lobe and Melanocyte-Stimulating Hormone In lampreys and hagfish (jawless fishes), amphibians, reptiles, and most mammals, the adenohypophysis includes a third, well-defined intermediate lobe (pars intermedia). Although absent in birds and cetaceans (whales and dolphins),

Biological clocks have been known for over a century, but the molecular mechanisms have only been uncovered in the last two decades, with the fullest details uncovered in the fungus *Neurospora*, certain plants, fruit flies, and mice. Numerous clock genes have been discovered and their expression activities tracked. In mice, transcription of clock genes named *BMAL1* and *CLOCK* within the nuclei of SCN neurons start the cycle via synthesis of the corresponding proteins *Bmal1* and *Clock* in the cytosol. *Bmal1* and *Clock* proteins are transported back into the nucleus, where they bind to and activate specific promoter sequences for genes that ultimately increase their own production. They also bind to and activate promoters for genes called *PERIOD* and *CRYPTOCHROME* (*CRY*). Thus, there is increasing production of *Bmal1*, *Clock*, *Period*, and *CRY* proteins. However, *Period* and *CRY* slowly but increasingly block the actions of *Bmal1* and *Clock* proteins, thus

reducing the transcription of all four genes. The level of clock proteins gradually dwindles as they degrade. This removes the inhibitory influence of *Period* and *CRY*. No longer being blocked, the *BMAL1* and *CLOCK* genes once again rev up the production of more clock proteins, as the cycle repeats itself. Each cycle takes about a day. The fluctuating levels of clock proteins bring about cyclical changes in neural output from the SCN that in turn lead to cyclic changes in effector organs throughout the day. An example is the diurnal variation in cortisol secretion (see Figure 7-6). Circadian rhythms are thus linked to fluctuations in clock proteins, which use a feedback loop to control their own production at the transcriptional (gene) level. In this way, internal timekeeping is a self-sustaining mechanism built into the genetic makeup of the SCN neurons.

These clock protein cycles allow the clock mechanism to run without any input

from the environment. But at some point, all clocks need to be synchronized with external signals (see text). This appears to be the role of one or more light-sensitive proteins, such as *CRY*. *CRY* belongs to the larger class of *cryptochromes* found first in plants and later in the retinas and SCN of fruit flies, mice, and humans. *Cryptochromes* in the retina react to blue light and are probably activated at dawn, and appear (based on knockout experiments) to be crucial to setting clocks in *Drosophila*. In mammals, **melanopsin** is thought to have that function. This protein is found in retinas of fishes, frogs, and mammals. It is a type of *opsin*, a family of genes used to make proteins for light absorption in vision (see Figure 6-35, p. 247). Melanopsin's gene, though related to visual opsins, is distinctly different enough to suggest a function other than vision. Knockout mice unable to make melanopsin were found to have 50 to 80% less sensitivity to light in setting their SCN clocks.

an intermediate lobe exists in the human fetus but becomes rudimentary after birth. Compared to the other regions of the pituitary gland and endocrine tissues in general, the intermediate lobe is poorly vascularized. Generally the size of the intermediate lobe is correlated with the ability of the animal to adapt to the coloration of its environment. For example, the lobe is enlarged in the chameleon, a champion of color change in lizards.

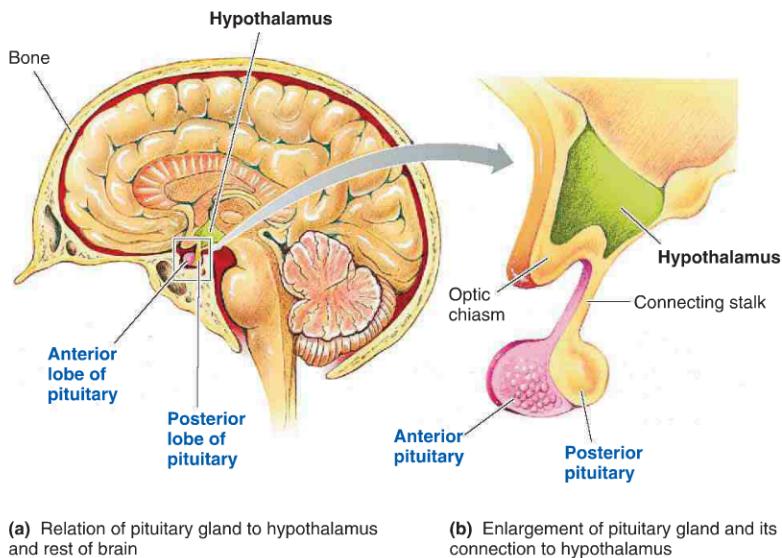
The intermediate lobe secretes several **melanocyte-stimulating hormones**, or **MSHs**. MSH is under primarily inhibitory control, as evidenced from experiments where ectopic transplantation of the entire pituitary gland lead to hypertrophy of the intermediate lobe and an increase in MSH secretion. Inhibition of MSH secretion by the hypothalamus is by the catecholamine dopamine. The two forms of melanocyte-stimulating hormone, **α -MSH** and **β -MSH**, are derived from the larger precursor protein *POMC* (p. 271). β -MSH has no known physiological role and may only be a structural component of *POMC*, whereas α -MSH controls skin coloration via the dispersion of storage granules containing the pigment **melanin**. These granules are in **melanocytes** (melanin-containing cells), found in the skin of most vertebrate species.

Melanocytes in the epidermis synthesize the colored substance melanin using the precursor amino acid tyrosine. Melanins that appear brown or black are referred to as **eumelanins**, whereas red or lighter colored melanins are termed **phaeomelanins**. Melanin is stored in melanin granules, or **melanosomes**, where it is released into the skin cells in response to environmental photic cues. By causing variable skin darkening in certain amphibians, reptiles, and

fishes, MSHs play a vital role in the camouflage of these species. In some lower vertebrates the action of α -MSH is opposed by an antagonistic pituitary hormone **melanin-concentrating hormone (MCH)**. Teleost MCH induced blanching of the skin when injected into dark-adapted fishes by stimulating melanosome pigment aggregation.

Some species of mammals and birds also rely on seasonal changes in melanin deposition in the pelage or feathers to minimize detection by predators or prey. MSH and steroid hormones can also differentially affect melanin deposition in the hairs and feathers of mammals and birds, although scientists do not understand the mechanism of melanin pigmentation of feathers. Nonetheless some mammals (such as the hare *Lepus americanus*) and some birds (such as the ptarmigan *Lagopus lagopus*) can change from a brown summer coat to a white winter coat in response to the dramatic changes in photoperiod.

In adult humans, the skin secretes small amounts of MSH. However, MSH is not involved in differences in the amount of melanin deposited in the skin in response to sunlight, nor with the process of skin tanning, although excessive MSH secretion does darken skin. Rather it is the activated form of vitamin D (alone or synergistically with other hormonal factors) that has been suggested to simulate melanogenesis (sun tanning). In animals without a pars intermedia (and so lacking a source of MSH), it is the intrinsic activity of the **melanocortin-1 receptor (MC1R)** that accounts for differences in skin color in humans, pelage (hair, fur, wool covering in a mammal), and feather pigmentation in birds. Another role for α -MSH lies in the appetite-suppressing neurons in the hypothalamus, which secrete to this hormone



(a) Relation of pituitary gland to hypothalamus and rest of brain

(b) Enlargement of pituitary gland and its connection to hypothalamus

FIGURE 7-9 Anatomy of the pituitary gland.

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Photo: Hiller Klandorf

Dispersion of pigment granules in the melanocytes by β -MSH permits the skin coloration of the California lizard, *Sceloporus*, to approximate that of the background.

control food intake (see p. 725). MSH has also been shown to suppress the immune system, possibly serving in a check-and-balance way to prevent excessive immune responses.

The hypothalamus and posterior pituitary form a neurosecretory system that secretes vasopressin and oxytocin

The release of hormones from both the posterior and the anterior pituitary is directly controlled by the hypothalamus, but the nature of the relationship is entirely different. The

posterior pituitary connects to the hypothalamus by a neural pathway, whereas the anterior pituitary connects to the hypothalamus by a unique vascular link.

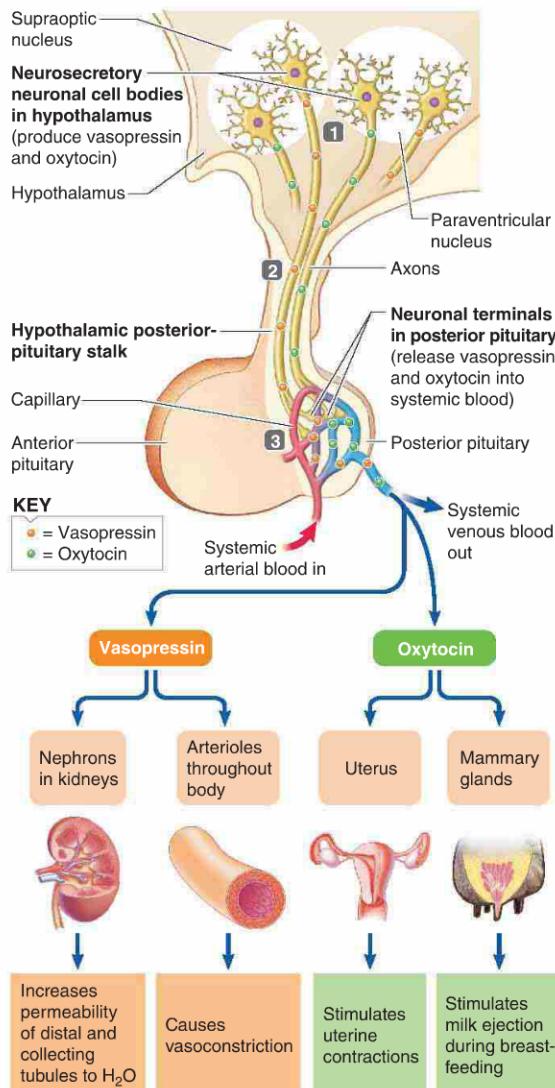
Let's look first at the posterior pituitary. The hypothalamus and posterior pituitary form a neuroendocrine system that consists of a population of neurosecretory neurons whose cell bodies lie in two well-defined clusters in the hypothalamus, the supraoptic and paraventricular nuclei. The axons of these neurons pass down through the thin connecting stalk to terminate on capillaries in the posterior pituitary (Figure 7-10). The posterior pituitary consists of these neuronal terminals plus glial-like supporting cells called pituicytes. Functionally as well as anatomically, the posterior pituitary is simply an extension of the hypothalamus. This is similar to the relationship between the X-organ and sinus gland in crustaceans (p. 279).

The posterior pituitary stores and, on appropriate stimulation, releases into the blood two small peptide neurohormones, vasopressin and oxytocin, which are synthesized by the neuronal cell bodies in the hypothalamus. The form of vasopressin in mammals is arginine vasopressin (AVP). Of note is the ancient origin of these two messengers—both hormones or closely related peptides appear in all animal species, from hydra to worms and snails, to fishes, birds, and mammals. In vertebrates the ancestor is thought to be arginine vasotocin (AVT), a peptide found in hagfishes and lampreys, primitive jawless fishes (agnathans) that originated over 500 million years ago. AVT also found in other vertebrates (see p. 574).

The synthesized hormones are packaged in secretory granules that are transported by axoplasmic flow down the cytoplasm of the axon (see Figure 4-21) to be stored in the neuronal terminals within the posterior pituitary. Each terminal stores either vasopressin or oxytocin but not both. Thus, these hormones can be released independently as needed. On stimulatory input to the hypothalamus, either vasopressin or oxytocin is released into the systemic blood from the posterior pituitary by exocytosis of the appropriate secretory granules. This hormonal release is triggered in response to action potentials that originate in the hypothalamic cell body and sweep down the axon to the neuronal terminal in the posterior pituitary. As in any other neuron, action potentials are generated in these neurosecretory neurons in response to synaptic input to their cell bodies.

The actions of vasopressin and oxytocin are only briefly summarized here, but they are described more thoroughly in later chapters.

Vasopressin In most mammals, vasopressin (also called antidiuretic hormone, ADH) has two major effects that correspond to its two names: (1) it enhances retention of H_2O by kidneys (an antidiuretic effect), and (2) it causes contraction of arteriolar smooth muscle (a vasoconstrictor effect).



- 1 The paraventricular and supraoptic nuclei both contain neurons that produce vasopressin and oxytocin. The hormone, either vasopressin or oxytocin depending on the neuron, is synthesized in the neuronal cell body in the hypothalamus.
- 2 The hormone travels down the axon to be stored in the neuronal terminals within the posterior pituitary.
- 3 When the neuron is excited, the stored hormone is released from the terminals into the systemic blood for distribution throughout the body.

FIGURE 7-10 Relationship of the hypothalamus and posterior pituitary.

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Under normal conditions, vasopressin is the primary endocrine factor that regulates urinary H_2O loss and overall H_2O balance. The major control for hypothalamic-induced release of vasopressin from the posterior pituitary is input from hypothalamic *osmoreceptors*, which increase vasopressin secre-

tion in response to a rise in plasma osmolarity (see Chapters 12 and 13). More recently, vasopressin has also been found to play roles in fever, learning, memory, and behavior.

Earlier we noted that the equivalent hormone in lower vertebrates is *arginine vasotocin* (AVT). In addition to its role in osmoregulation, AVT produces vasoconstriction and an increase in blood pressure in most ectotherms. In flounder, during the initial phase of adaptation from fresh water to seawater there is a transitory rise in plasma osmolarity, which increases plasma AVT. During metamorphosis of tadpoles into frogs, the increase in AVT stimulates ACTH-induced steroidogenesis, which raises concentrations of corticosterone (see p. 305). AVT's evolutionary role in smooth muscle contraction is also evidenced in birds, where it governs *oviposition*, the physical process of laying an egg; administering AVT into a laying hen causes contraction of the uterus (shell gland) and expulsion of the egg. AVT also causes uterine contractions that accompany birth in viviparous ("live birth") snakes (*Nerodia*).

Oxytocin Oxytocin in mammals has been described as the "hormone of love" for a variety of social bonding influences; for example, its release in lactating rat mothers provides the urge to nurse their pups. Behaviorally it keeps male prairie voles monogamous and induces trust in people (see Chapter 16 for details on these and other examples). Physiologically, through positive-feedback regulation, it stimulates contraction of the uterine smooth muscle to help expel the fetus during birth and promotes ejection of the milk from the mammary glands (see Chapter 16).

The nonmammalian homologue, *mesotocin* (MT), does not affect the uterus but rather influences the blood flow to some organs (for example, in poultry an increased concentration of MT reduces the blood flow to the lower limbs and comb) in addition to reducing the circulating concentrations of aldosterone.

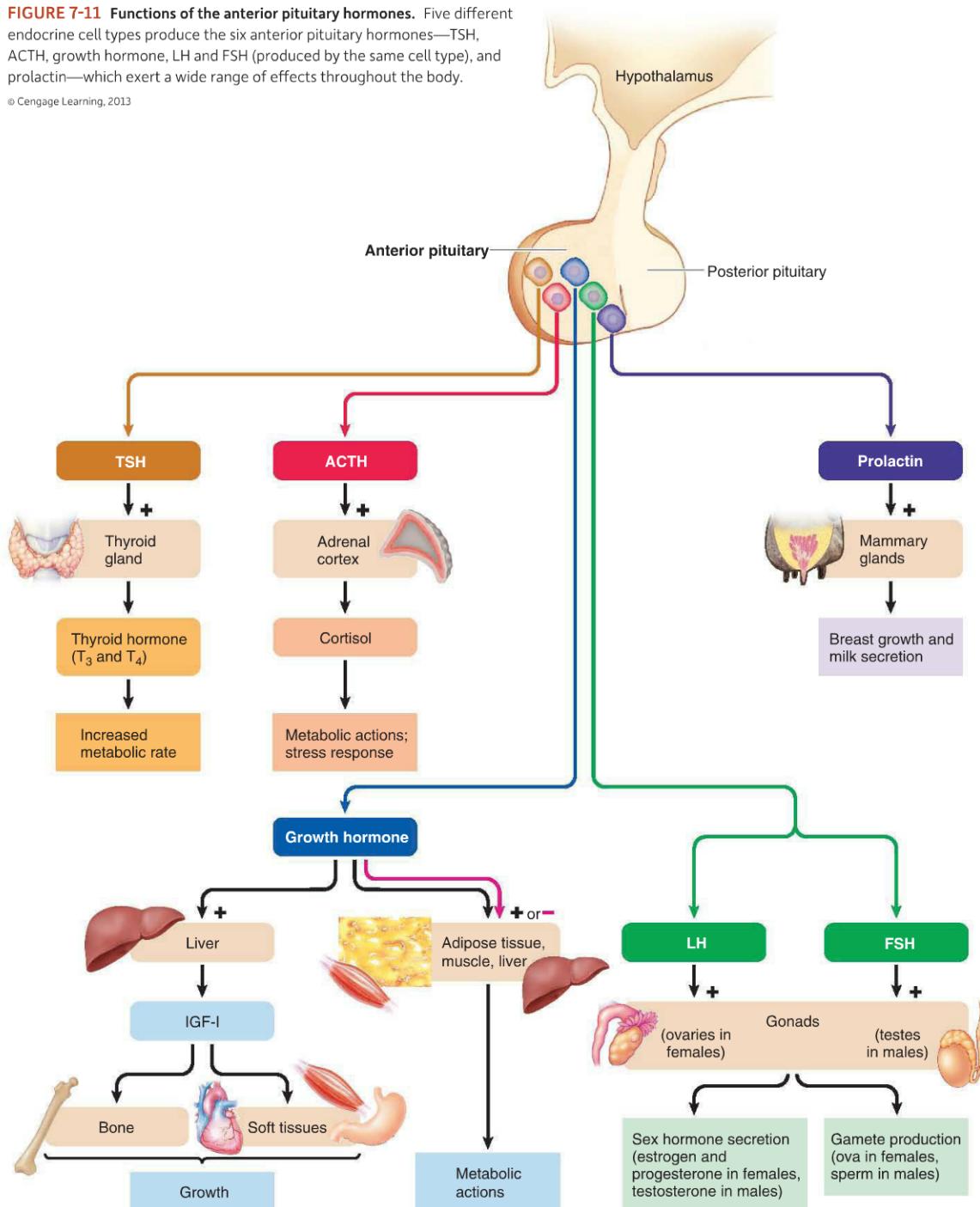
The anterior pituitary secretes six established hormones, many of which are tropic

Unlike the posterior pituitary, which releases hormones that are synthesized by the hypothalamus, the anterior pituitary itself synthesizes the hormones that it releases into the blood. Different cell populations within the anterior pituitary produce and secrete six established peptide hormones. The action of each of these hormones is discussed in detail in subsequent sections and chapters. For now, we briefly state their primary effects to explain their names (Figure 7-11):

1. The type of anterior pituitary cells known as *somatotropes* secrete *growth hormone* (GH, somatotropin), the primary hormone responsible for regulating overall body growth (*somato* means "body"). GH also exerts important metabolic actions.
2. *Thyrotropes* secrete *thyroid-stimulating hormone* (TSH, thyrotropin), which stimulates secretion of thyroid hormone and growth of the thyroid gland.
3. *Corticotropes* produce and release *adrenocorticotrophic hormone* (ACTH, or *corticotropin*), the hormone that stimulates cortisol secretion by the adrenal cortex and promotes growth of the adrenal cortex. In advanced vertebrates ACTH is derived from the large precursor molecule *POMC* (p. 271) produced within the endoplas-

FIGURE 7-11 Functions of the anterior pituitary hormones. Five different endocrine cell types produce the six anterior pituitary hormones—TSH, ACTH, growth hormone, LH and FSH (produced by the same cell type), and prolactin—which exert a wide range of effects throughout the body.

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- mic reticulum of the anterior pituitary's ACTH-secreting cells.
4. Gonadotropes secrete two **gonadotropins**, hormones that act on the gonads (reproductive organs, namely the ova-

ries and testes)—follicle-stimulating hormone and luteinizing hormone. Follicle-stimulating hormone (FSH) helps regulate gamete (reproductive cells, namely ova and sperm) production in both sexes. In females it stimulates

- growth and development of ovarian follicles, within which the ova, or eggs, develop. It also promotes secretion of the sex steroid hormone *estrogen* by the ovaries. In males FSH is required for sperm production.
5. **Luteinizing hormone (LH)**, the other gonadotropin, helps control sex hormone secretion in both sexes, among other important actions in females. In females LH is responsible for ovulation and luteinization (that is, the formation of a hormone-secreting corpus luteum in the ovary following ovulation). LH also regulates ovarian secretion of the female sex hormones, estrogen and progesterone. In males the same hormone stimulates the Leydig (interstitial) cells in the testes to secrete the male sex steroid hormone, *testosterone*.
 6. **Lactotropes** secrete **prolactin**, which is structurally similar to growth hormone and exhibits some overlapping functions. Prolactin was originally determined to be involved in mammalian reproductive functions; for example, in female mammals prolactin stimulates milk production and nurturing of young whereas in males, evidence indicates it may induce production of testicular LH receptors and paternal bonding with offspring. However, throughout the vertebrates, prolactin now known to be involved in a remarkable spectrum of functions beyond reproduction, including osmoregulation, promotion of growth, support of metabolism, water drive, and metamorphosis. No other polypeptide hormone has such a wide repertoire of biological actions, some of which we will cover in this chapter later (p. 296) and Chapter 16. Prolactin's osmoregulatory roles have been primarily demonstrated in freshwater fishes, a topic we explore in Chapter 13. Thus, unlike other pituitary hormones, prolactin was not committed early in evolution to the control of one or few related processes but remained diversified and adaptive in nature. This multiplicity of functions is likely why lactotropes constitute the largest category of the anterior pituitary cell types.

TSH, ACTH, FSH, and LH all act at their target organs by binding with G-protein coupled receptors that activate the cAMP second-messenger system (see p. 97). GH and PRL both exert their effects via a different second-messenger pathway, which we have not previously mentioned—the **JAK/STAT** pathway. Binding of these hormones to their target-cell surface membrane receptors on the ECF side activates the enzyme *Janus kinase (JAK)* attached to the cytosolic side of the receptor. JAK phosphorylates *signal transducers and activators of transcription (STAT)* within the cytosol. Phosphorylated STAT moves to the nucleus and turns on gene transcription, resulting in the synthesis of new proteins that carry out the cellular response.

Hypothalamic releasing and inhibiting hormones that regulate secretion in the anterior pituitary are delivered to it by the hypothalamic-hypophyseal portal system

None of the anterior pituitary hormones are secreted at a constant rate. Even though each of these hormones has a unique control system, there are some common regulatory patterns. The two most important factors that regulate se-

cretion of anterior pituitary hormone are (1) hypothalamic hormones and (2) feedback by target gland hormones.

Because the anterior pituitary secretes hormones that control the secretion of various other hormones, it has long had the undeserved title of “master gland.” It is now known that the release of each of the anterior pituitary hormones is largely controlled by still other hormones produced by the hypothalamus, and that secretion of these regulatory neurohormones in turn is controlled by a variety of neural and hormonal inputs to the hypothalamic neurosecretory cells.

Role of Hypothalamic Releasing and Inhibiting Hormones

The secretion of each anterior pituitary hormone is stimulated or inhibited by hypothalamic **hypophysiotropic (hypophysis means “pituitary”) hormones**. Depending on their actions, these hormones are called **releasing hormones** or **inhibiting hormones**. Their names and basic functions are:

1. **Thyrotropin-releasing hormone (TRH)**: Stimulates release of TSH (thyrotropin) and prolactin.
2. **Corticotropin-releasing hormone (CRH)**: Stimulates release of ACTH (corticotropin).
3. **Gonadotropin-releasing hormone (GnRH)**: Stimulates release of FSH and LH (gonadotropins).
4. **Growth hormone-releasing hormone (GHRH)**: Stimulates release of growth hormone.
5. **Growth hormone-inhibiting hormone (GHIH)**: Inhibits release of growth hormone and TSH.
6. **Prolactin-releasing hormone (PRH)**: Stimulates release of prolactin.
7. **Prolactin-inhibiting hormone (PIH)**: Inhibits release of prolactin.

Also, in most vertebrates, including birds, amphibians, and fishes, there is evidence of a **gonadotropin-inhibitory hormone (GnIH)**. Most of these are small peptides, although PIH is **dopamine** (the neurotransmitter found in the “pleasure” pathways in the brain).

Note that vertebrate hypophysiotropic hormones in most cases are involved in a three-hormone hierarchical chain of command (Figure 7-12): The hypothalamic hypophysiotropic hormone (hormone 1) controls the output of an anterior pituitary tropic hormone (hormone 2). This tropic hormone in turn regulates secretion of the target endocrine gland’s hormone (hormone 3), which exerts the final physiological effect. This three-hormone sequence is called an **endocrine axis**, as in the hypothalamus–pituitary–thyroid axis.

Although scientists originally proposed a neat one-to-one correspondence—one hypophysiotropic hormone for each anterior pituitary hormone—it is now clear that many of the hypothalamic hormones have more than one effect, so their names indicate only the function that was initially attributed to them. Moreover, a single anterior pituitary hormone may be regulated by two or more hypophysiotropic hormones. Several substances elicit release of prolactin in certain species, for example. Note also that some of these hormones exert opposing effects. For example, **growth hormone-releasing hormone (GHRH)** stimulates growth hormone secretion, whereas **growth hormone-inhibiting hormone (GHIH)**, also known as **somatostatin**, inhibits it. The output of the anterior pituitary growth hormone secreting cells (that is, the rate of growth hormone secretion) in response to two such opposing inputs depends on the relative concentrations of these hypothalamic hormones as well as

on the intensity of other regulatory inputs. This is analogous to the output of a nerve cell (that is, the rate of action potential propagation) depending on the relative magnitude of excitatory and inhibitory synaptic inputs (EPSPs and IPSPs) to it (see p. 137).

Role of the Hypothalamic-Hypophyseal Portal System

Portal System The hypothalamic regulatory hormones reach the anterior pituitary by means of a unique vascular link. In contrast to the direct neural connection between the hypothalamus and posterior pituitary, the link between the hypothalamus and anterior pituitary is an unusual capillary-to-capillary connection, the **hypothalamic-hypophyseal portal system**. A portal system is a vascular arrangement in which venous blood flows directly from one capillary bed through a connecting vessel to another capillary bed before going back to the heart. The largest and best-known portal system is the *hepatic portal system* (see p. 685). Although much smaller, the hypothalamic-hypophyseal portal system is no less important, because it provides a critical link between the brain and much of the endocrine system. It begins in the base of the hypothalamus with a group of capillaries that recombine into small portal vessels, which pass down through the connecting stalk into the anterior pituitary. Here they branch to form most of the anterior pituitary capillaries, which in turn drain into the venous system (Figure 7-13).

As a result, almost all the blood supply to the anterior pituitary must first pass through the hypothalamus. Because materials can be exchanged between the blood and surrounding tissue only at the capillary level, the hypothalamic-hypophyseal portal system provides a route where releasing and inhibiting hormones can be picked up at the hypothalamus and delivered immediately and directly to the anterior pituitary at relatively high concentrations, completely bypassing the general circulation.

The axons of the neurosecretory neurons that produce the hypothalamic regulatory hormones terminate on the capillaries at the origin of the portal system. These hypothalamic neurons secrete their (neuro) hormones in the same way as the hypothalamic neurons that produce vasopressin and oxytocin, but into the portal vessels rather than into the general circulation.

Control of Hypothalamic Releasing and Inhibiting Hormones

What regulates the secretion of these hypophysiotropic hormones? Like other neurons, the neurons secreting these regulatory hormones receive abundant input of information (both neural and hormonal and both excitatory and inhibi-

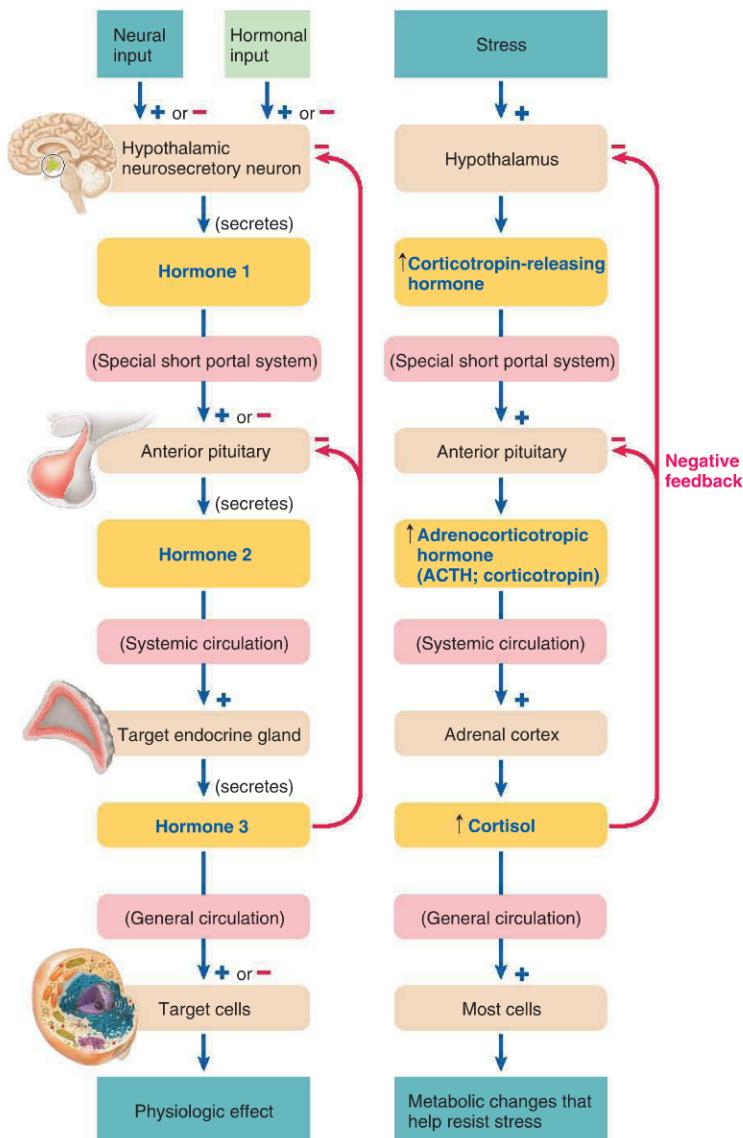


FIGURE 7-12 Hierarchic chain of command in endocrine control.

The general pathway involved in the hierarchic chain of command among the hypothalamus, anterior pituitary, and peripheral target endocrine gland is depicted on the left. The pathway on the right leading to cortisol secretion provides a specific example of this endocrine chain of command.

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tory) that they must integrate. Studies are still in progress to unravel the complex neural input from many diverse areas of the brain to the hypophysiotropic secretory neurons. Some of these inputs carry information about a variety of environmental conditions. One example is the marked increase in the secretion of corticotropin-releasing hormone (CRH) in response to stressful situations (Figure 7-12).

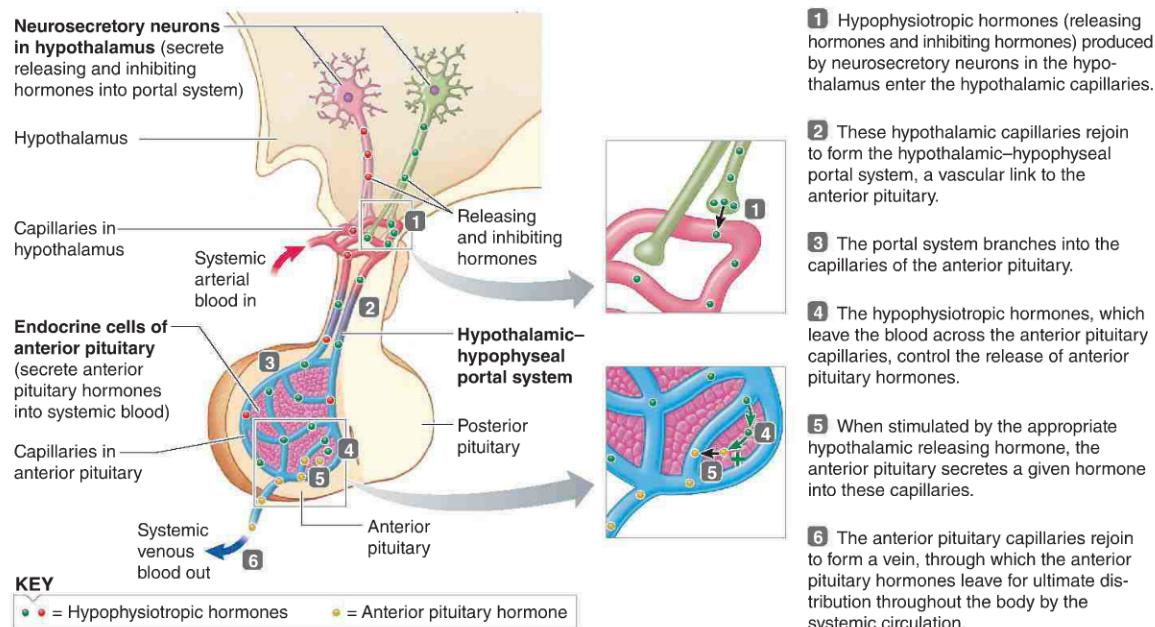


FIGURE 7-13 Vascular link between the hypothalamus and anterior pituitary.

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Numerous neural connections also exist between the hypothalamus and the portions of the brain concerned with emotions (such as the *amygdala*—see p. 187). Thus, secretion of hypophysiotropic hormones can be greatly influenced by emotions. The reproductive irregularities sometimes experienced by animals maintained under stressful conditions are a common manifestation of this relationship.

In addition to being regulated by different regions of the brain, the hypophysiotropic neurons are also controlled by various chemical inputs that reach the hypothalamus through the blood. Unlike other regions of the brain, portions of the hypothalamus are not guarded by the blood-brain barrier, so the hypothalamus can easily monitor chemical changes in the blood. The most common blood-borne factors that influence hypothalamic neurosecretion are the negative-feedback effects of either anterior pituitary or target gland hormones, to which we now turn our attention.

Target gland hormones inhibit hypothalamic and anterior pituitary hormone secretion via negative feedback

In most cases, hypophysiotropic hormones initiate a three-hormone sequence: (1) hypophysiotropic hormone, (2) anterior pituitary tropic hormone, and (3) peripheral target-endocrine gland hormone (Figure 7-12). Typically, in addition to producing its physiologic effects, the target gland hormone also acts to suppress secretion of the tropic hormone that is driving it. This negative feedback is accomplished by the target gland hormone acting either directly on the pituitary itself or on the release of hypothalamic hor-

mones, which in turn regulate anterior pituitary function. As an example, consider the CRH-ACTH-cortisol system. Hypothalamic CRH stimulates the anterior pituitary to secrete ACTH (corticotropin), which in turn stimulates the adrenal cortex to secrete cortisol. The final hormone in the system, cortisol, inhibits the hypothalamus to reduce CRH secretion and also acts directly on the corticotropes in the anterior pituitary to reduce synthesis of pro-opiomelanocortin (POMC) and ACTH secretion. Through this double-barreled approach, cortisol exerts negative-feedback control to stabilize its own plasma concentration. If plasma cortisol levels start to rise above a prescribed set level, cortisol suppresses its own further secretion by these inhibitory actions. If plasma cortisol levels fall below the desired set point, cortisol's inhibitory actions are reduced, so cortisol secretion (CRH-ACTH) increases accordingly. The other target-gland hormones act by similar negative-feedback loops to maintain their plasma levels relatively constant at a set point. For example, feedback of testosterone to the hypothalamus maintains levels of LH, FSH, and sex steroids via GnRH production. Male mammals injected with testosterone-like steroids can become sterile because of this feedback, which causes FSH levels to decline. Birth control pills with female sex steroids work similarly.

The one exception to the negative-feedback relationship just described is the preovulatory positive-feedback effect of estrogen on LH secretion in female mammals. This causes an extremely dramatic rise in LH secretion that triggers ovulation. This relationship is discussed further in Chapter 16.

Diurnal rhythms are superimposed on this type of stabilizing negative-feedback regulation; that is, the set point changes as a function of the time of day. Furthermore, other controlling inputs may break through the negative-feedback

control to alter hormone secretion (that is, change the set point level) at times of special need. For example, stress raises the set point for cortisol secretion.

In addition, other hormones outside a particular sequence may also exert important influences, either stimulatory or inhibitory, on the secretion of hypothalamic or anterior pituitary hormones within a given sequence. For example, even though estrogen is not in the direct chain of command for prolactin secretion, this sex steroid notably enhances prolactin secretion by the anterior pituitary. This is but one example of the common phenomenon in the endocrine system that one seemingly unrelated hormone can have pronounced effects on the secretion or actions of another hormone.

check your understanding 7.3

What is the role of melatonin in determining the onset of the breeding season?

What is the importance of biological clocks in an animal, and how do they work?

How is regulation of anterior hormone release different from that of the posterior pituitary?

Under what conditions is MSH released from the pars intermedia?

7.5 Thyroid Gland

The **thyroid gland** is a major regulator of metabolism and other metabolic and developmental processes. Thyroid hormones are produced by endocrine cells arranged in a very characteristic anatomical structure called a *thyroid follicle*. In mammals the thyroid gland consists of two lobes of thyroid follicles joined in the middle by a narrow portion of the gland, giving it a bowtie shape (Figure 7-16a). The gland is even located in the appropriate place for a bow tie in a human, lying over the trachea just below the larynx. In contrast, the thyroid gland of most nonmammalian vertebrates consists of discrete clusters of thyroid follicles, sometimes central, sometimes paired, lying at varying distances lateral to the esophagus; in agnathans and most teleosts the thyroid

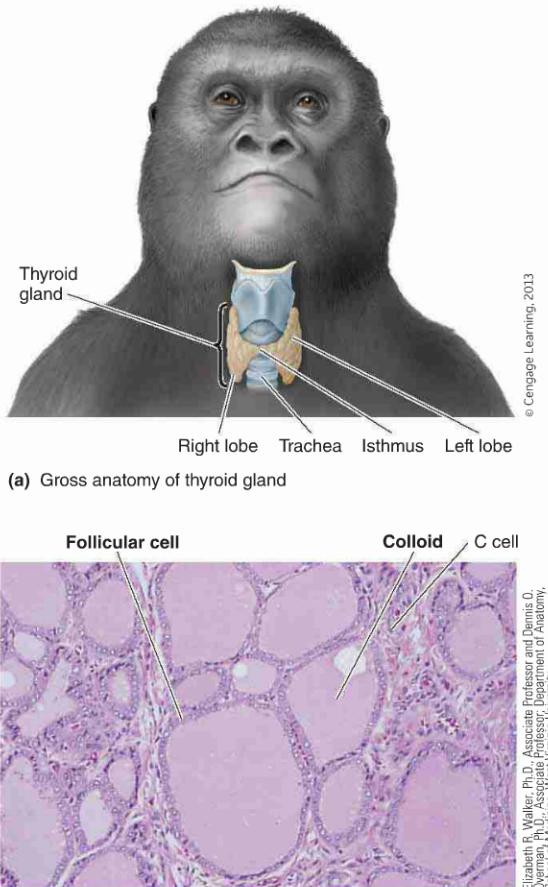


FIGURE 7-16 Anatomy of the thyroid gland. (a) Gross anatomy of the thyroid gland, anterior view. The thyroid gland lies over the trachea just below the larynx and consists of two lobes connected by a thin strip called the *isthmus*. (b) Light-microscopic appearance of the thyroid gland. The thyroid gland consists primarily of colloid-filled spheres enclosed by a single layer of follicular cells.

consists of diffuse clusters of follicles distributed throughout the ventral region of the head. In spite of the varied gross morphology of the thyroid gland, the follicular structure is highly conserved and essential for the unique method of extracellular hormone synthesis utilized by this gland.

The major thyroid hormone secretory cells are organized into colloid-filled follicles

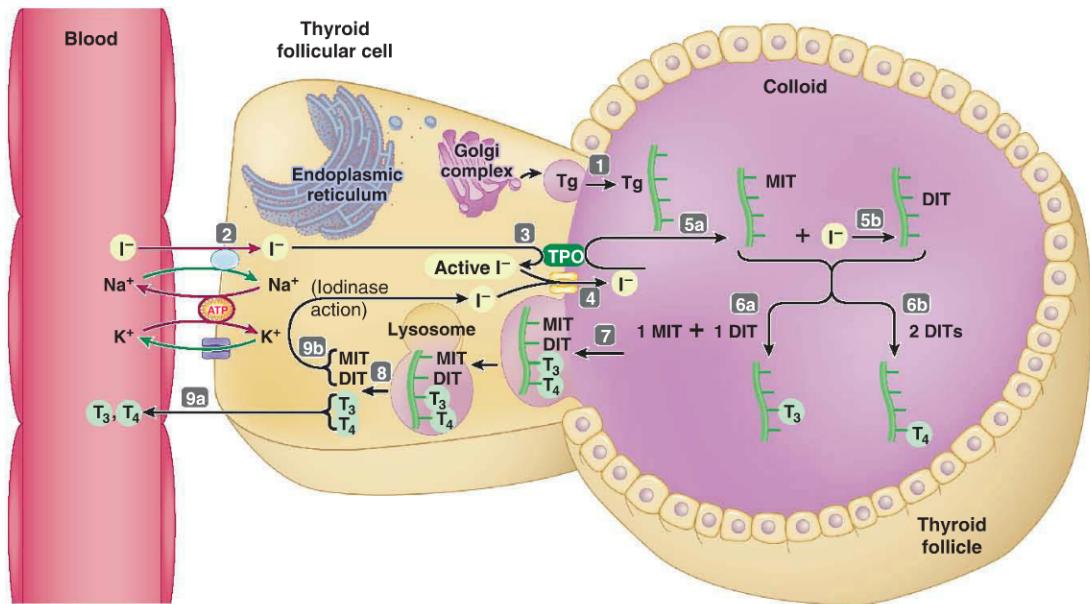
The major thyroid secretory cells, known as **follicular cells**, are arranged into fluid-filled spheres, each of which forms a functional unit called a **follicle**. On a microscopic section (Figure 7-16b), the follicles appear as rings of follicular cells enclosing an inner lumen filled with **colloid**, a substance that serves as an extracellular storage site for thyroid hormones.

The chief constituent of the colloid is a large, complex glycoprotein known as **thyroglobulin (Tg)**, within which are incorporated the thyroid hormones in their various stages of synthesis. Extracellular hormone storage is unique to the thyroid gland and probably exists because the thyroid evolved from an exocrine-secreting digestive organ called the endostyle. As we'll see, the colloid indirectly stores the scarce trace element iodine, which is an essential component of the thyroid gland, and prevents diffusion of the steroid-like thyroid hormone out of the colloid.

Thyroid hormone is synthesized and stored on the thyroglobulin molecule

The follicular cells of vertebrates produce two iodine-containing hormones derived from the amino acid tyrosine: **tetraiodothyronine (T₄, or thyroxine)** and **tri-iodothyronine (T₃)**. The prefixes *tetra* and *tri* and the subscripts 4 and 3 denote the number of iodine atoms incorporated into each of these hormones. These two hormones, together referred to as **thyroid hormone**, are important regulators of development and overall basal metabolic rate. The basic ingredients for thyroid hormone synthesis are tyrosine and iodine, both of which must be taken up from the blood by the follicular cells. Tyrosine, an amino acid, is synthesized in sufficient amounts by the body, so it is not an essential dietary requirement. By contrast, the iodine needed for thyroid hormone synthesis must be obtained from dietary intake. Dietary iodine (I) is reduced to iodide (I⁻) prior to absorption by the small intestine. The synthesis, storage, and secretion of thyroid hormone involve the following steps:

1. All steps of thyroid hormone synthesis take place on the thyroglobulin molecules within the colloid. Thyroglobulin itself is produced by the endoplasmic reticulum/Golgi complex of the thyroid follicular cells. The amino acid tyrosine becomes incorporated in the much larger thyroglobulin molecules as the latter are being produced. Once produced, tyrosine-containing thyroglobulin is exported from the follicular cells into the colloid by exocytosis (step 1 in Figure 7-17).
2. The thyroid captures I⁻ from the blood and transfers it into the colloid by means of an *iodide pump*, energy-requiring transport proteins located in the outer membranes of the follicular cells (step 2). The iodide pump is a symporter driven by the Na⁺ concentration gradient established by the Na⁺/K⁺ pump at the basolateral membrane (the outer membrane of the follicular cell in contact with the interstitial fluid). The iodide pump transports Na⁺ into the follicular cell down its concentration gradient and I⁻ into the cell against its concentration gradient. Almost all the I⁻ in the body is transported against its concentration gradient to become trapped in the thyroid for the purpose of thyroid hormone synthesis. Iodine serves no other known purpose in the vertebrate body.
3. Within the membrane–colloid interface, iodide is oxidized to “active” iodide by a membrane-bound enzyme, **thyroperoxidase (TPO)**, located at the luminal membrane, the membrane of the follicular cell in contact with the colloid (step 3). This active iodide exits through a channel in the luminal membrane to enter the colloid (step 4). Attachment of one iodine to tyrosine yields



KEY



= Primary active transport



= Secondary active transport (symporter)

Tg = Thyroglobulin
I⁻ = Iodide
TPO = Thyroperoxidase
MIT = Monoiodotyrosine

DIT = Di-iodotyrosine
T₃ = Tri-iodothyronine
T₄ = Tetraiodothyronine (thyroxine)

- 1 Tyrosine-containing Tg produced within the thyroid follicular cell by the endoplasmic reticulum/Golgi complex is transported by exocytosis into the colloid.
- 2 Iodide is carried by secondary active transport from the blood into the colloid by symporters in the basolateral membrane of the follicular cells.
- 3 In the follicular cell, the iodide is oxidized to active form by TPO at the luminal membrane.
- 4 The active iodide exits the cell through a luminal channel to enter the colloid.
- 5a Catalyzed by TPO, attachment of one iodide to tyrosine within the Tg molecule yields MIT.
- 5b Attachment of two iodides to tyrosine yields DIT.
- 6a Coupling of one MIT and one DIT yields T₃.
- 6b Coupling of two DITs yields T₄.
- 7 On appropriate stimulation, the thyroid follicular cells engulf a portion of Tg-containing colloid by phagocytosis.
- 8 Lysosomes attack the engulfed vesicle and split the iodinated products from Tg.
- 9a T₃ and T₄ diffuse into the blood (secretion).
- 9b MIT and DIT are deiodinated, and the freed iodide is recycled for synthesizing more hormone.

FIGURE 7-17 Synthesis, storage, and secretion of thyroid hormone. Note that the organelles are not drawn to scale. The endoplasmic reticulum/Golgi complex are proportionally too small.

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monoiodotyrosine (MIT) (step 5a). Attachment of two iodines to tyrosine yields di-iodotyrosine (DIT) (step 5b). Next, a coupling process occurs between the iodinated tyrosine molecules to form the thyroid hormones. Coupling of two DITs (each bearing two iodine atoms) yields tetraiodothyronine (T₄ or thyroxine), the four-iodine form of thyroid hormone (step 6b). Coupling of one MIT (with one iodine) and one DIT (with two iodines) yields tri-iodothyronine or T₃ (with three iodines) (step 6a). Coupling does not occur between two MIT molecules. All these products remain attached to thyro-

globulin by peptide bonds. Thyroid hormones remain stored in this form in the colloid until they are split off and secreted. Sufficient thyroid hormone is normally stored to supply the body's needs for several months.

Because these reactions occur within the thyroglobulin molecule, all the products remain attached to this large protein. Immobilized in this fashion they, contrary to their steroid-hormone-like behavior, cannot freely diffuse into the circulation after synthesis. Thyroid hormones remain stored in this form in the colloid until they are split off and

The anterior pituitary consists of the pars distalis (PD) (main body of the pituitary gland) and the pars tuberalis (PT), which forms the stalk of the pituitary gland immediately adjacent to the base of the brain. As we have seen, the PD receives signals from the hypothalamus via the portal system to regulate the multiple cell types in this tissue. The PT forms a specialized tissue that expresses melatonin receptors and thus responds to the daily light-dark cycle that regulates seasonal changes in pituitary function. In turn, *retrograde signaling* from the PT directs the hypothalamus to govern neuroendocrine control of reproduction, food intake, and other seasonal characteristics. PT thyrotrophs do not express TRH receptors and are not under inhibitory control by the thyroid gland, and also do not produce the transcription factor *PIT1* that drives normal PD cell differentiation. *PIT1* in

PD cells also regulates the genes for TSH and prolactin.

The primary cell type in the PT is a thyrotroph-like cell that is distinct from the thyrotrophs in the PD that secretes TSH to regulate the thyroid glands. In birds and mammals, the PT secretes TSH only locally, which then diffuses into the basal hypothalamus and binds to TSH receptors on the *tanyocytes* (specialized cells in the ependymal layer) that line the third ventricle. In this fashion, these nonneuronal tanyocytes can be induced to express the outer-ring (type 2) *deiodinase*, the enzyme that catalyzes the conversion of thyroxine to its biologically active form T_3 . This results in a local increase in T_3 concentration in the medial basal hypothalamus (MBH), which activates a major cascade of new secretory responses that drive reproduction and other centrally related functions, which have long

been recognized to be thyroid-hormone dependent. In seasonally breeding animals, the experimental introduction of TSH locally into the ventricle of the brain in animals exposed to winter photoperiod induces all the biological responses normally associated with summer photoperiod. Thus, it is the PT that initiates the response to spring photoperiods, relays the information to the brain, and activates the associated biology. In addition, it is believed that these local changes in thyroid hormone are required for neurogenesis within the tissue and this provides the basis for the long-term transformation in the cell biology of the brain. Thus, over a period of weeks and months, the animal transforms its physiology from winter to summer, readjusting a functional set point for homeostasis.

secreted. As a result of this unique extracellular synthetic process, researchers estimate that sufficient thyroid hormone to supply a mammal's needs for several months is normally stored in the colloid. Should a predator consume the thyroid gland of its prey, it would receive a physiologically significant dose upon consumption.

To secrete thyroid hormone, the follicular cells phagocytize thyroglobulin-laden colloid

The release of the thyroid hormones into the systemic circulation is a rather complex process, for two reasons. First, before their release T_4 and T_3 are still bound within the thyroglobulin molecule. Second, these hormones are stored in the follicular lumen, so they must be transported completely across the follicular cells to reach capillaries that course through the interstitial spaces between the follicles.

The process of thyroid hormone secretion essentially involves the follicular cells “biting off” a piece of colloid, breaking the thyroglobulin molecule down into its component parts, and “spitting out” the freed T_4 and T_3 into the blood. On appropriate stimulation for thyroid hormone secretion, the follicular cells internalize a portion of the thyroglobulin-hormone complex by phagocytizing a piece of colloid (step 7 of Figure 7-17). Within the cells, the membrane-enclosed droplets of colloid coalesce with lysosomes, whose enzymes split off the biologically active thyroid hormones, T_4 and T_3 , as well as the inactive iodotyrosines, MIT and DIT (step 8). The thyroid hormones, being lipophilic, pass through the outer membranes of the follicular cells and into the blood (step 9a).

The MIT and DIT have no known endocrine function. The follicular cells contain an enzyme that swiftly removes the iodine from MIT and DIT, allowing the freed iodine to be recycled for synthesis of more hormone (step 9b). Some intact thyroglobulin is also released into the general circulation, although this protein has no known physiological function.

For the most part, both T_4 and T_3 are transported bound to specific plasma proteins

Once released into the blood, the highly lipophilic thyroid hormone molecules very quickly bind with several plasma proteins. Less than 1% of the T_3 and less than 0.1% of the T_4 remain in the **unbound (free)** form. This is remarkable, considering that only the free portion of the total thyroid hormone pool has access to the target cell receptors and thus can exert a biological effect.

Three different plasma proteins synthesized within the liver are important in thyroid hormone binding: In mammals (excluding cats), **thyroxine-binding globulin (TBG)** selectively binds all thyroid hormones even though its name specifies only “thyroxine” (T_4); binding proteins in other species include **albumin**, which nonselectively binds many lipophilic hormones, including T_4 and T_3 ; and **transthyretin (TTR)**, which binds the remaining T_4 . TTR appears to be produced in the liver of amphibians and fish during transient periods of hyperthyroidism and more constantly in endotherms. TTR appears to be selectively secreted into the CSF by the choroid plexus of animals with a neocortex, supporting a role for this hormone in CNS development and function. The turnover of T_4 is comparatively slow in species that utilize TBG as a binding protein.

Most of the secreted T₄ is converted into T₃ outside the thyroid

In general, the proportion of T₄ and T₃ present in the thyroid gland of vertebrates is variable, although most thyroids secrete primarily T₄, most likely because more DIT is made than MIT. Regardless, in the peripheral tissues (e.g., liver and kidney), most of the secreted T₄ is converted into T₃, or *activated*, by an outer-ring deiodinase enzyme (Type II) that strips off one of its iodines. T₃ is the major biologically active form of thyroid hormone at the cellular level. T₄ can also be *inactivated* by inner-ring deiodinase (Type I) and converted into the metabolically inactive **reverse tri-iodothyronine**, or rT₃. Peripherally produced T₃ can bind to receptors with 10 times the affinity of T₄, giving peripheral cells the ability to activate their own hormone stimulation (or inactivate it by conversion to rT₃). It is now becoming apparent that regulation of these deiodinase enzymes is a major determinant of thyroid hormone stimulation of targets. For example, the stimulation of neuron growth during development of the brain is dependent on the deiodination of T₄ by astrocytes. Cells in the chick embryo produce only rT₃ until the time of piping (the bill piercing the air sack), whereon the enzymatic machinery begins to synthesize the metabolically active T₃. These inactivation pathways are also important in preserving energy stores during periods of limited food availability and are associated with reduced activity of the enzymatic machinery that generates T₃.

Thyroid hormone is the primary determinant of overall metabolic rate and exerts other effects as well

Thyroid hormone does not have any discrete target organs. It affects virtually every tissue in the body. Like all lipophilic hormones, thyroid hormone crosses the plasma membrane and binds with an intracellular receptor, in this case a nuclear receptor bound to the **thyroid-response element** of DNA. This binding alters the transcription of specific mRNAs and thus synthesis of specific new proteins, typically enzymes that carry out the cellular response.

Compared to other hormones, the action of thyroid hormone is “sluggish.” The response to an increase in thyroid hormone is detectable only after a delay of several hours, and the maximal response is not evident for several days. The duration of the response is also quite long, partially because thyroid hormone is not rapidly degraded but also because the response to an increase in secretion continues to be expressed for days or even weeks after the plasma thyroid hormone concentrations have declined.

The effects of T₃ and T₄ can be grouped into several overlapping categories.

Effect on Metabolic Rate and Heat Production The evolution from ectothermy to endothermy necessitated development of a mechanism to regulate metabolic heat production. The solution provided by thyroid hormones is to increase a bird’s or mammal’s overall basal metabolic rate (BMR), or “idling speed” (see p. 320). This occurs by regulating mitochondrial function as well as certain mitochondrial proteins. For example, the number of active Na⁺/K⁺ ATPase pump units in the membrane is closely regulated in endotherms.

The transport of Na⁺ relies on the hydrolysis of ATP, which yields heat as a by-product. Considering that as much as 20 to 40% of the total cell energy supply is required to maintain the pump activity, a considerable amount of heat is liberated in the process. Thyroid hormone is thus the most important regulator of the rate of O₂ consumption and energy expenditure under resting conditions. Inhibition of the Na⁺/K⁺ ATPase pump activity by ouabain (p. 87) markedly reduces the effect of thyroid hormone on heat production and oxygen consumption. Whereas thyroid hormones are generally elevated in endotherms, they are selectively elevated in ectotherms during periods of metabolically demanding activity (e.g., mating, migration, active feeding), although much less is known about their regulation in ectotherms.

Effect on Intermediary Metabolism In addition to increasing the general metabolic rate, thyroid hormone modulates the rates of many specific reactions involved in fuel metabolism. The effects of thyroid hormone on the metabolic fuels are multifaceted; not only can it influence both the synthesis and degradation of carbohydrate, fat, and protein, but small or large amounts of the hormone may induce opposite effects. For example, conversion of glucose to glycogen, the storage form of glucose, is facilitated by small amounts of thyroid hormone, but the reverse—breakdown of glycogen into glucose—occurs with large amounts of the hormone. Similarly, adequate amounts of thyroid hormone are essential for the protein synthesis needed for normal bodily growth, yet protein degradation effects predominate at high doses. In general, at abnormally high plasma levels of thyroid hormone, as in thyroid hypersecretion, the overall effect is to favor consumption rather than storage of fuel, as shown by depleting liver glycogen stores, depleting fat stores, and muscle wasting from protein degradation.

In many birds and mammals thyroid hormone levels vary on daily and/or seasonal bases. For example, in birds, daily changes in circulating levels of thyroid hormone are driven in part by food intake, T₃ increasing during the day associated with a reciprocal decline in T₄. In the American black bear, serum levels of T₃ and T₄ decrease during winter sleep (often loosely called *hibernation*; see p. 751) in association with reduced metabolism. An increase in thyroid hormone is also associated with the molt process in mammals and birds as well as the formation of new feathers and growth of horns or hair. For other seasonal changes, see the box *Molecular Biology and Genomics: Crosstalk between the Pituitary and Hypothalamus*.

Sympathomimetic Effect Any action similar to one produced by the sympathetic nervous system is known as a **sympathomimetic** (“sympathetic-mimicking”) effect. Thyroid hormone increases target cell responsiveness to catecholamines (epinephrine and norepinephrine), the chemical messengers used by the sympathetic nervous system and its hormonal reinforcements from the adrenal medulla. Thyroid hormone presumably accomplishes this permissive action by causing a proliferation of specific catecholamine target-cell receptors (see p. 309). Because of this action, many of the effects observed when thyroid hormone secretion is elevated are similar to those that accompany activation of the sympathetic nervous system (a sympathomimetic effect).

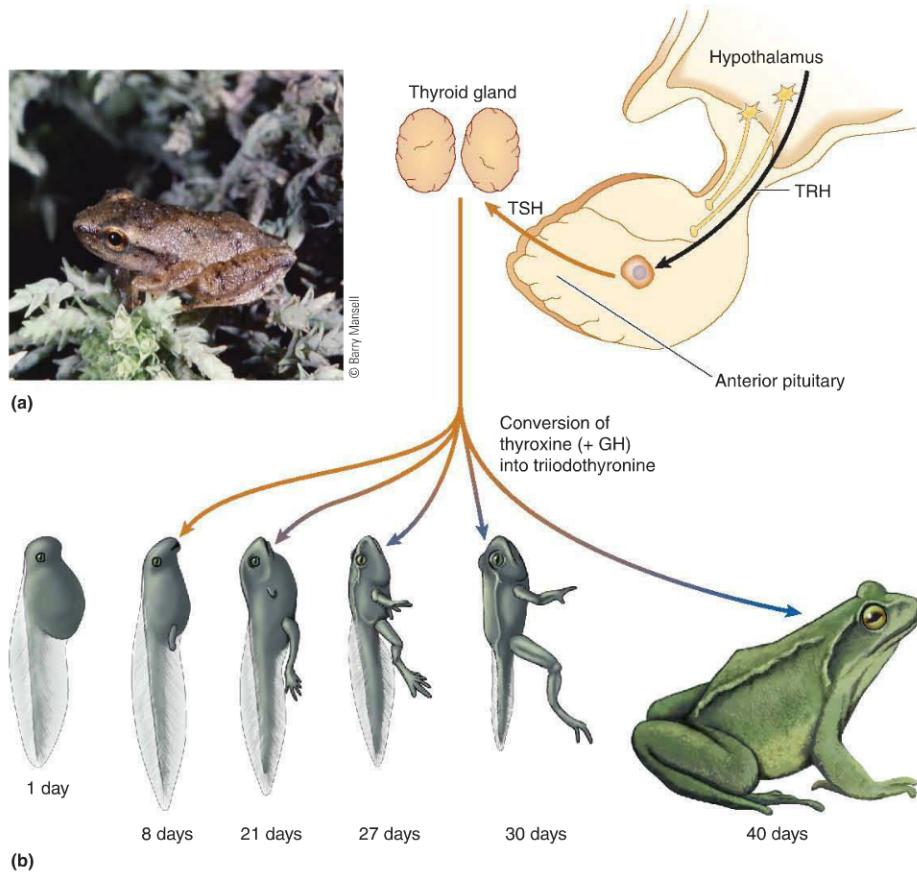


FIGURE 7-18 Thyroid hormones and amphibian metamorphosis. (a) A grass frog. The frog spends the first weeks of its life as an aquatic herbivore—a tadpole—in which the thyroid gland and other organs gradually mature. During this period, its skeletal muscles and other tissues are relatively insensitive to thyroxine, which is being synthesized in the thyroid, although little is released. At about 21 days (b), a spurt in thyroxine secretion begins to trigger major remodeling of the amphibian body. These developmental changes only occur if growth hormone also is present. The entire process may be triggered by changing environmental conditions. As metamorphosis gets under way, shifts in gene expression in cells of various tissues lead to major changes in body structures and physiological functions. Among other alterations, the tail regresses, digested away by newly synthesized lysosomal enzymes, and limbs grow. Lungs develop and gills degenerate, and the digestive tract becomes more suited to processing animal foods such as insects. The kidneys shift from excreting nitrogenous wastes as ammonia—an adaptation typical of aquatic animals—to eliminating urea.

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Effect on the Cardiovascular System Through its effect of increasing the heart's responsiveness to circulating catecholamines, thyroid hormone increases heart rate and force of contraction, thus increasing cardiac output. In addition, in response to the heat load generated by the calorogenic effect of thyroid hormone, peripheral vasodilation occurs to carry the extra heat to the body surface for elimination to the environment.

Effect on Growth and the Nervous System Thyroid hormone is essential for normal growth. Thyroid hormones act *permissively* (indirectly) in concert with other hormones in

stimulating the growth process. Thyroid hormone is required for GH secretion in mammals and also promotes the effects of GH (or IGFs) on the synthesis of new structural proteins and on skeletal growth. Thyroid-deficient animals have stunted growth that is reversible with thyroid replacement therapy. Unlike excess GH, however, excess thyroid hormone does not result in excessive growth.

Thyroid hormone plays a crucial role in normal development of the nervous system, especially the CNS, an effect impeded in animals with thyroid deficiency from birth (or hatch). Thyroid hormone is also essential for normal CNS activity in adult animals. Furthermore, the conduction ve-

locity of peripheral nerves varies directly with the availability of thyroid hormone.

Developmental Effects of Thyroid Hormone Thyroid hormone also controls *metamorphosis* in amphibians (Figure 7-18). **Metamorphosis** is associated with radical developmental changes in body structure that permit transition of an amphibian from an aquatic to a terrestrial habitat. The enzyme *hyaluronidase* is normally induced when tissues mature and thus serves as a signal for differentiation. Concentrations of hyaluronic acid are elevated in proliferating tissue and decline as the cells become increasingly differentiated (specialized). Researchers have recognized that at the time of tadpole differentiation, generation of T_3 increases, paralleled by a decrease in hyaluronic acid. Administering thyroid hormone to a tadpole also accelerates metamorphosis of the juvenile stage into the adult stage. Conversely, if the thyroid gland is prematurely removed from a tadpole, metamorphosis does not occur and the animals eventually develop into giant juveniles.

In at least one species of fish, an increase in thyroid hormone is associated with metamorphosis. In flounder, migration of the eye from one side of the head to the other is triggered by increased thyroid hormone secretion.

Thyroid hormone is regulated by the hypothalamus–pituitary–thyroid axis

Thyroid-stimulating hormone (TSH), the thyroid tropic hormone from the anterior pituitary, is the most important physiological regulator of thyroid hormone secretion (Figure 7-19). TSH stimulates almost every step of thyroid hormone synthesis and release.

In addition to enhancing thyroid hormone secretion, TSH maintains structural integrity of the thyroid gland. In the absence of TSH, the thyroid atrophies (decreases in size) and secretes its hormones at a very low rate. Conversely, it undergoes hypertrophy (increase in the size of each follicular cell) and hyperplasia (increase in number of follicular cells) in response to excess TSH stimulation, which results in thyroid enlargement or goiter.

In mammals, hypothalamic thyrotropin-releasing hormone (TRH), in tropic fashion, “turns on” TSH secretion by the anterior pituitary, whereas thyroid hormone, in negative-feedback fashion, “turns off” TSH secretion by inhibiting the anterior pituitary and hypothalamus. TRH functions via the $IP_3/DAG/Ca^{2+}$ second-messenger pathway. Like other negative-feedback loops, the one between thyroid hormone and TSH tends to maintain a stable thyroid hormone output. However, in some nonmammalian vertebrates CRH has been found to be more important in the regulation of TSH secretion. Various types of stress inhibit TSH and thyroid hormone secretion, presumably through neural influences on the hypothalamus, although the adaptive importance of this inhibition is unclear.

Unlike most other hormonal systems, hormones in the thyroid axis in an adult mammal normally do not undergo sudden, wide swings in secretion. The relatively steady rate of thyroid hormone secretion is in keeping with the sluggish, long-lasting responses that this hormone induces; there would be no adaptive value in suddenly increasing or decreasing plasma thyroid-hormone levels. Seasonal changes in TRH are known to occur in some mammals; however, the

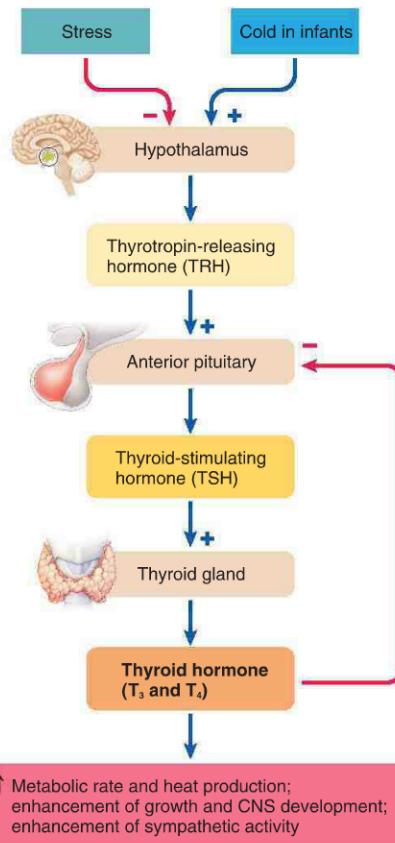


FIGURE 7-19 Regulation of thyroid hormone secretion.

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only known consistent factor that increases TRH secretion in mammals (and, accordingly, TSH and thyroid hormone secretion) is exposure to cold. This mechanism is highly adaptive in newborn mammals. The dramatic increase in heat-producing thyroid hormone secretion is thought to help maintain body temperature in the abrupt drop in surrounding temperature at birth, as the infant passes from the mother's warm body to the cooler environmental air. A similar TSH response to cold exposure does not occur in adult mammals. Some evidence suggests that on a longer-term basis during acclimatization to a cold environment, the concentration of hormones in this axis does increase as a means to increase the BMR and heat production.

Abnormalities of thyroid function include both hypothyroidism and hyperthyroidism

Normal thyroid function is called **euthyroidism**. Abnormalities of thyroid function are among the most common of all endocrine disorders in humans and domestic (and some wild) birds and mammals. Disorders fall into two major categories—**hypothyroidism** and **hyperthyroidism**—reflecting deficient and excess thyroid-hormone secretion, respectively.

A number of specific causes can give rise to each of these conditions. Whatever the cause, the consequences of too little or too much thyroid hormone secretion are largely predictable, given a knowledge of the functions of thyroid hormone.

Hypothyroidism Low thyroid activity, or **hypothyroidism**, can result (1) from primary failure of the thyroid gland itself; (2) secondary to a deficiency of TRH, TSH, or both; or (3) from an inadequate dietary supply of iodine. The symptoms of hypothyroidism largely stem from reduced overall metabolic activity. Among other things, a mammal with hypothyroidism has a reduced basal metabolic rate; displays poor tolerance of cold (lack of the calorogenic effect); has a tendency to gain excessive weight (not burning fuels at a normal rate); is easily fatigued (lower energy production); has a slow, weak pulse (caused by reduced rate and strength of cardiac contraction and lowered cardiac output); and exhibits slow reflexes and slow mentation (because of the effect on the nervous system), characterized by diminished alertness, and poor memory.

In most endotherms, hypothyroidism diminishes quality of fur or feathers. For example, without adequate thyroid hormone concentrations, the seasonal growth in their pelage fails to occur, whereas in birds plumage fails to develop.

Hyperthyroidism As you would expect, the hyperthyroid mammal has an elevated basal metabolic rate. The resulting increase in heat production leads to excessive perspiration or panting and poor tolerance of heat. Despite the increased appetite and food intake in response to the increased metabolic demands, body weight typically falls because the body is burning fuel abnormally fast. Net degradation of endogenous carbohydrate, fat, and protein stores occurs. The loss of skeletal muscle protein results in weakness. Various cardiovascular abnormalities are associated with hyperthyroidism, caused both by the direct effects of thyroid hormone and by its interactions with catecholamines. Heart rate and strength of contraction may rise to dangerous levels. In severe cases, the heart may fail to meet the body's metabolic demands in spite of increased cardiac output. Nervous system involvement is manifested by excessive mental alertness to the point where the animal is irritable, tense, and anxious.

Three general methods of treatment are available for suppressing excess thyroid-hormone secretion: surgical removal of a portion of the oversecreting thyroid gland; administration of radioactive iodine, which, after being concentrated in the thyroid gland by the iodine pump, selectively destroys thyroid glandular tissue; and antithyroid drugs that specifically interfere with thyroid hormone synthesis and generation of T_3 .

check your understanding 7.5

How is the concentration of T_3 regulated in the circulation?

What is the role of thyroid hormone in endotherms and ectotherms?

What is the role of thyroglobulin in the synthesis of active thyroid hormone?

7.6 Adrenal Glands

The **adrenal gland** (*adrenal*, “next to the kidney”) (Figure 7-20a) of higher vertebrates consists of two distinct cell types: **chromaffin** (*chroma*, “color”; *affinis*, “affinity”) cells, which are derived from the neural crest, and **steroidogenic** cells, which are of mesodermal origin.

In most vertebrates, the adrenal gland consists of a steroid-secreting cortex intermingled with chromaffin tissue

The term *chromaffin* arises from the observation that the tissue stains the color brown when reacted with oxidizing agents such as chromate. In mammals there are two adrenal glands, one embedded above each kidney in a capsule of fat. The shape of the adrenal varies considerably and in some species actually fuses with the kidney. In most mammals the adrenal gland consists of an outer, steroid-secreting **adrenal cortex** and an inner, catecholamine-secreting **adrenal medulla**. For this reason the chromaffin tissue is referred to as the adrenal medulla. However, in most nonmammalian species the chromaffin tissue is not associated with any surrounding cortex and in many instances, rather than forming distinct zones, the two tissue types are intermingled in the adrenal gland. In elasmobranchs, **interrenal tissue**, which is homologous with the adrenal cortex of higher vertebrates, is organized into glands situated between the posterior regions of the kidneys.

The steroid-secreting adrenal cortex and catecholamine-secreting medulla produce hormones belonging to different chemical categories, whose functions, mechanisms of action, and regulation are entirely different.

The adrenal cortex secretes mineralocorticoids, glucocorticoids, and sex hormones

About 80% of the adrenal gland of most mammals is composed of the cortex, which consists of three different layers or zones: the **zona glomerulosa**, the outermost layer; the **zona fasciculata**, the middle and largest portion; and the **zona reticularis**, the innermost zone (Figure 7-20b). The adrenal cortex produces a number of different adrenocortical hormones, all of which are steroids derived from the common precursor molecule, cholesterol. All steroidogenic (“steroid-producing”) cells are filled with lipid droplets (**liposomes**) containing cholesterol. Cholesterol is first converted to *pregnenolone*, then modified by stepwise enzymatic reactions to produce active steroid hormones (Figure 7-3). Each steroidogenic tissue has a complement of enzymes to produce one or several but not all steroid hormones. Slight variations in structure confer different functional capabilities on the various adrenocortical hormones. On the basis of their primary actions, the adrenal steroids can be divided into three categories:

1. **Mineralocorticoids**, mainly *aldosterone*, which influence mineral (electrolyte) balance, specifically Na^+ and K^+ balance (produced exclusively in the zona glomerulosa). The actions and regulation of the primary adrenocortical mineralocorticoid, *aldosterone*, are described thoroughly elsewhere (Chapter 12).
2. **Glucocorticoids**, primarily *cortisol* and *corticosterone*, which play a major role in glucose metabolism as well

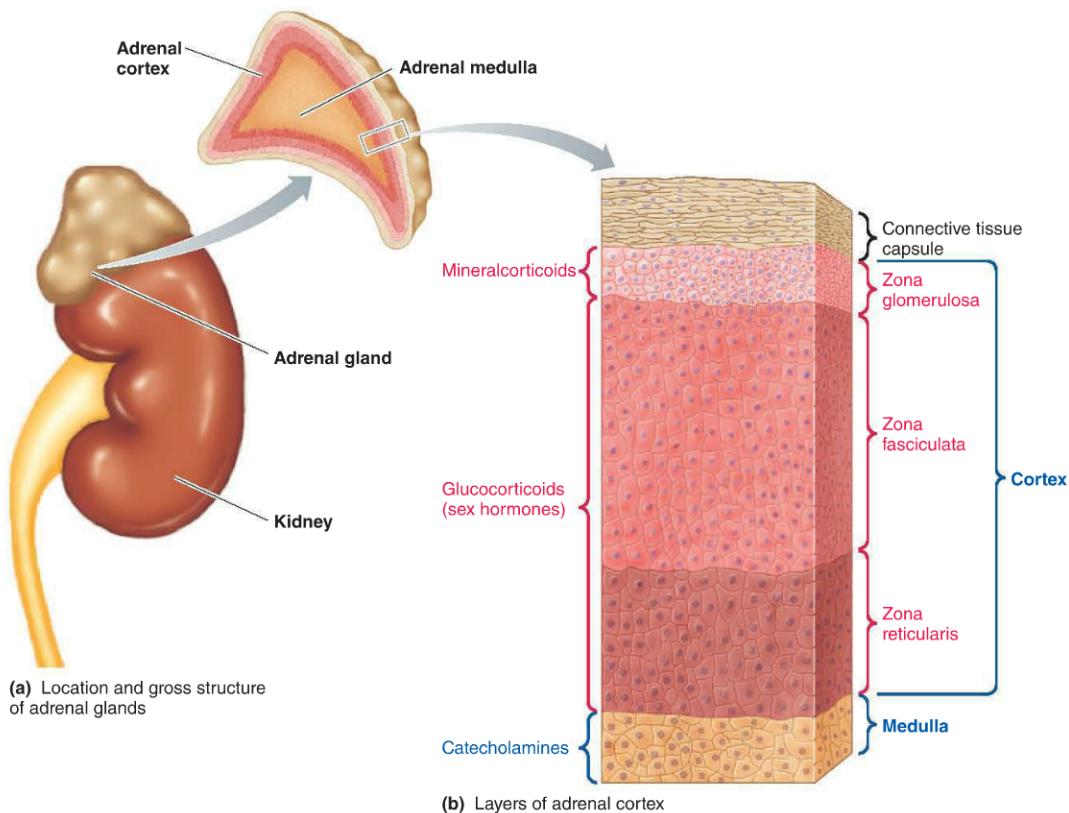


FIGURE 7-20 Anatomy of the adrenal glands.

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as in protein and lipid metabolism (synthesized in the two inner layers, with the zona fasciculata being the major source of this glucocorticoid).

3. **Sex steroids** identical or similar to those produced by the gonads (testes in males, ovaries in females). The most abundant and physiologically important of the adrenocortical sex hormones is *dehydroepiandrosterone* (*DHEA*), a “male” sex hormone (produced by the two inner zones).

The production of adrenocortical and other steroid hormones requires a series of steps in which the cholesterol molecule undergoes various enzymatic modifications (see p. 272). The enzymes that carry out the synthesis of the major steroids are highly conserved among vertebrates and homologous to those characterized in mammals. The different functional types of adrenal steroids are produced in anatomically distinct portions of the adrenal cortex, as noted in the preceding list.

Being lipophilic, the adrenocortical hormones are all carried in the blood extensively bound to plasma proteins. About 60% of circulating aldosterone is protein bound, primarily to nonspecific albumin, whereas approximately 90% of the glucocorticoids are bound, mostly to a plasma protein specific for it called **corticosteroid-binding globulin**

(*transcortin*). Likewise, 98% of dehydroepiandrosterone is bound, in this case, exclusively to albumin.

Each of the adrenocortical steroid hormones binds with a receptor specific for it within the cytoplasm of the hormone's target cells: Mineralocorticoids bind to the **mineralocorticoid receptor (MR)**, glucocorticoids to the **glucocorticoid receptor (GR)**, and dehydroepiandrosterone to the **androgen receptor (AR)**. As is true of all steroid hormones, each hormone-receptor complex moves to the nucleus and binds with a complementary hormone-response element in DNA, namely the *mineralocorticoid response element*, *glucocorticoid response element*, and *androgen response element*. This binding initiates specific gene transcription leading to synthesis of new proteins that carry out the effects of the hormone.

Glucocorticoids exert metabolic effects and have an important role in adaptation to stress

Cortisol and corticosterone play an important role in carbohydrate, protein, and fat metabolism; execute significant permissive actions for other hormonal activities; and help animals cope with stress.

Metabolic Effects The overall effect of glucocorticoids' metabolic actions is to *increase the concentration of blood glucose* at the expense of protein and fat stores. Specifically, cortisol performs the following functions:

- It stimulates hepatic **gluconeogenesis**, the conversion of noncarbohydrate sources (namely, amino acids) into carbohydrate within the liver (*gluco* means “glucose”; *neo* means “new”; *genesis* means “production”). Between meals or during periods of fasting, when no new nutrients are being absorbed into the blood for use and storage, the glycogen (stored glucose) in the liver tends to become depleted as it is broken down to release glucose into the blood. Gluconeogenesis is an important factor in replenishing hepatic glycogen stores and thus in maintaining normal blood-glucose levels between meals. This is essential because the vertebrate brain can use only glucose as its metabolic fuel, yet nervous tissue cannot store glycogen to any extent. The concentration of glucose in the blood must therefore be maintained at an appropriate level to adequately supply the glucose-dependent brain with nutrients.
- It *inhibits glucose uptake* and use by many tissues, but not the brain, thus sparing glucose for use by the brain, which absolutely requires it as a metabolic fuel. This action contributes to the increase in blood glucose concentration brought about by gluconeogenesis.
- It *stimulates protein degradation* in many tissues, especially muscle. By breaking down a portion of muscle proteins into their constituent amino acids, cortisol increases the blood amino acid concentration. These mobilized amino acids are available for use in gluconeogenesis or wherever else they are needed, such as for repair of damaged tissue or synthesis of new cellular structures. For example, an anuran amphibian's cortisol is markedly elevated during metamorphosis of tadpole into frog (metamorphic climax). This is associated with increased mRNA levels of POMC (see p. 271) during this developmental stage.
- It *facilitates lipolysis* (*lysis*, “breakdown”), the breakdown of lipid (fat) stores in adipose tissue, releasing free fatty acids into the blood. The mobilized fatty acids are available as an alternative metabolic fuel for tissues that can use this energy source in lieu of glucose, conserving glucose for the brain.
- It stimulates *acclimatization to seawater* in euryhaline fishes (see pp. 626–627).

Permissive Actions Glucocorticoids are extremely important for their permissiveness (see p. 278). For example, in mammals glucocorticoids must be present in adequate amounts to permit the catecholamines to induce vasoconstriction. An animal lacking cortisol, if untreated, may go into circulatory shock in a stressful situation that demands immediate widespread vasoconstriction.

Effects on the Brain Glucocorticoids also affect neural functions such as memory. For example, elevated concentrations of plasma cortisol in Pacific salmon during home-stream migration aids in recalling the imprinted memory of the home-stream chemical aroma. Mammalian memory centers (such as the hippocampus) have cortisol receptors of uncertain function. In contrast to salmon, prolonged elevation in

cortisol from stress is associated with memory loss in humans and laboratory mammals, but this is considered an abnormal situation.

Role in Adaptation to Long-Term Stress Glucocorticoids play a key role in adaptation to stress, particularly *long-term* stress (you will learn in the section on adrenal medulla hormones about *short-term* stress responses). Stress is the generalized, nonspecific response to any factor that overwhelms, or threatens to overwhelm, the body's compensatory abilities to maintain homeostasis. Contrary to popular usage, the agent inducing the response is correctly called a *stressor*, whereas *stress* refers to the state induced by the stressor. Stressors include those that are *physical* (trauma, intense heat or cold); *chemical* (reduced O₂ supply, acid–base imbalance, nutritional deficit); *physiological* (hemorrhagic shock, pain); *psychological* or *emotional* (anxiety, fear such as that generated from an approaching thunderstorm); and *social* (conflict, isolation from a group). The following types of noxious stimuli illustrate the range of factors that can induce a stress response in fish: poor water quality, handling, and confinement.

Dramatic increases in glucocorticoid secretion, mediated by the central nervous system, occur in response to all kinds of stressful situations. For this reason, measurement of cortisol/corticosterone in an animal's blood is one of the best indicators of stress. For example, cortisol levels skyrocket in infant chimps separated from their mothers, and conversely, cortisol levels decline below average when their mothers are grooming these chimps. Similarly, a horse that is separated from its herd exhibits increased cortisol and other stress symptoms, showing the importance of social contact in this herd animal. The magnitude of the increase in plasma glucocorticoid concentration is generally proportional to the intensity of the stressful stimulation; a greater increase in glucocorticoid concentrations is evoked in response to severe stress than to mild stress.

Although the precise role of glucocorticoids in adapting to stress is not known, a speculative but plausible explanation might be as follows. An animal wounded or faced with a life-threatening situation must forgo eating. A glucocorticoid-induced enhancement of breakdown of carbohydrate stores (which increases the availability of blood glucose) would help protect the brain from malnutrition during the imposed fasting period. Also, the amino acids liberated by protein degradation would provide a readily available supply of building blocks for tissue repair should physical injury occur. Thus, an increased pool of glucose, amino acids, and fatty acids is available for use as needed.

Anti-Inflammatory and Immunosuppressive Effects When stress is accompanied by tissue injury, inflammatory and immune responses accompany the stress response. Cortisol exerts *anti-inflammatory* and *immunosuppressive* effects to help hold these immune system responses in check and balance. An exaggerated inflammatory response has the potential of causing harm. Cortisol interferes with almost every step of inflammation. For example, among other anti-inflammatory actions, cortisol partially blocks production of inflammatory chemical mediators, such as prostaglandins and leukotrienes (see p. 470); it suppresses migration of neutrophils to the injured site and interferes with their phagocytic activity (see Figure 10-7, p. 468); and it inhibits proliferation of fibroblasts in wound repair (see p. 469). Cortisol also inhibits immune

responses by interfering with antibody production by lymphocytes. Blurring the line between endocrine and immune control, lymphocytes have been shown to secrete ACTH, and some of the cytokines (such as IL-1, IL-2, and IL-6; see p. 460) released from immune cells can stimulate the hypothalamus–pituitary–adrenal axis. In feedback fashion, cortisol in turn has a profound dampening (turning-down) impact on the immune system. These interactions between the immune system and cortisol secretion help maintain immune homeostasis, an area only beginning to be explored.

Administering large amounts of glucocorticoid inhibits almost every step of the inflammatory response, making these steroids effective drugs in treating conditions in which the inflammatory response itself has become destructive. Glucocorticoids used in this manner do not affect the underlying disease process; they merely suppress the body's response to the disease. Because glucocorticoids also exert multiple inhibitory effects on the overall immune process, such as "knocking out of commission" the white blood cells responsible for antibody production as well as those that directly destroy foreign cells, these agents have also proved useful in managing various allergic disorders and in preventing organ transplant rejections.

When glucocorticoids are administered at pharmacological levels (that is, at higher-than-physiologic concentrations), not only are their anti-inflammatory and immunosuppressive effects increased but their metabolic effects are also magnified. Therefore, synthetic glucocorticoids have been developed that maximize the anti-inflammatory and immunosuppressive effects of these steroids while minimizing the metabolic effects.

Glucocorticoid secretion is directly regulated by the hypothalamic–pituitary–adrenal axis

Glucocorticoid secretion by the adrenal cortex is regulated by a negative-feedback system involving the hypothalamus and anterior pituitary (Figure 7-21). ACTH from the anterior pituitary corticotropes, acting through the cAMP pathway, stimulates the adrenal cortex to secrete cortisol. Hormonal steroid output by the adrenal cortex is seen within two minutes of exposure to ACTH, with the rate-limiting step in the biosynthesis of glucocorticoid being the conversion of cholesterol into pregnenolone (see Figure 7-3). Being tropic to the zona fasciculata and zona reticularis, ACTH stimulates both the growth and the secretory output of these two inner layers of the cortex, which shrink considerably in the absence of adequate amounts of ACTH.

The ACTH-producing cells in turn secrete only at the command of CRH from the hypothalamus. CRH stimulates the corticotropes via the cAMP pathway. The feedback control loop is completed by glucocorticoid's inhibitory actions on CRH and ACTH secretion by the hypothalamus and anterior pituitary, respectively. Superimposed on the basic negative-feedback control system are two additional factors that influence plasma glucocorticoid concentrations by changing the set points: These are *stress* and *circadian rhythms*, both of which act on the hypothalamus to vary the secretion rate of CRH.

Influence of Circadian Rhythm on Cortisol Secretion Recall that there is a characteristic circadian rhythm in plasma cortisol concentration, with the highest level occurring in

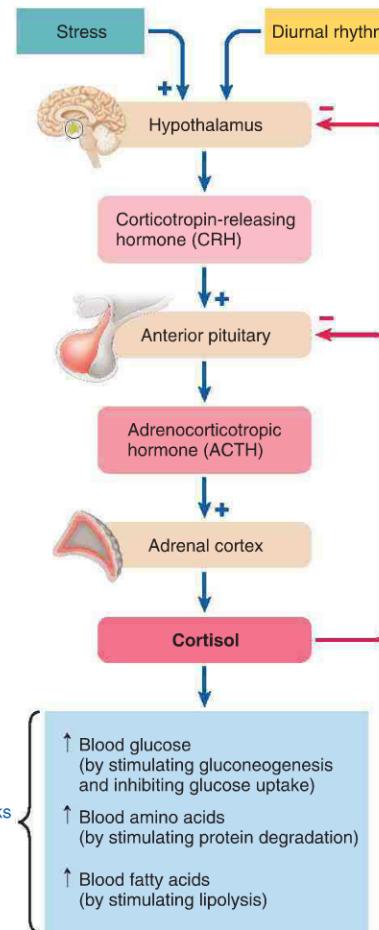


FIGURE 7-21 Control of cortisol secretion.

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diurnal animals in the morning and the lowest level at night (see Figure 7-6). This rhythm, which is governed by the SCN (the master biological clock we described earlier), is related primarily to the sleep–wake cycle. The peak and low levels are thus reversed in animals that are nocturnal.

The adrenal cortex secretes both male and female sex hormones in both sexes

In both sexes, the adrenal cortex produces both *androgens*, or "male" sex hormones, and *estrogens*, or "female" sex hormones. Under normal circumstances in mammals, the adrenal androgens and estrogens are not sufficiently abundant or powerful to induce masculinizing or feminizing effects, respectively. The only adrenal sex hormone that has any biological importance is the androgen **dehydroepiandrosterone (DHEA)**. Adrenal DHEA is overpowered by testicular testosterone in males but is of physiological significance in female humans, who otherwise lack androgens. This adrenal androgen is responsible for androgen-dependent processes in the female such as growth of pubic and axillary (armpit) hair,

enhancement of the pubertal growth spurt, and development and maintenance of the female sex drive. Because the enzymes required for producing estrogens are found in very low concentrations in the adrenocortical cells, estrogens are normally produced in very small quantities from this source.

The adrenal cortex may secrete too much or too little of any of its hormones

There are a number of different disorders of adrenocortical function. Excessive cortisol secretion (*Cushing's syndrome*), which occurs in many older dogs, is most commonly caused by overstimulation of the adrenal cortex by excessive amounts of CRH and/or ACTH. A rarer cause is an adrenal tumor that uncontrollably secretes cortisol independent of ACTH. Regardless of the cause, the prominent characteristics of this syndrome are related to the exaggerated effects of glucocorticoid, with the main symptoms being reflections of excessive gluconeogenesis. When too many amino acids are converted into glucose, the body suffers from combined glucose excess (high blood glucose) and protein shortage. Because the resultant hyperglycemia, glucosuria (glucose in the urine), and thirst mimic diabetes mellitus, the condition is sometimes referred to as *adrenal diabetes*. For reasons that are unclear, some of the extra glucose is deposited as body fat in locations characteristic for this disease, typically in the abdomen in dogs.

In primary adrenocortical insufficiency, also known as *Addison's disease*, all layers of the adrenal cortex are undersecreting. Certain dog breeds are prone to this condition, which is most commonly caused by autoimmune destruction of the cortex by erroneous production of adrenal cortex-attacking antibodies, in which case both aldosterone and cortisol are deficient. The symptoms associated with aldosterone deficiency in Addison's disease are the most threatening. If severe enough, the condition is fatal because aldosterone is essential for life. Symptoms of cortisol deficiency are as would be expected: poor response to stress, hypoglycemia caused by reduced gluconeogenic activity, and lack of permissive action for many metabolic activities.

Having completed discussion of the adrenal cortex, we now shift attention to the adrenal medulla.

The catecholamine-secreting adrenal medulla is a modified sympathetic ganglion

The adrenal medulla is actually a modified part of the sympathetic nervous system. A sympathetic pathway consists of two neurons in sequence—a *preganglionic neuron* originating in the CNS, whose axonal fiber terminates on a second peripherally located *postganglionic neuron*, which in turn terminates on the effector organ (see Figure 5-8, p. 162). The neurotransmitter released by sympathetic postganglionic fibers is norepinephrine (NE), which interacts locally with the innervated organ by binding with specific target receptors known as *adrenergic receptors*.

The adrenal medulla consists of modified postganglionic sympathetic neurons called *chromaffin cells*. Unlike ordinary postganglionic sympathetic neurons, chromaffin cells do not have axonal fibers that terminate on effector organs. Instead, on stimulation by the preganglionic fiber the chromaffin cells release their chemical transmitter di-

rectly into the circulation (see Figure 5-9, p. 163) as a neuromodulator. Like sympathetic fibers, the adrenal medulla does release NE, but in mammals its most abundant secretory output is the similar chemical messenger *epinephrine*. Both epinephrine and NE belong to the chemical class of *catecholamines*, which are derived from the amino acid tyrosine (see Table 7-1). Epinephrine is similar in structure to NE except that it has a methyl group added to it. In species where the chromaffin tissue is separated from the steroidogenic tissue, such as the dogfish shark, NE is the only catecholamine produced. However, in frogs, where chromaffin tissue is loosely intermingled with steroidogenic tissue, NE is reduced to about 55 to 70% of the total catecholamine content.

Storage of Catecholamines in Chromaffin Granules Catecholamine synthesis in vertebrates is accomplished almost entirely within the cytosol of the adrenomedullary secretory cells, with only one step taking place within the hormonal storage granules. Whereas epinephrine is produced exclusively by the adrenal medulla, the bulk of NE is produced by sympathetic postganglionic fibers. Once produced, epinephrine and NE are stored in *chromaffin granules*, which are similar to the transmitter storage vesicles in sympathetic nerve endings. Catecholamines are ultimately secreted into the circulation by exocytosis of chromaffin granules; their release is analogous to the release mechanism for secretory vesicles that contain stored peptide hormones or the release of NE at sympathetic postganglionic terminals. Once in the circulation catecholamines are rapidly degraded resulting in a fast turnover: they are specialized for short-term actions associated with the stress response.

Sympathetic stimulation of the adrenal medulla is solely responsible for epinephrine release

Catecholamine secretion by the adrenal medulla is controlled entirely by sympathetic input to the gland. When the sympathetic system is activated under conditions of fear or stress, it simultaneously triggers a surge of adrenomedullary catecholamine release, flooding the circulation with up to 300 times the normal concentration of epinephrine. Although a number of different factors influence adrenal catecholamine secretion, they all act by increasing preganglionic sympathetic impulses to the adrenal medulla. Among the major factors that stimulate increased adrenomedullary output are a variety of stressful conditions such as physical or environmental disturbances, hemorrhage, illness, exercise, hypoxia (low arterial O₂), cold exposure, and hypoglycemia.

Epinephrine reinforces the sympathetic nervous system in “fight-or-flight” short-term stress, and exerts additional metabolic effects

Catecholamine hormones are not essential for life, but virtually all organs in the body are affected by them. They play important roles in stress responses, regulation of arterial blood pressure, and control of fuel metabolism. Together, the sympathetic nervous system and adrenomedullary epinephrine mobilize the body's resources to support peak physical exertion in the face of impending danger (“short-

term" stress). The sympathetic and epinephrine actions constitute a "fight-or-flight" response that prepares the animal to deal with a range of physical and environmental disturbances. An arthropod and molluscan equivalent of NE is octopamine (first discovered in octopus), a biogenic amine derived from the amino acid tyrosine. In many of these animals, octopamine is a neurotransmitter, neuromodulator, and neurohormone. In response to stressful situations in insects, such as handling or during the early stage of flight, octopamine mobilizes stores from the fat body for release into the hemolymph.

The following sections discuss epinephrine's major effects, which it accomplishes in collaboration with NE or performs alone to complement direct sympathetic response.

Effects on Organ Systems Together, the sympathetic nervous system and adrenomedullary epinephrine mobilize the body's resources that are ideally suited for fight-or-flight responses (see p. 159). Specifically, the sympathetic system and epinephrine increase the rate and strength of cardiac contraction, increasing cardiac output, and their generalized vasoconstrictor effects increase total peripheral resistance. These effects cause an increase in arterial blood pressure, thus ensuring an appropriate driving pressure to force blood to the organs that are most vital for meeting the emergency. Meanwhile, vasodilation of coronary and skeletal-muscle blood vessels induced by epinephrine and local metabolic factors shifts blood to the heart and skeletal muscles from other vasoconstricted regions of the body. In fishes, the physiological effects of catecholamines are also used to maintain levels of energy and oxygen supply under conditions such as hypoxia. However, in teleosts, adrenergic control of the heart is mainly neuronal, and it is only under severe stress that circulating levels of epinephrine increase sufficiently to affect cardiac function. Catecholamines also increase oxygen delivery to the tissues, change gill diffusion capacity, increase erythrocyte release from the spleen, increase the blood oxygen capacity by elevating intracellular pH, and increase blood flow and ventilation rate.

Epinephrine (but not NE) dilates the respiratory airways to reduce the resistance encountered in moving air in and out of the lungs. Epinephrine also reduces digestive activity and inhibits bladder emptying, both activities that can be "put on hold" during a fight-or-flight situation.

Metabolic Effects Epinephrine exerts some important metabolic effects, even at blood hormone concentrations lower than required for eliciting the cardiovascular responses. In general, epinephrine prompts mobilization of stored carbohydrate and fat to provide immediately available energy to fuel muscular work. Specifically, epinephrine increases the blood glucose level by several different mechanisms. First, it stimulates both hepatic (liver) gluconeogenesis and glycogenolysis, the latter being the breakdown of stored glycogen into glucose, which is released into the blood. Epinephrine also stimulates glycogenolysis in skeletal muscles. Because of the difference in enzyme content between liver and muscle, however, muscle glycogen is not converted to glucose for the blood. Instead, muscle glycogen is broken down via glycolysis into lactate, providing a burst of ATP for muscles in the emergency situation. In addition to raising blood glucose levels, epinephrine also raises the blood fatty-acids level by promoting lipolysis.

Epinephrine's metabolic effects are appropriate for transient fight-or-flight situations. The elevated levels of glucose and fatty acids provide additional fuel to power the muscular movement required by the situation and also ensure adequate nourishment for the brain during the crisis when no new nutrients are being consumed. Muscles can use fatty acids for energy production, but the brain cannot.

Because of its other widespread actions, epinephrine also increases overall metabolic rate. Under the influence of epinephrine, many tissues metabolize faster. For example, the work of the heart and respiratory muscles is increased, and the pace of liver metabolism is stepped up. Thus, epinephrine as well as thyroid hormone can increase metabolic rate.

Other Effects Epinephrine affects the central nervous system to promote a state of arousal and increased CNS alertness, also useful to fight-or-flight situations.

Both epinephrine and NE cause sweating in mammals that have sweat glands, which helps the body rid itself of extra heat generated by increased muscular activity. Also, epinephrine acts on smooth muscles within the eyes to dilate the pupil and flatten the lens. These actions adjust the eyes for more encompassing vision so that the whole threatening scene can be quickly viewed.

Epinephrine and norepinephrine vary in their affinities for the different adrenergic receptor types

Epinephrine and NE have differing affinities for four distinctive receptor types: α_1 , α_2 , β_1 , and β_2 adrenergic receptors (see p. 165). NE binds predominantly with α and β_1 receptors located near postganglionic sympathetic-fiber terminals. Hormonal epinephrine, which can reach all α and β_1 receptors via its circulatory distribution, interacts with these same receptors. NE has a slightly greater affinity than epinephrine for the α receptors, and the two hormones have approximately the same potency at the β_1 receptors. Thus, epinephrine and NE exert similar effects in many tissues, with epinephrine generally reinforcing sympathetic nervous activity. In addition, epinephrine activates β_2 receptors, over which the sympathetic nervous system exerts little influence. Many of the essentially epinephrine-exclusive β_2 receptors are located at tissues not even supplied by the sympathetic nervous system but reached by epinephrine through the blood. Examples include skeletal muscle and its blood vessels and bronchiolar smooth muscle, with the effects we just discussed.

Sometimes epinephrine, through its exclusive β_2 -receptor activation, brings about a different action from that elicited by NE and epinephrine action through their mutual activation of other adrenergic receptors. For example, NE and epinephrine bring about a generalized vasoconstrictor effect mediated by α_1 -receptor stimulation. By contrast, epinephrine promotes vasodilation of the blood vessels that supply skeletal muscles and the heart through β_2 -receptor activation.

Realize, however, that epinephrine functions only at the bidding of the sympathetic nervous system, which is solely responsible for stimulating its secretion from the adrenal medulla. Epinephrine secretion always accompanies a generalized sympathetic nervous system discharge, so sympathetic

activity indirectly controls actions of epinephrine. By having the more versatile circulating epinephrine at its call, the sympathetic nervous system has a means of reinforcing its own neurotransmitter effects plus a way of executing additional actions on tissues that it does not directly innervate.

The stress response is a generalized, nonspecific pattern of neural and hormonal reactions to any situation that threatens homeostasis

Because both components of the adrenal gland play an extensive role in responding to stress, this is an appropriate place to pull together the various major factors involved in the stress response. Recall that a variety of noxious physical, chemical, physiological, and psychosocial stimuli that threaten to overwhelm the body's compensatory ability to maintain homeostasis all can elicit a stress response. Different stressors may produce some specific responses characteristic of that stressor; for example, in some mammals the specific response to cold exposure is shivering and skin vasoconstriction, whereas the specific response to bacterial invasion includes increased phagocytic activity and antibody production. In addition to their specific response, however, all stressors also produce a similar nonspecific, generalized response regardless of the type of stressor.

In the 1930s, Hans Selye was the first to recognize this commonality of responses to noxious stimuli in what he called the **general adaptation syndrome**. When a stressor is recognized, both nervous and hormonal responses are called into play to bring about defensive measures to cope with the emergency. Across the entire vertebrate lineage, the result is a state of intense readiness and mobilization of biochemical resources.

To appreciate the value of the multifaceted stress response, imagine a gazelle that has just seen a lion lurking in the grass. The major neural response to such a stressful stimulus is generalized activation of the sympathetic nervous system. The resultant increase in cardiac output and ventilation as well as diversion of blood from vasoconstricted regions of suppressed activity, such as the digestive tract and kidneys, to the more active vasodilated skeletal muscles and heart prepare the body for a fight-or-flight response. Simultaneously, the sympathetic system calls forth hormonal reinforcements in the form of a massive outpouring of epinephrine from the adrenal medulla. Epinephrine strengthens sympathetic responses and reaches places not innervated by the sympathetic system to perform additional functions, such as mobilizing carbohydrate and fat stores.

Besides epinephrine, a number of other hormones are involved in the overall stress response (Table 7-3). As you have seen, the other predominant hormonal response is activation of the CRH–ACTH–glucocorticoid system, usually for longer-term stress. In our gazelle, this system would dominate if it escapes the lion but receives a serious wound (such as a bite in its leg). Note that a major difference between epinephrine and cortisol is that the former does not promote muscle protein breakdown, whereas the latter does. It would be maladaptive to cannibalize muscles during short-term fight-or-flight, but during long-term trauma it is useful to mobilize amino acids for tissue repair in the event of an injury.

In addition to the effects of cortisol in the hypothalamus–pituitary–adrenal cortex axis, there is much evidence that

TABLE 7-3 Major Hormonal Changes during the Stress Response

| Hormone | Change | Purpose Served |
|--|--------|--|
| Epinephrine | ↑ | Reinforces the sympathetic nervous system to prepare the body for "fight-or-flight" |
| | ↑ | Mobilizes carbohydrate and fat energy stores; increases blood glucose and blood fatty acids |
| CRH–ACTH–Cortisol | ↑ | Mobilizes energy stores and metabolic building blocks for use as needed; increases blood glucose, blood amino acids, and blood fatty acids |
| | ↑ | ACTH facilitates learning and behavior |
| Glucagon | ↑ | Act in concert to increase blood glucose and blood fatty acids |
| Insulin | ↓ | |
| Renin–Angiotensin–Aldosterone; Vasopressin | ↑ | Conserve salt and H ₂ O to expand the plasma volume; help sustain blood pressure when acute loss of plasma volume occurs |
| | | Angiotensin II and vasopressin cause arteriolar vasoconstriction to increase blood pressure |
| | | Vasopressin facilitates learning |

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ACTH may play a role in resisting stress. ACTH suppresses release of GH, TSH, and gonadotropins, suppressing growth, metabolism, and reproduction, respectively. This helps divert energy toward stress needs. ACTH is one of several peptides that facilitate learning and behavior. Thus, it is possible that an increase in ACTH during psychosocial stress might help the body cope more readily with similar stressors in the future by facilitating the learning of appropriate behavioral responses. Furthermore, ACTH is not released alone from its anterior pituitary storage vesicles. Pruning of the large POMC precursor molecule yields not only ACTH but also morphine-like **β-endorphin** and similar compounds. These compounds are cosecreted with ACTH on stimulation by CRH during stress. As a potent endogenous opiate, β-endorphin may exert a role in mediating **analgesia** (reduced pain perception) should physical injury be inflicted during stress (see p. 261), allowing an animal to ignore pain.

The multifaceted stress response is coordinated by the hypothalamus

All the individual responses to stress just described are either directly or indirectly influenced by the hypothalamus (Figure 7-22). The hypothalamus receives input concerning physical and emotional stressors from many areas of the brain and from many receptors throughout the body. In response, the

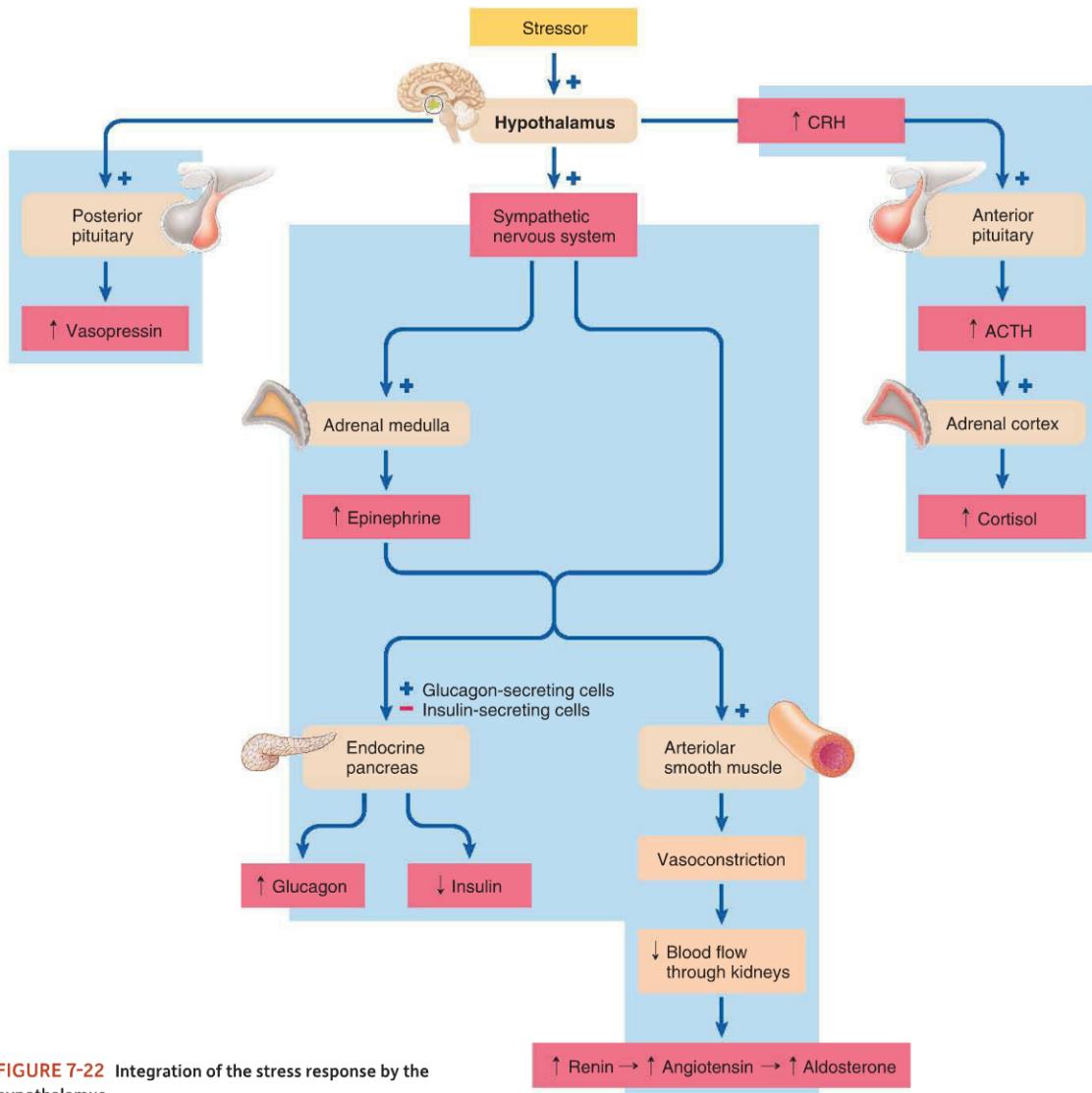


FIGURE 7-22 Integration of the stress response by the hypothalamus.

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hypothalamus directly activates the sympathetic nervous system, secretes CRH to stimulate ACTH and cortisol release, and triggers the release of vasopressin. Sympathetic stimulation in turn brings about the secretion of epinephrine, with which it has a conjoined effect on the pancreatic secretion of insulin and glucagon. Furthermore, vasoconstriction of the renal afferent arterioles by the catecholamines indirectly triggers the secretion of renin by reducing the flow of oxygenated blood through the kidneys. Renin in turn sets in motion the renin-angiotensin-aldosterone mechanism. In this way, the hypothalamus integrates the responses of both the sympathetic nervous system and the endocrine system during stress.

Activation of the stress response by chronic psychosocial stressors may be harmful

Acceleration of cardiovascular and respiratory activity, retention of salt and H_2O , and mobilization of metabolic fuels and building blocks can be of benefit in response to a physical stressor. Many stressors in an animal's life are psychosocial in nature, yet they induce these same magnified responses. Although the mobilization of body resources is appropriate in the face of real or threatened physical injury, it is often inappropriate in response to nonphysical stress. If no extra energy is demanded, no tissue damaged, and no blood lost, body stores are being broken down and fluid retained needlessly.

Other responses can also be harmful. In the acute phase of the stress response, useful behaviors necessary for dealing with an imminent threat (avoidance, escape) emerge, while feeding and reproductive behaviors are temporarily suspended. Such suspension is useful in the short term, but can be harmful in extreme stress. In every animal in which it has been investigated, severe psychological or physical stress reduces appetite and food intake often to dangerous levels. Chronic stress, such as social subordination, may completely shut down reproductive behavior in many vertebrates, where diminished sex-hormone concentrations correlate with elevated levels of POMC, ACTH, and corticosterone. Perhaps most importantly, prolonged glucocorticoid elevation also suppresses the immune system (p. 470).

Overall, chronic stress responses are often to the detriment of the stressed animal, which will have a much greater susceptibility to diseases. You may be aware that overly stressed humans are more prone to diseases; so are zoo animals in poorly designed enclosures, as are social animals in the wild in certain situations. For example, a male baboon entering a troop for the first time must become highly aggressive to be accepted in the social hierarchy. During prolonged aggressive states, cortisol levels rise in this baboon, but his actions also elevate cortisol levels in the rest of the troop. As a result, the number of white blood cells in all the males declines.

The suppression of immunity in these social stresses suggests that this phenomenon is not an adaptation but is rather an inappropriate activation of a system that evolved for more ancient, nonsocial stresses. Considerable work remains to be done to evaluate the contributions that stressors make toward disease in these situations.

Epigenetics Inadequate nutrition and other stresses affecting a pregnant mammal have long been recognized to harm the development of the offspring. More recently it has been recognized that chronic stress during pregnancy can also affect gene expression in the offspring for a number of subsequent generations. This is a type of **epigenetics**—heritable changes in genes that are not due to changes in the underlying DNA code itself. The most common way this occurs is by *methylation* of cytosine (C base of DNA). Methylation occurs in many genes during an organism's life as a regulatory mechanism, but the added methyl groups were long thought to be stripped off in developing gametes so that "original" genes are passed on to the next generation. However, we now know that some gamete genes can be methylated in different ways according to parental sex and environmental effects, a process called **genetic imprinting**. Such methylation patterns may be passed on to more than one generation. In terms of stress, several studies appear to show such effects. For example, studies in the 1980s on birth and death records of humans in an isolated Swedish town show that a severe famine may genetically affect the longevity of grandchildren. More recently, Isabelle Mansuy and colleagues reported that male mice stressed by lack of maternal care not only developed anxiety behaviors but also passed this behavior on to their offspring, which were not stressed.

check your understanding 7.6

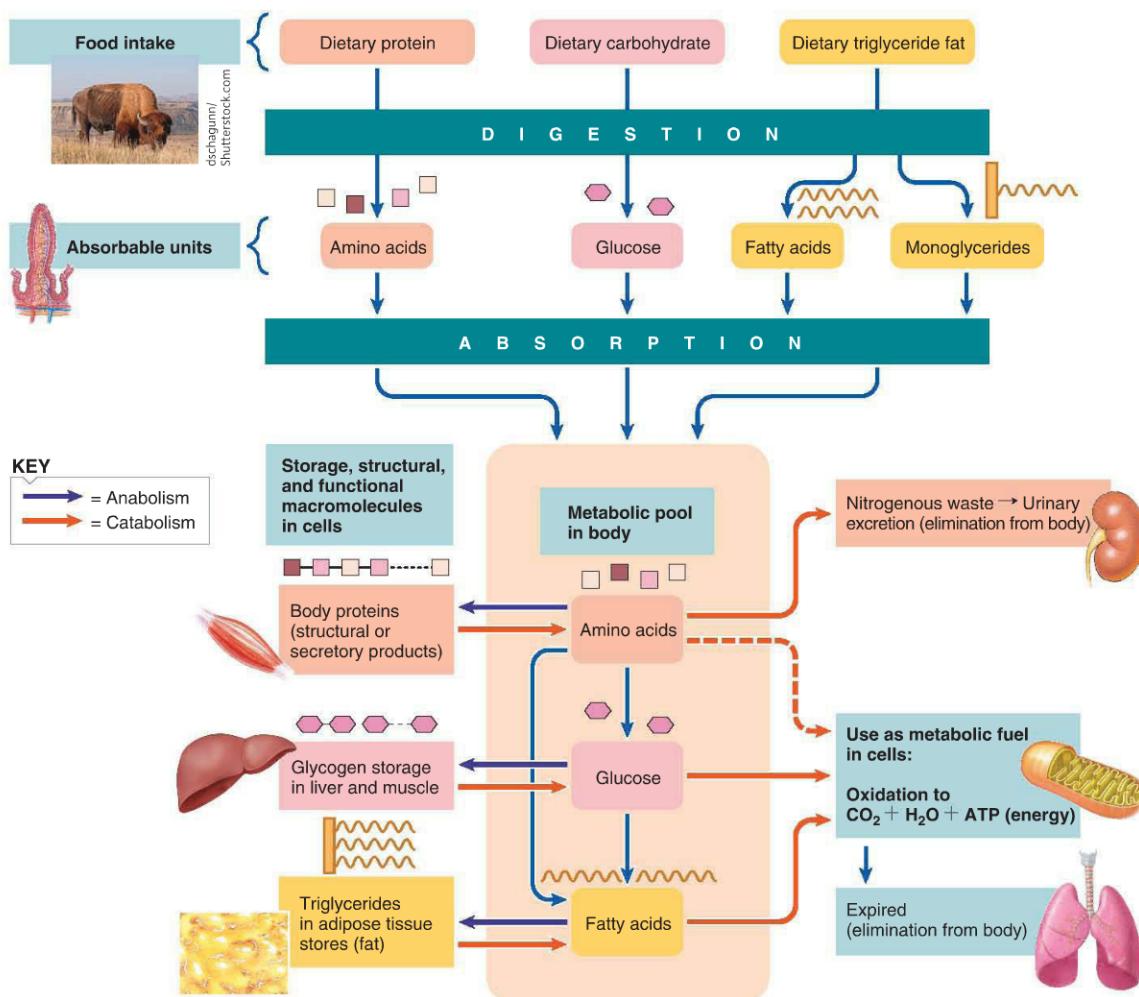
What is stress? How is the response to short-term stress different to that of long-term stress?

What is the role of the catecholamines in the stress response?

TABLE 7-4 Summary of Reactions in Fuel Metabolism

| Metabolic Process | Reaction | Consequence |
|--|--|--------------------------------|
| Glycogenesis | Glucose \rightarrow glycogen | \downarrow Blood glucose |
| Glycogenolysis | Glycogen \rightarrow glucose | \uparrow Blood glucose |
| Gluconeogenesis | Amino acids \rightarrow glucose | \uparrow Blood glucose |
| Protein Synthesis | Amino acids \rightarrow protein | \downarrow Blood amino acids |
| Protein Degradation | Protein \rightarrow amino acids | \uparrow Blood amino acids |
| Fat Synthesis (Lipogenesis or Triglyceride Synthesis) | Fatty acids and glycerol \rightarrow triglycerides | \downarrow Blood fatty acids |
| Fat Breakdown (Lipolysis or Triglyceride Degradation) | Triglycerides \rightarrow fatty acids and glycerol | \uparrow Blood fatty acids |

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**FIGURE 7-23** Summary of the major pathways involving organic nutrient molecules.

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