

## A Closer Look at Adaptation

### Brood Patch Development: Some Have It, Others Don't!

The vast majority of birds incubate their eggs by transfer of heat between parts of their body, usually but not always their ventral surface, and the clutch of eggs. That region of the incubating bird in contact with the egg is commonly termed the incubation or **brood patch**. Hormonal regulation of this patch of skin differs between sexes as well as species of birds.

Although the evolution of this structure is open to conjecture, one possibility is that the appearance of a brood patch was a definitive step in the evolution of birds from reptiles, and it has been thus suggested to share a common ancestry with the mammalian mammary gland. The nature, formation, and structure of this patch varies enormously between species, reflecting the diverse mechanisms and methods adopted by different species in the incubation of eggs. In some birds such as the domestic pigeon and ring dove, there is a form of pocket or apterum on the ventral surface of both sexes, which is devoid of feathers throughout adult life. In other species, patch formation occurs periodically and is closely related to the period of egg laying and incubation. Furthermore, although both sexes may have the potential to develop a brood patch, it is a general observation that the patch only develops in the sex actually involved in incubation. There is also a relationship between the gender that incubates, and the form of steroid that is most effective, in combination with prolactin, to produce a full brood patch. In those species in which the female alone incu-



Courtesy of Dr. Robert Whitmore

**The brood patch of a female bluebird (*Sialia sialis*).** Its function is to transfer heat to the developing chicks. Brood patch development is hormonally controlled, primarily by prolactin secretion from the adenohypophysis. In some species, only the female develops a brood patch, while in others, both the male and female develop patches.

bates, it is estrogen, whereas in those species in which the male incubates, it is androgen. Consistent with this, species that might be considered as intermediate, such as the California quail and laughing gull, are sensitive, in terms of brood patch development, to both estrogen plus prolactin and androgen plus prolactin.

In most species, brood patch development involves a number of morphological changes to the ventral body area: defeathering (mainly down feathers); a significant increase in the folding of the skin, together with an infiltration of leukocytes (edema formation); a thickening of the cornified

layer of the ventral skin surface (epidermal hyperplasia); and an increase in both size and number of local blood vessels (vascularization). The structure is surprisingly sophisticated in that the musculature of arterioles supplying blood to the patch also increases and thus can shut down blood flow to this region when the parent is off the nest. In some species, such as the house sparrow (*Passer domesticus*), there is also an increase in the amount of underlying defatted tissue.

Taken together, these dramatic changes are superbly evolved to facilitate a closer contact and more effective heat transfer between the parenting bird and the surface of the eggs, while minimizing any possible damage caused to the skin by the sustained period of contact time. The function of the brood patch during the incubatory period of the breeding cycle is complex and multifactorial. Much still remains to be understood, and one early suggestion for a possible purpose of the patch, that the bird finds relief from the peripheral irritation of the developing brood patch by sitting on eggs, remains plausible.

Not all birds have such patches. For example, the northern gannet (see chapter opening picture) does not develop one and instead incubates its egg by increasing blood flow (and heat exchange) through the webbing in its feet. Because these birds dive into the cold waters of the Atlantic Ocean, this adaptation reduces potential heat loss to the environment.

gene is highly expressed in the anterior pituitary gland and in the hypothalamus.

In the previous sections, we discussed the major central endocrine glands of vertebrates, and noting the peripheral endocrine role of the liver. We now turn our attention to other peripheral glands.

### check your understanding 7.4

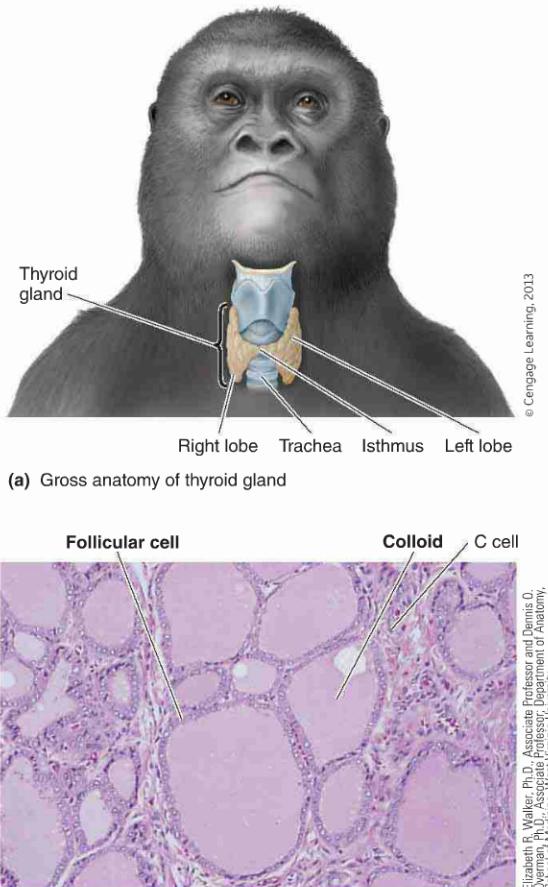
How do the direct functions of GH differ from the indirect?

How does GH usage change body composition?

What endocrine factors influence brood patch development?

## 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

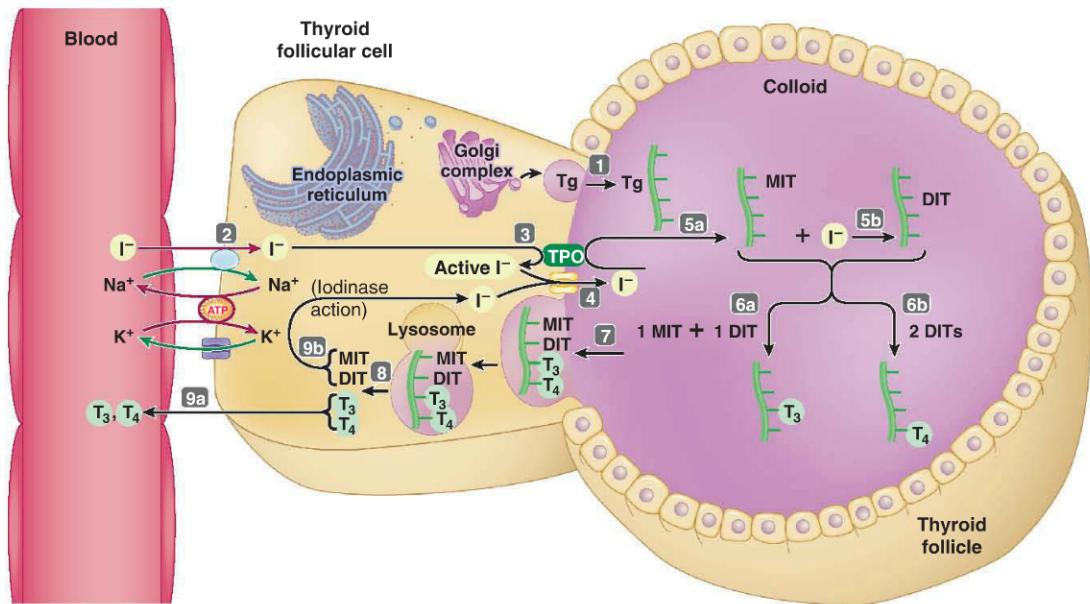
The major thyroid secretory cells, known as **follicular cells**, are arranged into fluid-filled spheres, each of which forms a functional unit called a **follicle**. On a microscopic section (Figure 7-16b), the follicles appear as rings of follicular cells enclosing an inner lumen filled with **colloid**,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

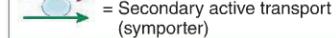
#### Thyroid hormone is synthesized and stored on the thyroglobulin molecule

The follicular cells of vertebrates produce two iodine-containing hormones derived from the amino acid tyrosine: **tetraiodothyronine (T<sub>4</sub>, or thyroxine)** and **tri-iodothyronine (T<sub>3</sub>)**. 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<sup>-</sup>) 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<sup>-</sup> 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<sup>+</sup> concentration gradient established by the Na<sup>+</sup>/K<sup>+</sup> pump at the basolateral membrane (the outer membrane of the follicular cell in contact with the interstitial fluid). The iodide pump transports Na<sup>+</sup> into the follicular cell down its concentration gradient and I<sup>-</sup> into the cell against its concentration gradient. Almost all the I<sup>-</sup> 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<sup>-</sup> = Iodide  
TPO = Thyroperoxidase  
MIT = Monoiodotyrosine

DIT = Di-iodotyrosine  
T<sub>3</sub> = Tri-iodothyronine  
T<sub>4</sub> = Tetra-iodothyronine (thyroxine)

- 1 Tyrosine-containing Tg produced within the thyroid follicular cells 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 T<sub>3</sub>.
- 6b Coupling of two DITs yields T<sub>4</sub>.
- 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 T<sub>3</sub> and T<sub>4</sub> 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 (T<sub>4</sub> 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 T<sub>3</sub> (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 T<sub>4</sub> is converted into T<sub>3</sub> outside the thyroid

In general, the proportion of T<sub>4</sub> and T<sub>3</sub> present in the thyroid gland of vertebrates is variable, although most thyroids secrete primarily T<sub>4</sub>, most likely because more DIT is made than MIT. Regardless, in the peripheral tissues (e.g., liver and kidney), most of the secreted T<sub>4</sub> is converted into T<sub>3</sub>, or *activated*, by an outer-ring deiodinase enzyme (Type II) that strips off one of its iodines. T<sub>3</sub> is the major biologically active form of thyroid hormone at the cellular level. T<sub>4</sub> can also be *inactivated* by inner-ring deiodinase (Type I) and converted into the metabolically inactive **reverse tri-iodothyronine**, or rT<sub>3</sub>. Peripherally produced T<sub>3</sub> can bind to receptors with 10 times the affinity of T<sub>4</sub>, giving peripheral cells the ability to activate their own hormone stimulation (or inactivate it by conversion to rT<sub>3</sub>). 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 T<sub>4</sub> by astrocytes. Cells in the chick embryo produce only rT<sub>3</sub> until the time of piping (the bill piercing the air sack), whereon the enzymatic machinery begins to synthesize the metabolically active T<sub>3</sub>. 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 T<sub>3</sub>.

### 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 T<sub>3</sub> and T<sub>4</sub> can be grouped into several overlapping categories.

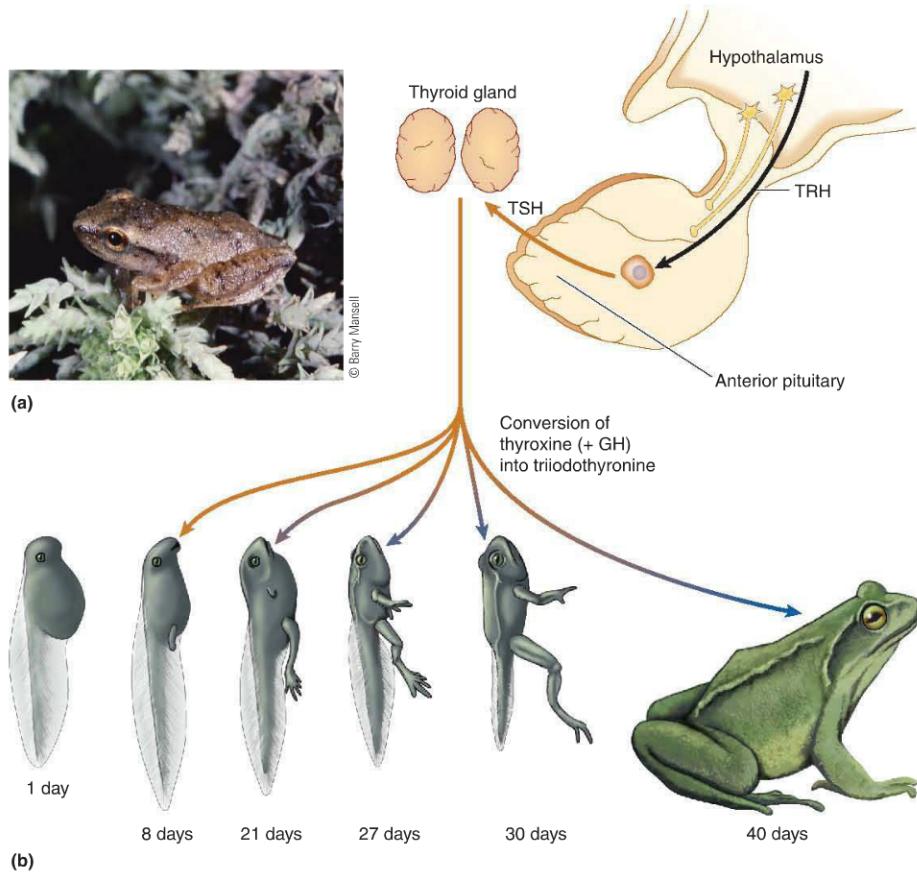
**Effect on Metabolic Rate and Heat Production** The evolution from ectothermy to endothermy necessitated development of a mechanism to regulate metabolic heat production. The solution provided by thyroid hormones is to increase a bird’s or mammal’s overall basal metabolic rate (BMR), or “idling speed”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

The transport of Na<sup>+</sup> 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 O<sub>2</sub> consumption and energy expenditure under resting conditions. Inhibition of the Na<sup>+</sup>/K<sup>+</sup> 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, T<sub>3</sub> increasing during the day associated with a reciprocal decline in T<sub>4</sub>. In the American black bear, serum levels of T<sub>3</sub> and T<sub>4</sub> 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

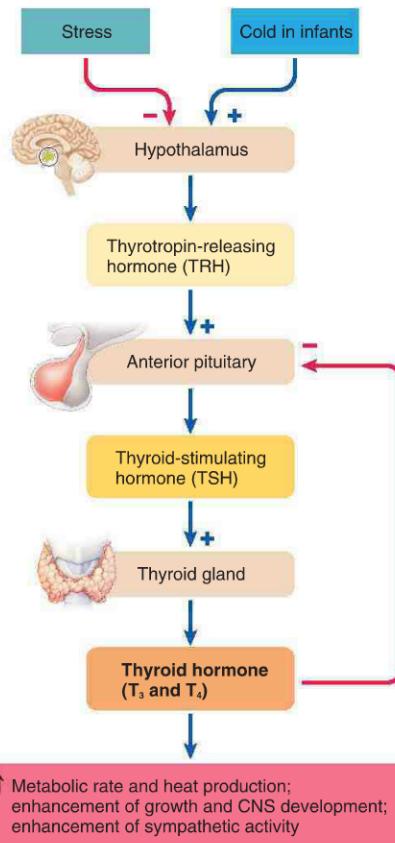


FIGURE 7-19 Regulation of thyroid hormone secretion.

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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

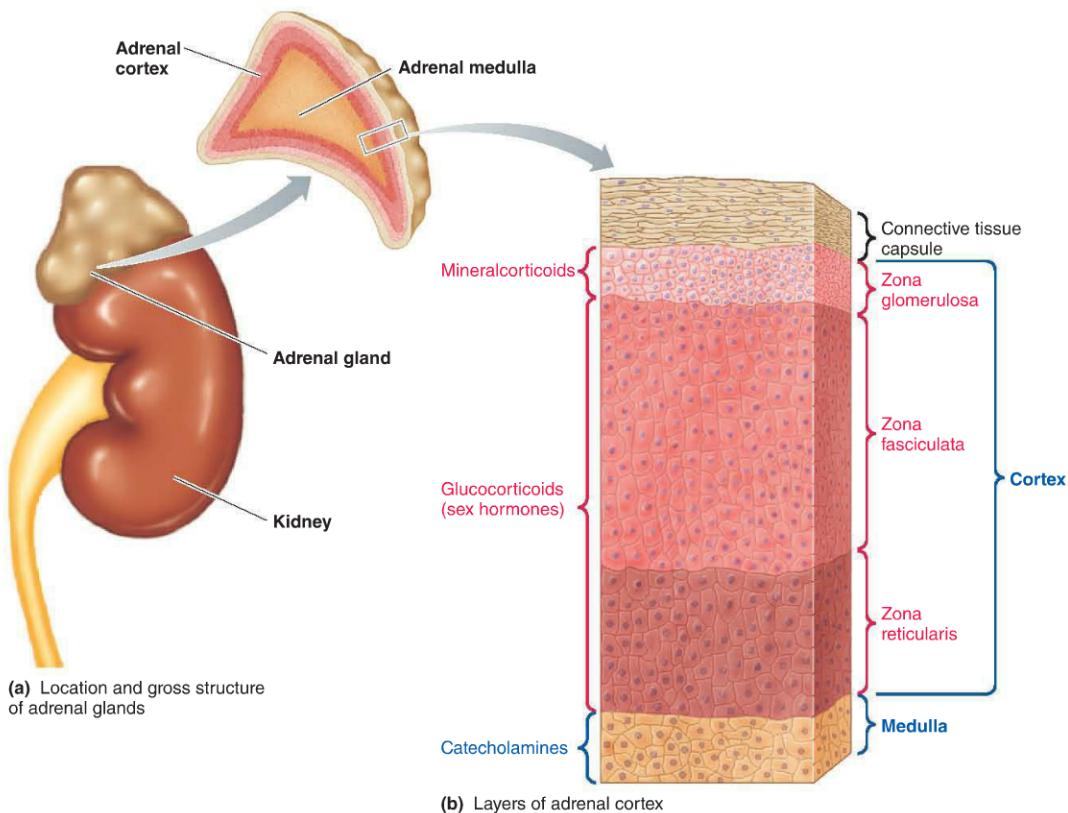
The term **chromaffin** arises from the observation that the tissue stains the color brown when reacted with oxidizing agents such as chromate. In mammals there are two adrenal glands, one embedded above each kidney in a capsule of fat. The shape of the adrenal varies considerably and in some species 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  $\text{Na}^+$  and  $\text{K}^+$  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 O<sub>2</sub> 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