7

Introduction to the Endocrine System

The separation of the endocrine system into isolated subsystems must be recognized as an artificial one, convenient from a pedagogical point of view but not accurately reflecting the interrelated nature of all these systems.

—Howard Rasmussen, *in* Williams' Textbook of Endocrinology, 1974

Background Basics

- Receptors
- Peptides and proteins
- Comparison of endocrine and nervous systems
- Signal transduction
- Steroids
- Specificity

Gamma scan of a goiter of the thyroid gland

David was seven years old when the symptoms first appeared. His appetite at meals increased, and he always seemed to be in the kitchen looking for food. Despite eating more, however, he was losing weight. When he started asking for water instead of soft drinks, David's mother became concerned, and when he wet the bed three nights in a row, she knew something was wrong. The doctor confirmed the suspected diagnosis after running tests to determine the concentration of glucose in David's blood and urine. David had diabetes mellitus. In his case, the disease was due to lack of insulin, a hormone produced by the pancreas. David was placed on insulin injections, a treatment he would continue for the rest of his life.

One hundred years ago, David would have died not long after the onset of symptoms. The field of **endocrinology,** the study of hormones, was then in its infancy. Most hormones had not been discovered, and the functions of known hormones were not well understood. There was no treatment for diabetes, no birth control pill for contraception. Babies born with inadequate secretion of thyroid hormone did not grow or develop normally.

Today, all that has changed. We have identified a long and growing list of hormones. The endocrine diseases that once killed or maimed can now be controlled by synthetic hormones and sophisticated medical procedures. Although physicians do not hesitate to use these treatments, we are still learning exactly how hormones act on their target cells. This chapter provides an introduction to the basic principles of hormone structure and function. You will learn more about individual hormones as you encounter them in your study of the various systems.

Hormones

Hormones are chemical messengers secreted into the blood by specialized cells. Hormones are responsible for many functions that we think of as long-term, ongoing functions of the body. Processes that fall mostly under hormonal control include growth and development, metabolism, regulation of the internal environment (temperature, water balance, ions), and reproduction. Hormones act on their target cells in one of three basic ways: (1) by controlling the rates of enzymatic reactions, (2) by controlling the transport of ions or molecules across cell membranes, or (3) by controlling gene expression and the synthesis of proteins.

RUNNING PROBLEM

Graves' Disease

The ball slid by the hole and trickled off the green: another bogey. Ben Crenshaw's golf game was falling apart. The 33-year-old professional had won the Masters Tournament only a year ago, but now something was not right. He was tired and weak, had been losing weight, and felt hot all the time. He attributed his symptoms to stress, but his family thought otherwise. At their urging, he finally saw a physician. The diagnosis? Graves' disease, which results in an overactive thyroid gland.

Hormones Have Been Known Since Ancient Times

Although the scientific field of endocrinology is relatively young, diseases of the endocrine system have been documented for more than a thousand years. Evidence of endocrine abnormalities can even be seen in ancient art. For example, one pre-Colombian statue of a woman shows a mass on the front of her neck (■ Fig. 7.1). The mass is an enlarged thyroid gland, or *goiter,* a common condition high in the Andes, where the dietary iodine needed to make thyroid hormones was lacking.

The first association of endocrine structure and function was probably the link between the testes and male sexuality. Castration of animals and men was a common practice in both Eastern and Western cultures because it decreased the sex drive and rendered males infertile.

■ **Fig. 7.1** ***An endocrine disorder in ancient art.*** This pre-Colombian stone carving of a woman shows a mass at her neck. This mass is an enlarged thyroid gland, a condition known as goiter. It was considered a sign of beauty among the people who lived high in the Andes mountains.

In 1849, A. A. Berthold performed the first classic experiment in endocrinology. He removed the testes from roosters and observed that the castrated birds had smaller combs, less aggressiveness, and less sex drive than uncastrated roosters. If the testes were surgically placed back into the donor rooster or into another castrated bird, normal male behavior and comb development resumed. Because the reimplanted testes were not connected to nerves, Berthold concluded that the glands must be secreting something into the blood that affected the entire body.

Experimental endocrinology did not receive much attention, however, until 1889, when the 72-year-old French physician Charles Brown-Séquard made a dramatic announcement of his sexual rejuvenation after injecting himself with extracts made from bull testes ground up in water. An international uproar followed, and physicians on both sides of the Atlantic began to inject their patients with extracts of many different endocrine organs, a practice known as *organotherapy*.

We now know that the increased virility Brown-Séquard reported was most likely a placebo effect because testosterone is a hydrophobic steroid that cannot be extracted by an aqueous preparation. His research opened the door to hormone therapy, however, and in 1891 organotherapy had its first true success: a woman was treated for low thyroid hormone levels with glycerin extracts of sheep thyroid glands.

As the study of "internal secretions" grew, Berthold's experiments became a template for endocrine research. Once a gland or structure was suspected of secreting hormones, the classic steps for identifying an endocrine gland became:

1. **Remove the suspected gland.** This is equivalent to inducing a state of *hormone deficiency*. If the gland does produce hormones, the animal should start to exhibit anatomical, behavioral, or physiological abnormalities.
2. **Replace the hormone**. This can be done by placing the gland back in the animal or administering an extract of the gland. This *replacement therapy* should eliminate the symptoms of hormone deficiency.
3. **Create a state of hormone excess**. Take a normal animal and implant an extra gland or administer extract from the gland to see if symptoms characteristic of *hormone excess* appear.

Once a gland is identified as a potential source of hormones, scientists purify extracts of the gland to isolate the active substance. They test for hormone activity by injecting animals with the purified extract and monitoring for a response.

Hormones identified by this technique are sometimes called *classic hormones*. They include hormones of the pancreas, thyroid, adrenal glands, pituitary, and gonads, all discrete endocrine glands that could be easily identified and surgically removed. Not all hormones come from identifiable glands, however, and we have been slower to discover them. For example, many hormones involved in digestion are secreted by endocrine cells scattered throughout the wall of the stomach or intestine, which has made them difficult to identify and isolate.

The Anatomy Summary in ■ Figure 7.2 lists the major hormones of the body and the glands or cells that secrete them, along with the major effects of each hormone.

CLINICAL FOCUS: DIABETES

The Discovery of Insulin

Diabetes mellitus, the metabolic condition associated with pathologies of insulin function, has been known since ancient times. Detailed clinical descriptions of insulin-deficient diabetes were available to physicians, but they had no means of treating the disease. Patients invariably died. However, in a series of classic experiments in endocrine physiology, Oscar Minkowski at the University of Strasbourg (Germany) pinpointed the relationship between diabetes and the pancreas. In 1889, Minkowski surgically removed the pancreas from dogs (*pancreatectomy*) and noticed that they developed symptoms that mimicked those of diabetes. He also found that implanting pieces of pancreas under the dogs' skin would prevent development of diabetes. Subsequently, in 1921 Fredrick G. Banting and Charles H. Best (Toronto, Canada) identified an antidiabetic substance in pancreas extracts. Banting and Best and others injected pancreatic extracts into diabetic animals and found that the extracts reversed the elevated blood glucose levels of diabetes. From there, it was a relatively short process until, in 1922, purified insulin was used in the first clinical trials. Science had found a treatment for a once-fatal disease.

What Makes a Chemical a Hormone?

In 1905, the term *hormone* was coined from the Greek verb meaning "to excite or arouse." The traditional definition of a **hormone** is a chemical secreted by a cell or group of cells into the blood for transport to a distant target, where it exerts its effect at very low concentrations. However, as scientists learn more about chemical communication in the body, this definition is continually being challenged.

Hormones Are Secreted by a Cell or Group of Cells Traditionally, the field of endocrinology has focused on chemical messengers secreted by endocrine *glands,* the discrete and readily identifiable tissues derived from epithelial tissue. However, we now know that molecules that act as hormones are secreted not only by classic endocrine glands but also by isolated endocrine cells (hormones of the *diffuse endocrine system*), by neurons (*neurohormones*), and by cells of the immune system (*cytokines*).

Hormones Are Secreted into the Blood **Secretion** is the movement of a substance from inside a cell to the extracellular fluid or directly into the external environment. According to the traditional definition of a hormone, hormones are secreted into the blood. However, the term *ectohormone* {*ektos,* outside} has been given to signal molecules secreted into the external environment.

Pheromones {*pherein,* to bring} are specialized ectohormones that act on other organisms of the same species to elicit a physiological or behavioral response. For example, sea anemones secrete alarm pheromones when danger threatens, and ants release trail pheromones to attract fellow workers to food sources. Pheromones are also used to attract members of the opposite sex for mating. Sex pheromones are found throughout the animal kingdom, in animals from fruit flies to dogs.

But do humans have pheromones? This question is still a matter of debate. Some studies have shown that human *axillary* (armpit) sweat glands secrete volatile steroids related to sex hormones that may serve as human sex pheromones. In one study, when female students were asked to rate the odors of T-shirts worn by male students, each woman preferred the odor of men who were genetically dissimilar from her. In another study, female axillary secretions rubbed on the upper lip of young women altered the timing of their menstrual cycles. The selling of putative human pheromones as perfume is becoming the latest fad in the mating game, as you will see if you do a Google search for *human pheromone.* How humans may sense pheromones is discussed later.

Hormones Are Transported to a Distant Target By the traditional definition, a hormone must be transported by the blood to a distant target cell. Experimentally, this property is sometimes difficult to demonstrate. Molecules that are suspected of being hormones but not fully accepted as such are called *candidate hormones*. They are usually identified by the word *factor*. For example, in the early 1970s, the hypothalamic regulating hormones were known as "releasing factors" and "inhibiting factors" rather than releasing and inhibiting hormones.

Currently, **growth factors,** a large group of substances that influence cell growth and division, are being studied to determine if they meet all the criteria for hormones. Although many growth factors have been shown to act locally as *autocrines* or *paracrines*, most do not seem to be distributed widely in the circulation. A similar situation exists with the lipid-derived signal molecules called *eicosanoids*.

Complicating the classification of signal molecules is the fact that a molecule may act as a hormone when secreted from one location but as a paracrine or autocrine signal when secreted from a different location. For example, in the 1920s scientists discovered that *cholecystokinin* (CCK) in extracts of intestine caused contraction of the gallbladder. For many years thereafter, CCK was known only as an intestinal hormone. Then in the mid-1970s, CCK was found in neurons of the brain, where it acts as a neurotransmitter or neuromodulator. In recent years, CCK has gained attention because of its possible role in controlling hunger.

Hormones Exert Their Effect at Very Low Concentrations One hallmark of a hormone is its ability to act at concentrations in the nanomolar (10^{-9} M) to picomolar (10^{-12} M) range. Some chemical signals transported in the blood to distant targets are not considered hormones because they must be present in relatively high concentrations before an effect is noticed. For example, histamine released during severe allergic reactions may act on cells throughout the body, but its concentration exceeds the accepted range for a hormone.

As researchers discover new signal molecules and new receptors, the boundary between hormones and nonhormonal signal molecules continues to be challenged, just as the distinction between the nervous and endocrine systems has blurred. Many *cytokines* seem to meet the previously stated definition of a hormone. However, experts in cytokine research do not consider cytokines to be hormones because peptide cytokines are synthesized and released on demand, in contrast to classic peptide hormones, which are made in advance and stored in the parent endocrine cell. A few cytokines—for example, *erythropoietin,* the molecule that controls red blood cell production—were classified as hormones before the term *cytokine* was coined, contributing to the overlap between the two groups of signal molecules.

Hormones Act by Binding to Receptors

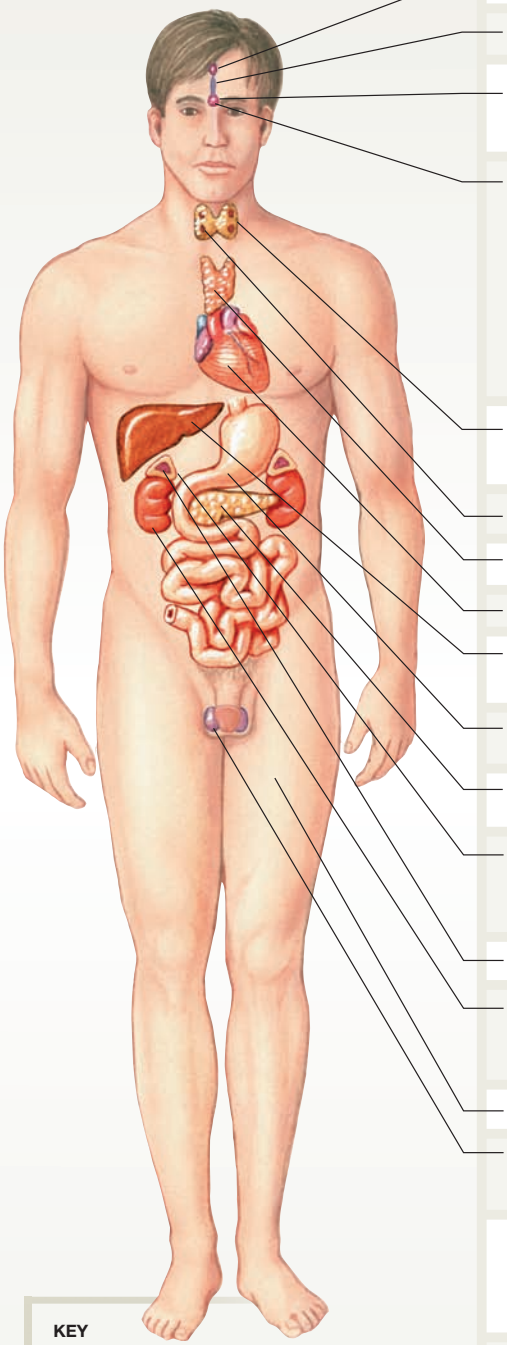
All hormones bind to target cell receptors and initiate biochemical responses. These responses are the **cellular mechanism of action** of the hormone. As you can see from the table in Figure 7.2, one hormone may act on multiple tissues. To complicate matters, the effects may vary in different tissues or at different stages of development. Or a hormone may have no effect at all in a particular cell. Insulin is an example of a hormone with varied effects. In muscle and adipose tissues, insulin alters glucose transport proteins and enzymes for glucose metabolism. In the liver, it modulates enzyme activity but has no direct effect on glucose transport proteins. In the brain and certain other tissues, glucose metabolism is totally independent of insulin.

Concept Check Answers: End of Chapter

1. Name the membrane transport process by which glucose moves from the extracellular fluid into cells.

The variable responsiveness of a cell to a hormone depends primarily on the cell's receptor and signal transduction pathways. If there are no hormone receptors in a tissue, its cells cannot respond. If tissues have different receptors and receptor-linked pathways for the same hormone, they will respond differently.

Hormones



KEY

G = gland
C = endocrine cells
N = neurons

P = peptide
S = steroid
A = amino acid–derived

Location	Hormone	Primary Target(s)
Pineal gland	Melatonin [A]	Brain, other tissues
Hypothalamus (N)	Trophic hormones [P] (see Fig. 7.8)	Anterior pituitary
Posterior pituitary (N)	Oxytocin [P]	Breast and uterus
	Vasopressin (ADH) [P]	Kidney
Anterior pituitary (G)	Prolactin [P]	Breast
	Growth hormone (somatotropin) [P]	Liver Many tissues
	Corticotropin (ACTH) [P]	Adrenal cortex
	Thyrotropin (TSH) [P]	Thyroid gland
	Follicle-stimulating hormone [P]	Gonads
	Luteinizing hormone [P]	Gonads
Thyroid gland	Triiodothyronine and thyroxine [A]	Many tissues
	Calcitonin [P]	Bone
Parathyroid gland	Parathyroid hormone [P]	Bone, kidney
Thymus gland	Thymosin, thymopoietin [P]	Lymphocytes
Heart (C)	Atrial natriuretic peptide [P]	Kidneys
Liver (C)	Angiotensinogen [P]	Adrenal cortex, blood vessels
	Insulin-like growth factors [P]	Many tissues
Stomach and small intestine (C)	Gastrin, cholecystokinin, secretin, and others [P]	GI tract and pancreas
Pancreas (G)	Insulin, glucagon, somatostatin, pancreatic polypeptide [P]	Many tissues
Adrenal cortex (G)	Aldosterone [S]	Kidney
	Cortisol [S]	Many tissues
	Androgens [S]	Many tissues
Adrenal medulla (N)	Epinephrine, norepinephrine [A]	Many tissues
Kidney (C)	Erythropoietin [P]	Bone marrow
	1,25 Dihydroxy-vitamin D_3 (calciferol) [S]	Intestine
Skin (C)	Vitamin D_3 [S]	Intermediate form of hormone
Testes (male) (G)	Androgens [S]	Many tissues
	Inhibin [P]	Anterior pituitary
Ovaries (female) (G)	Estrogen, progesterone [S]	Many tissues
	Inhibin [P]	Anterior pituitary
	Relaxin (pregnancy) [P]	Uterine muscle
Adipose tissue (C)	Leptin, adiponectin, resistin	Hypothalamus, other tissues
Placenta (pregnant females only) (C)	Estrogen, progesterone [S]	Many tissues
	Chorionic somatomammotropin [P]	Many tissues
	Chorionic gonadotropin [P]	Corpus luteum

	Main Effect(s)
	Circadian rhythms; immune function; antioxidant
	Release or inhibit pituitary hormones
	Milk ejection; labor and delivery; behavior Water reabsorption
	Milk production Growth factor secretion Growth and metabolism Cortisol release Thyroid hormone synthesis Egg or sperm production; sex hormone production Sex hormone production; egg or sperm production
	Metabolism, growth, and development Plasma calcium levels (minimal effect in humans)
	Regulates plasma Ca^{2+} and phosphate levels
	Lymphocyte development
	Increases Na^+ excretion
	Aldosterone secretion; increases blood pressure Growth
	Assist digestion and absorption of nutrients
	Metabolism of glucose and other nutrients
	Na^+ and K^+ homeostasis Stress response Sex drive in females
	Fight-or-flight response
	Red blood cell production Increases calcium absorption
	Precursor of 1,25 dihydroxy-vitamin D_3
	Sperm production, secondary sex characteristics Inhibits FSH secretion
	Egg production, secondary sex characteristics Inhibits FSH secretion Relaxes muscle
	Food intake, metabolism, reproduction
	Fetal, maternal development Metabolism Hormone secretion

Hormone Action Must Be Terminated

Signal activity by hormones and other chemical signals must be of limited duration if the body is to respond to changes in its internal state. For example, insulin is secreted when blood glucose concentrations increase following a meal. As long as insulin is present, glucose leaves the blood and enters cells. However, if insulin activity continues too long, blood glucose levels can fall so low that the nervous system becomes unable to function properly—a potentially fatal situation. Normally the body avoids this situation in several ways: by limiting insulin secretion, by removing or inactivating insulin circulating in the blood, and by terminating insulin activity in target cells.

In general, hormones in the bloodstream are *degraded* (broken down) into inactive metabolites by enzymes found primarily in the liver and kidneys. The metabolites are then excreted in either the bile or the urine. The rate of hormone breakdown is indicated by a hormone's **half-life** in the circulation, the amount of time required to reduce the concentration of hormone by one-half. Half-life is one indicator of how long a hormone is active in the body.

Hormones bound to target membrane receptors have their activity terminated in several ways. Enzymes that are always present in the plasma can degrade peptide hormones bound to cell membrane receptors. In some cases, the receptor-hormone complex is brought into the cell by endocytosis, and the hormone is then digested in lysosome. Intracellular enzymes metabolize hormones that enter cells.

Concept Check Answers: End of Chapter

2. What is the suffix in a chemical name that tells you a molecule is an enzyme? Use that suffix to name an enzyme that digests peptides.

The Classification of Hormones

Hormones can be classified according to different schemes. The scheme used in Figure 7.2 groups them according to their source. A different scheme divides hormones into those whose release is controlled by the brain and those whose release is not controlled by the brain. Another scheme groups hormones according to whether they bind to G protein–coupled receptors, tyrosine kinase–linked receptors, or intracellular receptors, and so on.

A final scheme divides hormones into three main chemical classes: peptide/protein hormones, steroid hormones, and amino acid-derived, or amine, hormones (■ Tbl. 7.1). The peptide/protein hormones are composed of linked amino acids. The steroid hormones are all derived from cholesterol. The amino acid-derived hormones, also called *amine hormones*, are modifications of single amino acids, either tryptophan or tyrosine.

Comparison of Peptide, Steroid, and Amino Acid-Derived Hormones — Table 7.1

	Peptide Hormones	Steroid Hormones	Amine Hormones (Tyrosine Derivatives)	
			Catecholamines	Thyroid Hormones
Synthesis and storage	Made in advance; stored in secretory vesicles	Synthesized on demand from precursors	Made in advance; stored in secretory vesicles	Made in advance; precursor stored in secretory vesicles
Release from parent cell	Exocytosis	Simple diffusion	Exocytosis	Simple diffusion
Transport in blood	Dissolved in plasma	Bound to carrier proteins	Dissolved in plasma	Bound to carrier proteins
Half-life	Short	Long	Short	Long
Location of receptor	Cell membrane	Cytoplasm or nucleus; some have membrane receptors also	Cell membrane	Nucleus
Response to receptor-ligand binding	Activation of second messenger systems; may activate genes	Activation of genes for transcription and translation; may have nongenomic actions	Activation of second messenger systems	Activation of genes for transcription and translation
General target response	Modification of existing proteins and induction of new protein synthesis	Induction of new protein synthesis	Modification of existing proteins	Induction of new protein synthesis
Examples	Insulin, parathyroid hormone	Estrogen, androgens, cortisol	Epinephrine, norepinephrine	Thyroxine (T_4)

Concept Check — Answers: End of Chapter

3. What is the classic definition of a hormone?
4. Based on what you know about the organelles involved in protein and steroid synthesis, what would be the major differences between the organelle composition of a steroid-producing cell and that of a protein-producing cell?

Most Hormones Are Peptides or Proteins

The peptide/protein hormones range from small peptides of only three amino acids to larger proteins and glycoproteins. Despite the size variability among hormones in this group, they are usually called peptide hormones for the sake of simplicity. You can remember which hormones fall into this category by exclusion: if a hormone is not a steroid hormone and not an amino-acid derivative, then it must be a peptide or protein.

Peptide Hormone Synthesis, Storage, and Release The synthesis and packaging of peptide hormones into membrane-bound secretory vesicles is similar to that of other proteins. The initial peptide that comes off the ribosome is a large inactive protein known as a preprohormone (■ Fig. 7.3 ①). **Preprohormones** contain one or more copies of a peptide hormone, a *signal sequence* that directs the protein into the lumen of the rough endoplasmic reticulum, and other peptide sequences that may or may not have biological activity.

As an inactive preprohormone moves through the endoplasmic reticulum and Golgi complex, the signal sequence is removed, creating a smaller, still-inactive molecule called a **prohormone** (Fig. 7.3 ④). In the Golgi complex, the prohormone is packaged into secretory vesicles along with *proteolytic* {*proteo-*, protein + *lysis*, rupture} enzymes that chop the prohormone into active hormone and other fragments. This process is called *post-translational modification*.

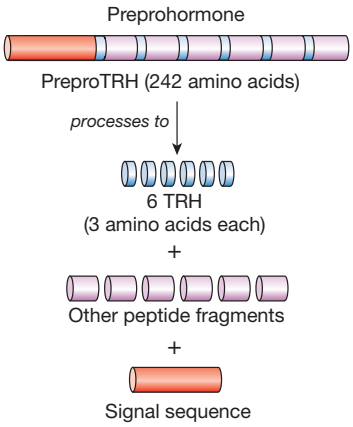
The secretory vesicles containing peptides are stored in the cytoplasm of the endocrine cell until the cell receives a signal for secretion. At that time, the vesicles move to the cell membrane and

Peptide Hormone Synthesis and Processing

Peptide hormones are made as large, inactive preprohormones that include a signal sequence, one or more copies of the hormone, and additional peptide fragments.

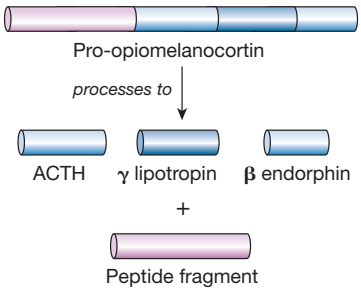
(a) Preprohormones

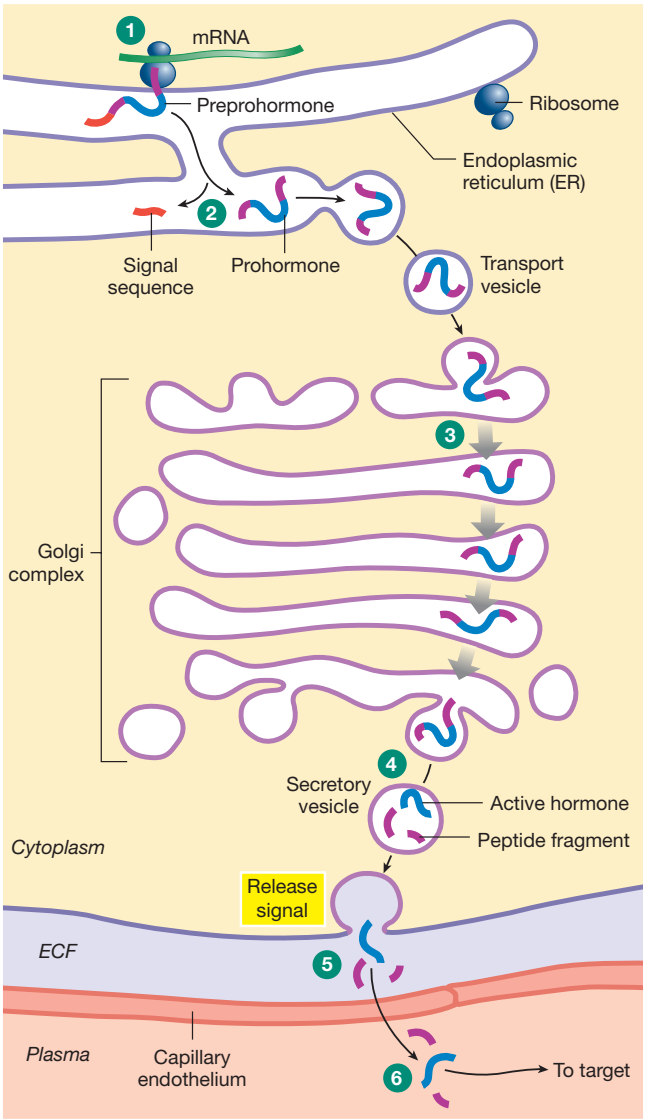
PreproTRH (thyrotropin-releasing hormone) has six copies of the 3-amino acid hormone TRH.



(b) Prohormones

Prohormones, such as pro-opiomelanocortin, the prohormone for ACTH, may contain several peptide sequences with biological activity.

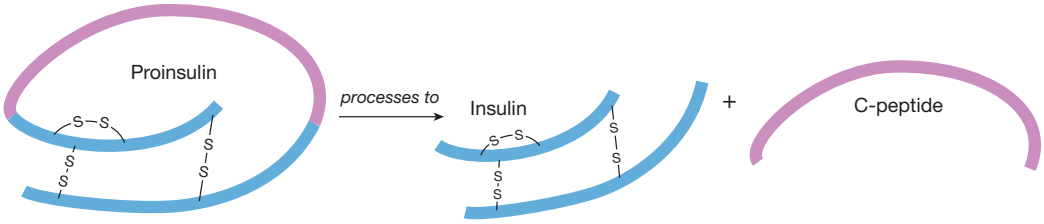




1. Messenger RNA on the ribosomes binds amino acids into a peptide chain called a **preprohormone**. The chain is directed into the ER lumen by a **signal sequence** of amino acids.
2. Enzymes in the ER chop off the signal sequence, creating an inactive **prohormone**.
3. The prohormone passes from the ER through the Golgi complex.
4. Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.
5. The secretory vesicle releases its contents by exocytosis into the extracellular space.
6. The hormone moves into the circulation for transport to its target.

(c) Prohormones Process to Active Hormone Plus Peptide Fragments

The peptide chain of insulin's prohormone folds back on itself with the help of disulfide (S—S) bonds. The prohormone cleaves to insulin and C-peptide.



release their contents by calcium-dependent exocytosis. All of the peptide fragments created from the prohormone are released together into the extracellular fluid, in a process known as *co-secretion* (Fig. 7.3 ⑤).

Post-Translational Modification of Prohormones Studies of prohormone processing have led to some interesting discoveries. Some prohormones, such as that for *thyrotropin-releasing hormone* (TRH), contain multiple copies of the hormone (Figure 7.3a). Another interesting prohormone is *pro-opiomelanocortin* (Figure 7.3b). This prohormone splits into three active peptides plus an inactive fragment. In some instances, even the fragments are clinically useful. For example, proinsulin is cleaved into active insulin and an inactive fragment known as *C-peptide* (Figure 7.3c). Clinicians measure the levels of C-peptide in the blood of diabetics to monitor how much insulin the patient's pancreas is producing.

Transport in the Blood and Half-Life of Peptide Hormones Peptide hormones are water soluble and therefore generally dissolve easily in the extracellular fluid for transport throughout the body. The half-life for peptide hormones is usually quite short, in the range of several minutes. If the response to a peptide hormone must be sustained for an extended period of time, the hormone must be secreted continually.

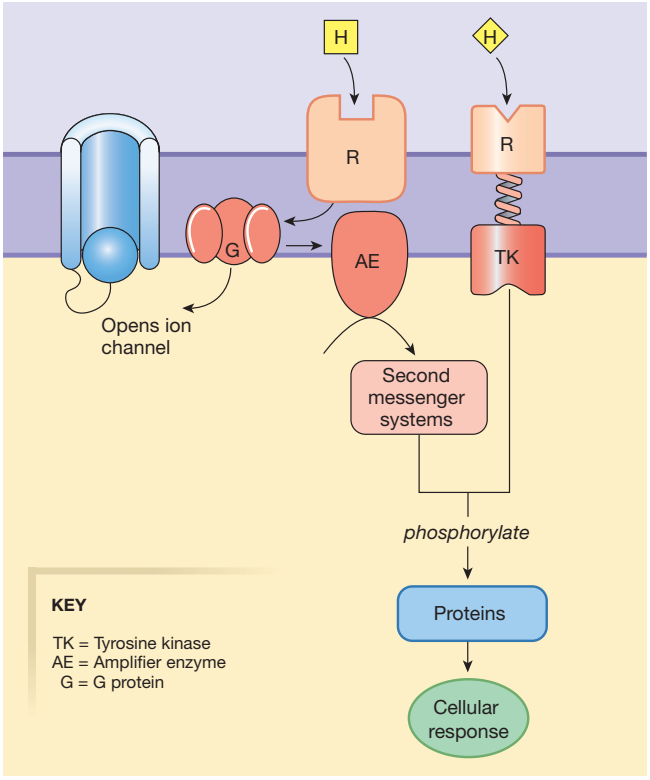
Cellular Mechanism of Action of Peptide Hormones Because peptide hormones are lipophobic, they are usually unable to enter the target cell. Instead, they bind to surface membrane receptors. The hormone-receptor complex initiates the cellular response by means of a *signal transduction* system (■ Fig. 7.4). Many peptide hormones work through cAMP second messenger systems. A few peptide hormone receptors, such as that of insulin, have tyrosine kinase activity or work through other signal transduction pathways.

The response of cells to peptide hormones is usually rapid because second messenger systems modify existing proteins. The changes triggered by peptide hormones include opening or closing membrane channels and modulating metabolic enzymes or transport proteins. Researchers have recently discovered that some peptide hormones also have longer-lasting effects when their second messenger systems activate genes and direct the synthesis of new proteins.

Steroid Hormones Are Derived from Cholesterol

Steroid hormones have a similar chemical structure because they are all derived from cholesterol (■ Fig. 7.5a). Unlike peptide hormones, which are made in tissues all over the body, steroid hormones are made in only a few organs. The **adrenal cortex**, the outer portion of the adrenal glands {*cortex,* bark}, makes several types of steroid hormones. One **adrenal gland** sits atop each kidney {*ad-,* upon + *renal,* kidney}. The gonads produce the sex steroids (estrogens, progesterone, and androgens). In pregnant women, the placenta is also a source of steroid hormones.

Peptide hormones (H) cannot enter their target cells and must combine with membrane receptors (R) that initiate signal transduction processes.



■ **Fig. 7.4** ***Membrane receptors and signal transduction for peptide hormones***

Steroid Hormone Synthesis and Release Cells that secrete steroid hormones have unusually large amounts of smooth endoplasmic reticulum, the organelle in which steroids are synthesized. Steroids are lipophilic and diffuse easily across membranes, both out of their parent cell and into their target cell. This property also means that steroid-secreting cells cannot store hormones in secretory vesicles. Instead, they synthesize their hormone as it is needed. When a stimulus activates the endocrine cell, precursors in the cytoplasm are rapidly converted to active hormone. The hormone concentration in the cytoplasm rises, and the hormones move out of the cell by simple diffusion.

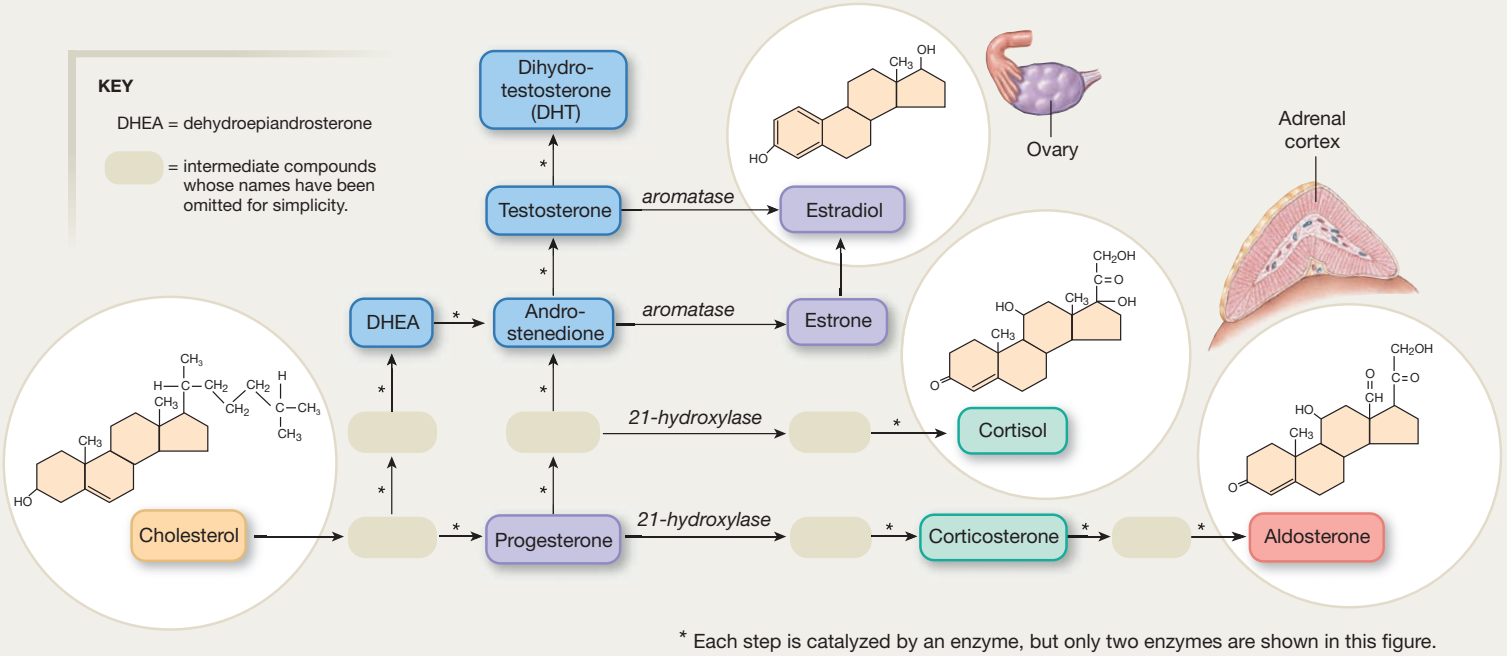
Transport in the Blood and Half-Life of Steroid Hormones Like their parent cholesterol, steroid hormones are not very soluble in plasma and other body fluids. For this reason, most of the steroid hormone molecules found in the blood are bound to protein carrier molecules (Fig. 7.5b ①). Some hormones have specific carriers, such as *corticosteroid-binding globulin*. Others simply bind to general plasma proteins, such as *albumin*.

The binding of a steroid hormone to a carrier protein protects the hormone from enzymatic degradation and results in an extended half-life. For example, **cortisol,** a hormone produced

Steroid Hormones

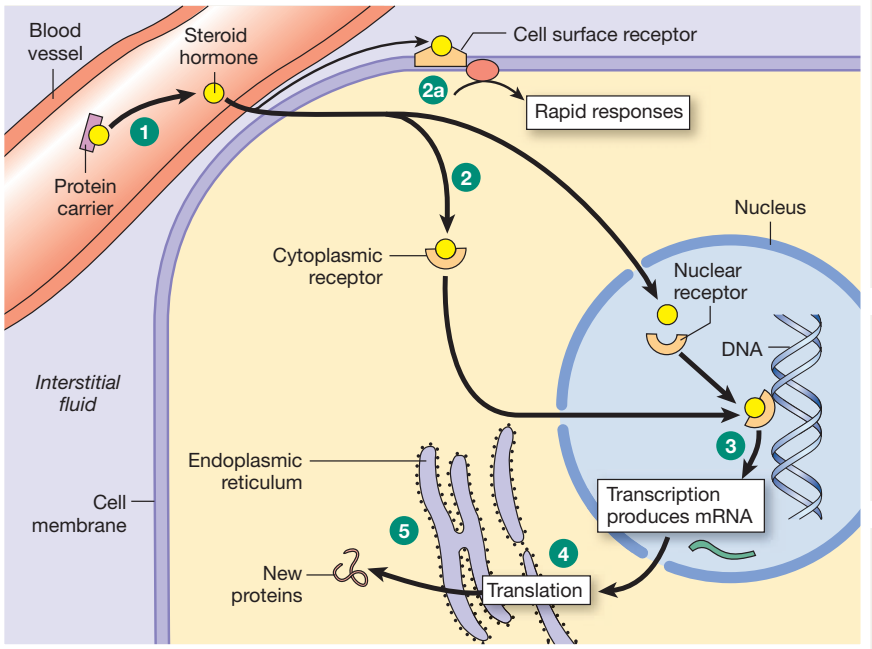
Most steroid hormones are made in the adrenal cortex or gonads (ovaries and testes). Steroid hormones are not stored in the endocrine cell because of their lipophilic nature. They are made on demand and diffuse out of the endocrine cell.

(a) Cholesterol is the parent compound for all steroid hormones.



* Each step is catalyzed by an enzyme, but only two enzymes are shown in this figure.

(b) Steroid hormones act primarily on intracellular receptors.



1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
2a. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins for cell processes.

by the adrenal cortex, has a half-life of 60–90 minutes. (Compare this with epinephrine, an amino acid–derived hormone whose half-life is measured in seconds.)

Although binding steroid hormones to protein carriers extends their half-life, it also blocks their entry into target cells. The carrier-steroid complex remains outside the cell because the carrier proteins are lipophobic and cannot diffuse through the membrane. Only an unbound hormone molecule can diffuse into the target cell (Fig. 7.5b ②). As unbound hormone leaves the plasma, the carriers obey the law of mass action and release hormone so that the ratio of unbound to bound hormone in the plasma remains constant [the K_d].

Fortunately, hormones are active in minute concentrations, and only a tiny amount of unbound steroid is enough to produce a response. As unbound hormone leaves the blood and enters cells, additional carriers release their bound steroid so that some unbound hormone is always in the blood and ready to enter a cell.

Cellular Mechanism of Action of Steroid Hormones The best-studied steroid hormone receptors are found within cells, either in the cytoplasm or in the nucleus. The ultimate destination of steroid receptor-hormone complexes is the nucleus, where the complex acts as a *transcription factor,* binding to DNA and either activating or *repressing* (turning off) one or more genes (Fig. 7.5b ③). Activated genes create new mRNA that directs the synthesis of new proteins. Any hormone that alters gene activity is said to have a *genomic effect* on the target cell.

When steroid hormones activate genes to direct the production of new proteins, there is usually a lag time between hormone-receptor binding and the first measurable biological effects. This lag can be as much as 90 minutes. Consequently, steroid hormones do not mediate reflex pathways that require rapid responses.

In recent years researchers have discovered that several steroid hormones, including estrogens and aldosterone, have cell membrane receptors linked to signal transduction pathways, just as peptide hormones do. These receptors enable those steroid hormones to initiate rapid **nongenomic responses** in addition to their slower genomic effects. With the discovery of nongenomic effects of steroid hormones, the functional differences between steroid and peptide hormones seem almost to have disappeared.

Some Hormones Are Derived from Single Amino Acids

The amino acid–derived, or amine, hormones are small molecules created from either tryptophan or tyrosine, both notable for the carbon ring structures in their R-groups. The pineal gland hormone **melatonin** is derived from tryptophan (see *Focus on the Pineal Gland,* Fig. 7.16) but the other amino acid–derived hormones—the catecholamines and thyroid hormones—are derived from tyrosine (■ Fig. 7.6). Catecholamines are a modification of a single tyrosine molecule. The thyroid hormones are made from two tyrosine molecules plus iodine atoms.

RUNNING PROBLEM

Shaped like a butterfly, the thyroid gland straddles the trachea just below the Adam's apple. Responding to hormonal signals from the hypothalamus and anterior pituitary, the thyroid gland concentrates iodine, an element found in food (most notably as an ingredient added to salt), and combines it with the amino acid tyrosine to make two thyroid hormones, thyroxine and triiodothyronine. These thyroid hormones perform many important functions in the body, including the regulation of growth and development, oxygen consumption, and the maintenance of body temperature.

Q1: a. To which of the three classes of hormones do the thyroid hormones belong?
b. If a person's diet is low in iodine, predict what happens to thyroxine production.

Despite a common precursor, the two groups of tyrosine-based hormones have little in common. The **catecholamines** (epinephrine, norepinephrine, and dopamine) are neurohormones that bind to cell membrane receptors the way peptide hormones do. The **thyroid hormones,** produced by the butterfly-shaped thyroid gland in the neck, behave more like steroid hormones, with intracellular receptors that activate genes.

Concept Check Answers: End of Chapter

5. What are the three chemical classes of hormones?
6. The steroid hormone aldosterone has a short half-life for a steroid hormone—only about 20 minutes. What would you predict about the degree to which aldosterone is bound to blood proteins?

Control of Hormone Release

A fundamental principle of homeostasis is the importance of reflex pathways in maintaining the internal environment. The sections that follow apply the basic patterns of reflex pathways to the control pathways for hormones. This discussion is not all-inclusive, and you will encounter a few hormones that do not fit exactly into these patterns.

Hormones Can Be Classified by Their Reflex Pathways

Reflex pathways are a convenient way to classify hormones and simplify learning the pathways that regulate their secretion. All reflex pathways have similar components: a stimulus, a sensor,

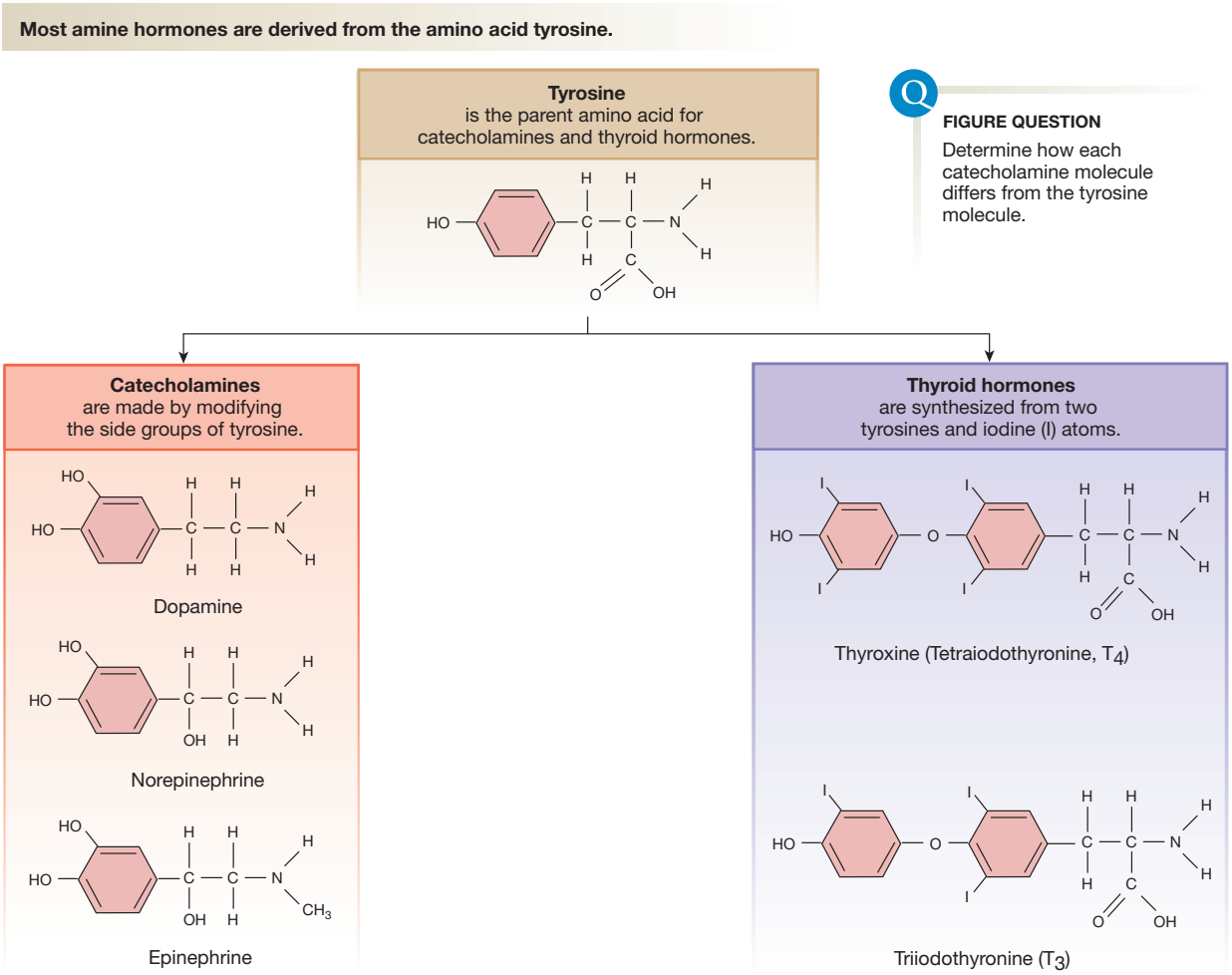


Fig. 7.6

an input signal, integration of the signal, an output signal, one or more targets, and a response. In endocrine and neuroendocrine reflexes, the output signal is a hormone or a neurohormone. Some hormones have clear stimuli that initiate their release, such as insulin secreted in response to increasing blood glucose concentrations. Other hormones have less obvious stimuli or are secreted continuously, often with a circadian rhythm.

The Endocrine Cell Is the Sensor in the Simplest Endocrine Reflexes

The simplest reflex control pathways in the endocrine system are those in which an endocrine cell directly senses a stimulus and responds by secreting its hormone. In this type of pathway, the endocrine cell acts as both sensor and integrating center. The hormone is the output signal, and the response usually serves as a *negative feedback* signal that turns off the reflex.

Parathyroid hormone (PTH) is an example of a hormone that operates via this simple endocrine reflex. PTH is secreted by four small parathyroid glands that lie behind the thyroid gland. The parathyroid endocrine cells monitor plasma Ca^{2+} concentration with the aid of G protein–coupled Ca^{2+} receptors on their cell membranes. When a certain number of receptors are bound to Ca^{2+}, PTH secretion is inhibited. If the plasma Ca^{2+} concentration falls below a certain level and fewer Ca^{2+} receptors are bound, inhibition ceases and the parathyroid cells secrete PTH (■ Fig. 7.7a). Parathyroid hormone travels through the blood to act on bone, kidney, and intestine, initiating responses that increase the concentration of Ca^{2+} in the plasma. The increase in plasma Ca^{2+} is a negative feedback signal that turns off the reflex, ending the release of parathyroid hormone.

Other hormones that follow a simple endocrine reflex pattern include the classic hormones insulin and glucagon, as well as some hormones of the diffuse endocrine system. For example, pancreatic beta cells are sensors that monitor blood

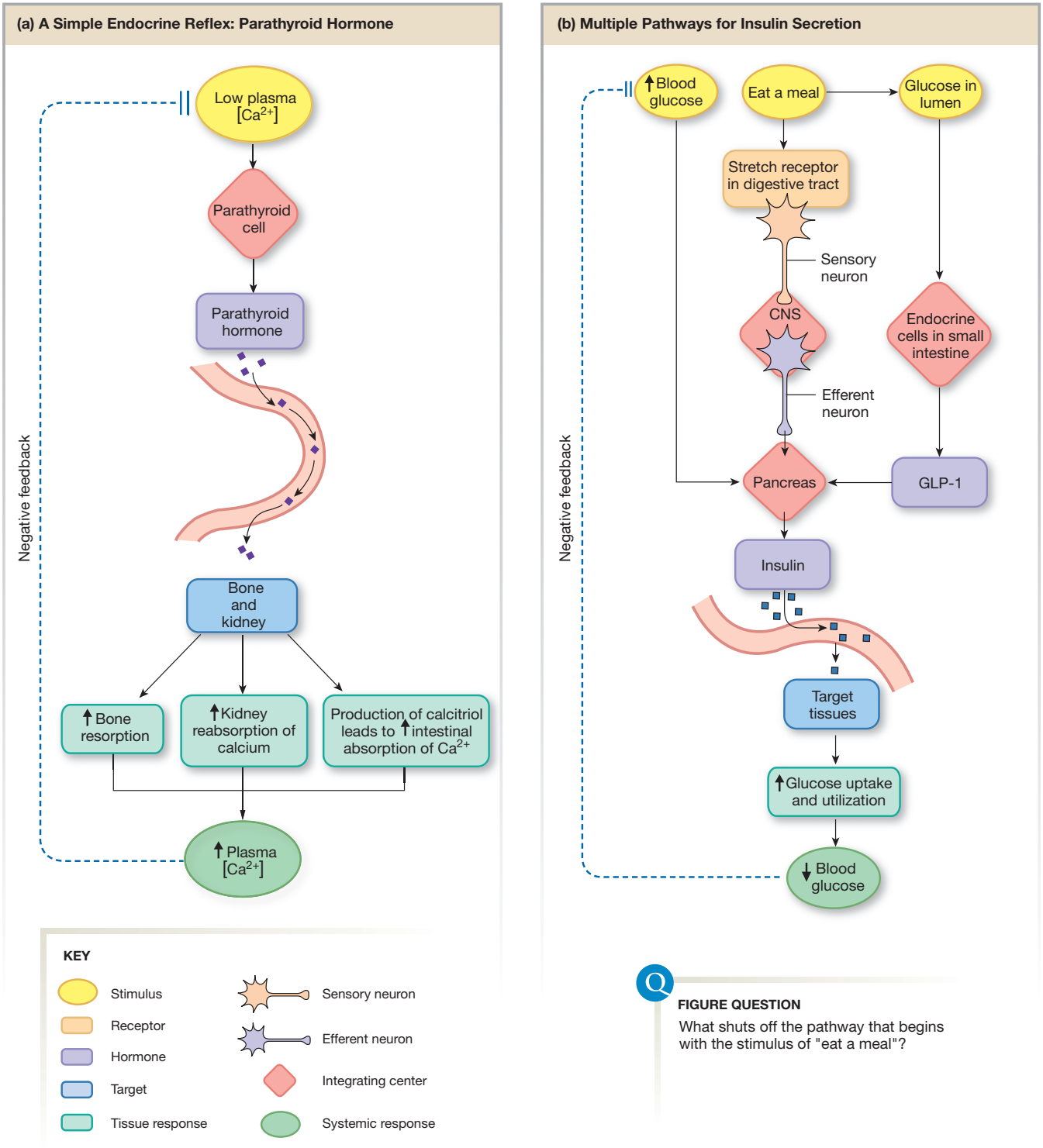


Fig. 7.7 ***Examples of simple endocrine pathways***

glucose concentration. If blood glucose increases, they respond by secreting insulin (Fig. 7.7b). Insulin travels through the blood to its target tissues, which increase their glucose uptake and metabolism. Glucose moving into cells decreases the blood concentration, which acts as a negative feedback signal that turns off the reflex, ending release of insulin.

Hormones can be released by more than one pathway, however. For example, insulin secretion can also be triggered

by signals from the nervous system or by a hormone secreted from the digestive tract after a meal is eaten (Fig. 7.7b). The pancreatic endocrine cells—the integrating center for these reflex pathways—therefore must evaluate input signals from multiple sources when "deciding" whether to secrete insulin.

Concept Check Answers: End of Chapter

7. In the blood glucose example, the increase in blood glucose corresponds to which step of a reflex pathway? Insulin secretion and the decrease in blood glucose correspond to which steps?
8. Which insulin release pathway in Figure 7.7b is a simple endocrine reflex? Which is a complex endocrine reflex? Which is a combination neural-endocrine reflex?
9. Glucagon is released from the endocrine pancreas when blood glucose levels decrease and it acts on multiple target tissues to increase blood glucose. Draw a reflex pathway to match this description.

Many Endocrine Reflexes Involve the Nervous System

The nervous system and the endocrine system overlap in both structure and function. Stimuli integrated by the central nervous system influence the release of many hormones through efferent neurons, as previously described for insulin. In addition, specialized groups of neurons secrete neurohormones, and two endocrine structures are incorporated in the anatomy of the brain: the pineal gland and the pituitary gland.

One of the most fascinating links between the brain and the endocrine system is the influence of emotions over hormone secretion and function. Physicians for centuries have recorded instances in which emotional state has influenced health or normal physiological processes. Women today know that the timing of their menstrual periods may be altered by stressors such as travel or final exams. The condition known as "failure to thrive" in infants can often be linked to environmental or emotional stress that increases secretion of some pituitary hormones and decreases production of others. The interactions among stress, the endocrine system, and the immune system are receiving intense study by scientists.

Neurohormones Are Secreted into the Blood by Neurons

As noted previously, neurohormones are chemical signals released into the blood by a neuron. The human nervous system produces three major groups of neurohormones: (1) catecholamines, (described earlier) made by modified neurons in the adrenal medulla, (2) hypothalamic neurohormones secreted from the posterior pituitary, and (3) hypothalamic neurohormones that control hormone release from the anterior pituitary. Because the latter two groups of neurohormones are associated with the pituitary gland, we describe that important endocrine structure next.

Concept Check Answers: End of Chapter

10. Catecholamines belong to which chemical class of hormone?

The Pituitary Gland Is Actually Two Fused Glands

The **pituitary gland** is a lima bean–sized structure that extends downward from the brain, connected to it by a thin stalk and cradled in a protective pocket of bone (■ Fig. 7.8a). The first accurate description of the function of the pituitary gland came from Richard Lower (1631–1691), an experimental physiologist at Oxford University. Using observations and some experiments, he theorized that substances produced in the brain passed down the stalk into the gland and from there into the blood.

Lower did not realize that the pituitary gland is actually two different tissue types that merged during embryonic development. The **anterior pituitary** is a true endocrine gland of epithelial origin, derived from embryonic tissue that formed the roof of the mouth. It is also called the *adenohypophysis* {*adeno-,* gland + *hypo-,* beneath + *phyein,* to grow}, and its hormones are *adenohypophyseal* secretions. The **posterior pituitary,** or *neurohypophysis,* is an extension of the neural tissue of the brain. It secretes neurohormones made in the *hypothalamus*, a region of the brain that controls many homeostatic functions.

The Posterior Pituitary Stores and Releases Two Neurohormones

The posterior pituitary is the storage and release site for two neurohormones: oxytocin and vasopressin (Fig. 7.8c). The neurons producing oxytocin and vasopressin are clustered together in areas of the hypothalamus known as the the *paraventricular* and *supraoptic nuclei*. (A cluster of nerve cell bodies in the central nervous system is called a nucleus.) Each neurohormone is made in a separate cell type, and the synthesis and processing follow the standard pattern for peptide hormones described earlier in this chapter.

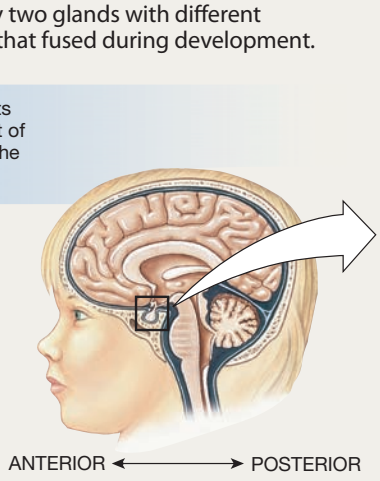
Once the neurohormones are packaged into secretory vesicles, the vesicles are transported to the posterior pituitary through long extensions of the neurons called *axons*. After vesicles reach the axon terminals, they are stored there, waiting for the release signal.

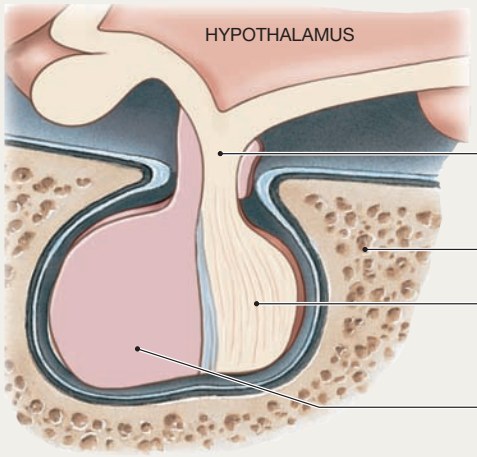
When a stimulus reaches the hypothalamus, an electrical signal passes from the neuron cell body in the hypothalamus to the *distal* (distant) end of the cell in the posterior pituitary.

The Pituitary Gland

The pituitary is actually two glands with different embryological origins that fused during development.

(a) The pituitary gland sits in a protected pocket of bone, connected to the brain by a thin stalk.





Infundibulum is the stalk that connects the pituitary to the brain.

Sphenoid bone

Posterior pituitary is an extension of the neural tissue.

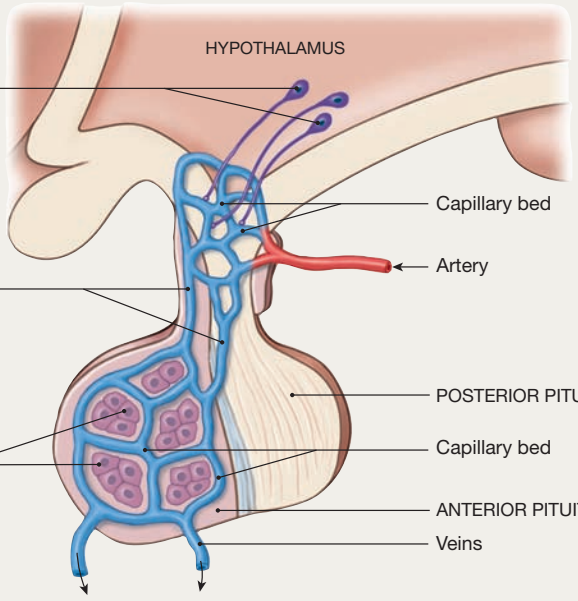
Anterior pituitary is a true endocrine gland of epithelial origin.

(b) The **anterior pituitary** is a true endocrine gland that secretes six classic hormones. Neurohormones from the hypothalamus control release of the anterior pituitary hormones. The hypothalamic hormones reach the anterior pituitary through a specialized region of the circulation called a portal system.

1 **Neurons** synthesizing trophic neurohormones release them into capillaries of the portal system.

2 **Portal vessels** carry the trophic neurohormones directly to the anterior pituitary, where they act on the endocrine cells.

3 **Endocrine cells** release their peptide hormones into the second set of capillaries for distribution to the rest of the body.



TO TARGET ORGANS

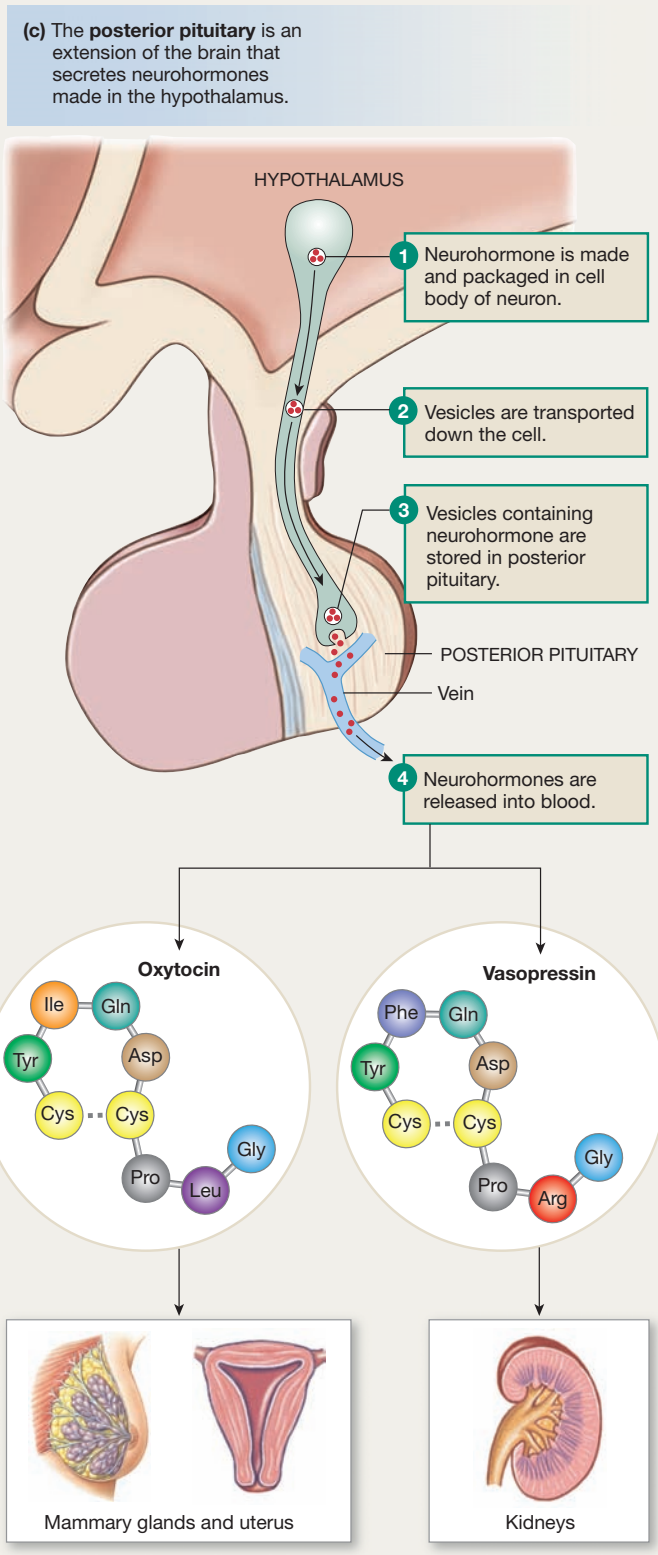
Prolactin — Mammary glands

GH — Musculoskeletal system

TSH — Thyroid gland

ACTH — Adrenal cortex

Gonadotropins (LH & FSH) — Gonads (Ovary, Testis)



Depolarization of the axon terminal opens voltage-gated Ca^{2+} channels, and Ca^{2+} enters the cell. Calcium entry triggers exocytosis and the vesicle contents are released into the circulation. Once in the blood, the neurohormones travel to their targets.

The two posterior pituitary neurohormones are composed of nine amino acids each. **Vasopressin,** also known as *antidiuretic hormone* or *ADH*, acts on the kidneys to regulate water balance in the body. In women, **oxytocin** released from the posterior pituitary controls the ejection of milk during breastfeeding and contractions of the uterus during labor and delivery.

A few neurons release oxytocin as a neurotransmitter or neuromodulator onto neurons in other parts of the brain. A number of animal experiments plus a few human experiments suggest that oxytocin plays an important role in social, sexual, and maternal behaviors. Some investigators postulate that *autism,* a developmental disorder in which patients are unable to form normal social relationships, may be related to defects in the normal oxytocin-modulated pathways of the brain.

Concept Check Answers: End of Chapter

11. What intracellular structure is used for transport of secretory vesicles within the cell?

12. Name the membrane process by which the contents of secretory vesicles are released into the extracellular fluid.

The Anterior Pituitary Secretes Six Hormones

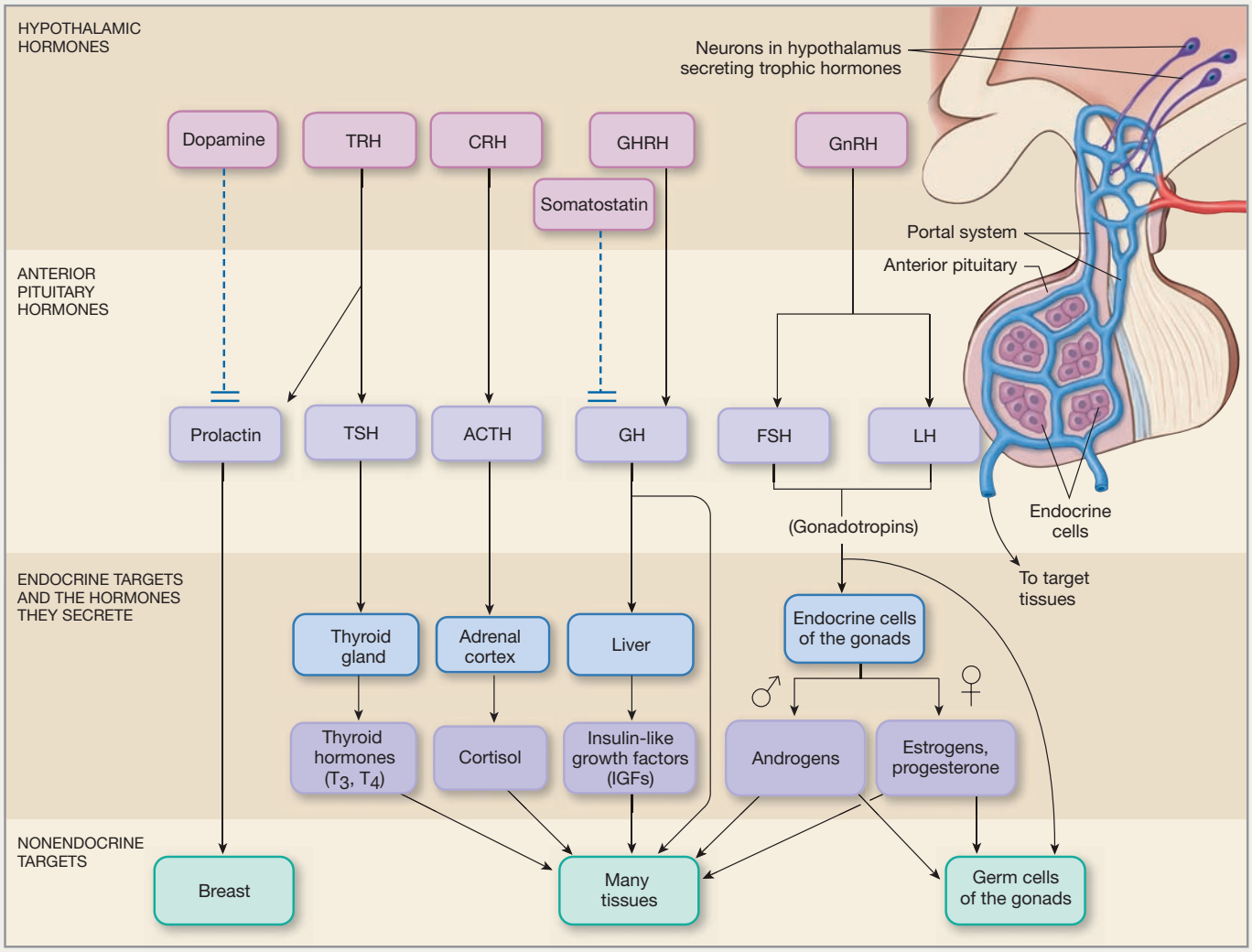
As late as 1889, it was being said in reviews of physiological function that the pituitary was of little or no use to higher vertebrates! By the early 1900s, however, researchers had discovered that animals with their anterior pituitary glands surgically removed were unable to survive more than a day or two. This observation, combined with the clinical signs associated with pituitary tumors, made scientists realize that the anterior pituitary is a major endocrine gland that secretes not one but six physiologically significant hormones: prolactin (PRL), thyrotropin (TSH), adrenocorticotropin (ACTH), growth hormone (GH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) (Fig. 7.8b). Secretion of all the anterior pituitary hormones is controlled by hypothalamic neurohormones.

The anterior pituitary hormones, their associated hypothalamic neurohormones, and their targets are illustrated in Fig 7.9. Notice that all the anterior pituitary hormones except prolactin have another endocrine gland or cell as one of their targets. A hormone that controls the secretion of another hormone is known as a **trophic hormone.**

The adjective *trophic* comes from the Greek word *trophikós,* which means "pertaining to food or nourishment" and refers to the manner in which the trophic hormone "nourishes" the target cell. Trophic hormones often have names that end with the

Hormones of the Hypothalamic–Anterior Pituitary Pathway

The hypothalamus secretes releasing hormones (-RH) and inhibiting hormones (-IH) that act on endocrine cells of the anterior pituitary to influence secretion of their hormones.



ANTERIOR PITUITARY HORMONE	HYPOTHALAMIC RELEASING HORMONE	HYPOTHALAMIC INHIBITING HORMONE
Prolactin (PRL)	Oxytocin ?	Dopamine
Thyrotropin, Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH)	
Adrenocorticotropin, Adrenocorticotrophic hormone (ACTH)	Corticotropin-releasing hormone (CRH)	
Growth hormone (GH), Somatotropin	GHRH (dominant)	Somatostatin (SS), also called growth hormone–inhibiting hormone (GHIH)
Gonadotropins: Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH)	

suffix *-tropin,* as in *gonadotropin*.* The root word to which the suffix is attached is the target tissue: the gonadotropins are hormones that are trophic to the gonads. The hypothalamic neurohormones that control release of the anterior pituitary hormones are also trophic hormones, but for historical reasons they are described as either *releasing hormones* (e.g., thyrotropin-releasing hormone) or *inhibiting hormones* (e.g., growth hormone–inhibiting hormone).

You should be aware that many of the hypothalamic and anterior pituitary hormones have multiple names as well as standardized abbreviations. For example, hypothalamic **somatostatin** (SS) is also called *growth hormone–inhibiting hormone* (GHIH), or in older scientific papers, *somatotropin release-inhibiting hormone* (SRIH). The table in Figure 7.9 lists the hypothalamic and anterior pituitary abbreviations and current alternate names.

A Portal System Delivers Hormones from Hypothalamus to Anterior Pituitary

The signals that regulate secretion of the anterior pituitary hormones come from the brain in the form of neurohormones. These hypothalamic releasing and inhibiting hormones are secreted into the circulation in the hypothalamus. They go directly from the hypothalamus to the pituitary through a special set of blood vessels known as the **hypothalamic-hypophyseal portal system** (Fig. 7.8b).

A **portal system** is a specialized region of the circulation consisting of two sets of capillaries connected in series (one after the other) by a set of larger blood vessels. There are three portal systems in the body: one in the kidneys, one in the digestive system, and this one in the brain.

Hormones secreted into a portal system have a distinct advantage over hormones secreted into the general circulation because, with a portal system, a much smaller amount of hormone can be secreted to elicit a given level of response. A dose of hormone secreted into the general circulation is rapidly diluted by the total blood volume, which is typically more than 5 L. The same dose secreted into the tiny volume of blood flowing through the portal system remains concentrated while it goes directly to its target. In this way, a small number of neurosecretory neurons in the hypothalamus can effectively control the anterior pituitary.

The minute amounts of hormone secreted into the hypothalamic-hypophyseal portal system posed a great challenge to the researchers who first isolated these hormones. Because such tiny quantities of hypothalamic-releasing hormones are secreted, Roger Guillemin and Andrew Shalley had to work with huge amounts of tissue to obtain enough hormone to analyze. Guillemin and his colleagues processed more than 50 tons of sheep hypothalami, and a major meat packer donated more than 1 million pig hypothalami to Shalley and his associates. For the final analysis, they needed 25,000 hypothalami to isolate and identify the amino acid sequence of just 1 mg of thyrotropin-releasing hormone (TRH), a tiny peptide made of three amino acids (see Fig. 7.3a). For their discovery, Guillemin and Shalley shared a Nobel prize in 1977 (see *http://nobelprize.org*).

*A few hormones whose names end in *-tropin* do not have endocrine cells as their targets. For example, melanotropin acts on pigment-containing cells in many animals.

Anterior Pituitary Hormones Control Growth, Metabolism, and Reproduction

The hormones of the anterior pituitary control so many vital functions that the pituitary is often called the master gland of the body. In general, we can say that the anterior pituitary hormones control metabolism, growth, and reproduction, all very complex processes.

One anterior pituitary hormone, **prolactin** (PRL), controls milk production in the female breast, along with other effects. In both sexes, prolactin appears to play a role in regulation of the immune system. **Growth hormone** (GH; also called *somatotropin*) affects metabolism of many tissues in addition to stimulating hormone production by the liver (■ Fig. 7.10). Prolactin and growth hormone are the only two anterior pituitary hormones whose secretion is controlled by both releasing hormones and inhibiting hormones, as you can see in Figure 7.9.

The remaining four anterior pituitary hormones all have another endocrine gland as their primary target. **Follicle-stimulating hormone** (FSH) and **luteinizing hormone** (LH), known collectively as the **gonadotropins,** were originally named for their effects on the ovaries, but both hormones are trophic on testes as well. **Thyroid-stimulating hormone** (TSH, or *thyrotropin*) controls hormone synthesis and secretion in the thyroid gland. **Adrenocorticotrophic hormone** (ACTH, or *adrenocorticotropin*) acts on certain cells of the adrenal cortex to control synthesis and release of the steroid hormone cortisol.

Concept Check Answers: End of Chapter

13. Map the pathways for:
- (a) the hypothalamic releasing hormone—prolactin—breast pattern just described
- (b) the growth hormone pathway shown in Figure 7.10

14. What is the target tissue of a hypothalamic neurohormone secreted into the hypothalamic-hypophyseal portal system?

Feedback Loops Are Different in the Hypothalamic-Pituitary Pathway

The pathways in which anterior pituitary hormones act as trophic hormones are among the most complex endocrine reflexes because they involve three integrating centers: the

The Growth Hormone Pathway

Hypothalamic growth hormone–releasing hormone (GHRH) stimulates growth hormone (GH) secretion. Growth hormone acts directly on many body tissues but also influences liver production of insulin-like growth factors (IGFs or somatomedins), another group of hormones that regulate growth.

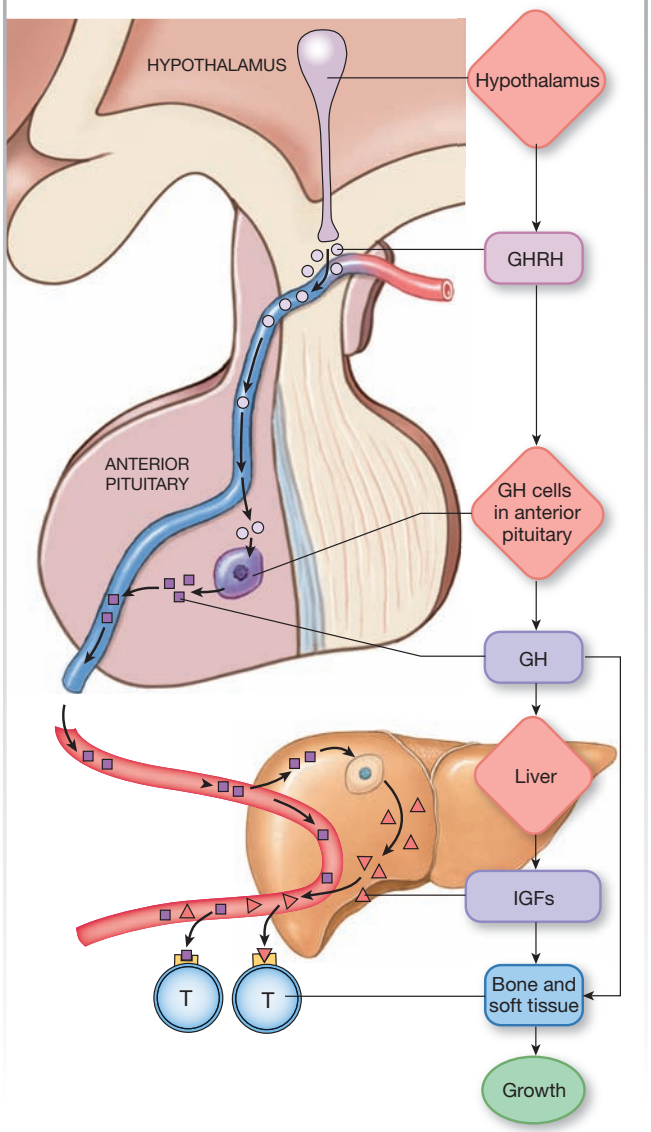


Fig. 7.10

hypothalamus, the anterior pituitary, and the endocrine target of the pituitary hormone (Fig. 7.11a). Feedback in these complex pathways follows a pattern that is different from the pattern described previously. Instead of the response acting as the negative feedback signal, the hormones themselves are the feedback signal. One reason this is necessary is that for most anterior pituitary hormone pathways, there is no single response that the body can easily monitor. The hormones of these pathways act on multiple tissues and have different, often subtle, effects in different tissues. There is no single parameter, such as blood glucose concentration, that can be the signal for negative feedback.

In hypothalamic-pituitary pathways, each hormone in the pathway feeds back to suppress hormone secretion by integrating centers earlier in the pathway. When secretion of one hormone changes, the secretion of other hormones also changes because of the feedback loops that link the hormones. In pathways with two or three hormones in sequence, the "downstream" hormone usually feeds back to suppress the hormone(s) that controlled its secretion. A major exception to this is feedback by ovarian hormones, where feedback alternates between positive and negative.

The hormones of the hypothalamic-pituitary-adrenal (HPA) pathway provide a good example of feedback loops. Cortisol secreted from the adrenal cortex feeds back to suppress secretion of hypothalamic corticotropin-releasing hormone (CRH) and adrenocorticotropin (ACTH) from the anterior pituitary (Fig. 7.11b). When the last hormone in a pathway feeds back to suppress secretion of its trophic hormones, the relationship is called **long-loop negative feedback**.

In **short-loop negative feedback**, pituitary hormones feed back to decrease hormone secretion by the hypothalamus. We see this type of feedback in cortisol secretion in Fig. 7.11b, where ACTH exerts short-loop negative feedback on the secretion of CRH. There can also be *ultra-short-loop feedback*, in which a hormone acts as an autocrine to influence the cell that secreted it.

With this hormone-based system of negative feedback, the hormones in a pathway normally stay within the range needed for an appropriate response. Feedback patterns are important in the diagnosis of endocrine pathologies, discussed later in the chapter.

RUNNING PROBLEM

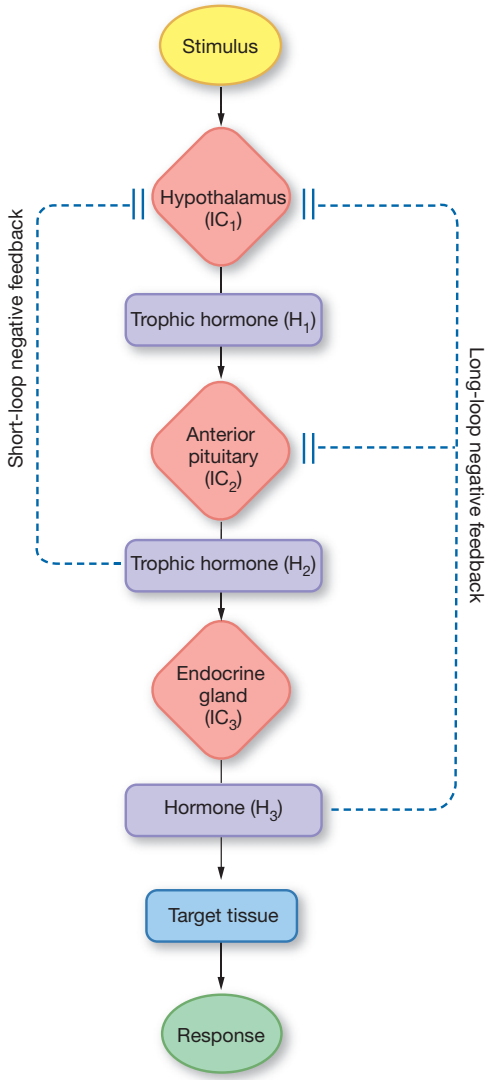
Thyroid hormone production is regulated by thyroid-stimulating hormone (TSH), a hormone secreted by the anterior pituitary. The production of TSH is in turn regulated by the neurohormone thyrotropin-releasing hormone (TRH) from the hypothalamus.

Q2: a. In a normal person, when thyroid hormone levels in the blood increase, will negative feedback increase or decrease the secretion of TSH?

b. In a person with a hyperactive gland that is producing too much thyroid hormone, would you expect the level of TSH to be higher or lower than in a normal person?

Negative Feedback in Complex Endocrine Pathways

(a) In complex endocrine pathways, the hormones of the pathway serve as negative feedback signals.



(b) Control Pathway for Cortisol Secretion
Cortisol is a steroid hormone secreted by the adrenal cortex. ACTH = corticotropin or adrenocorticotropic hormone; CRH =corticotropin-releasing hormone.

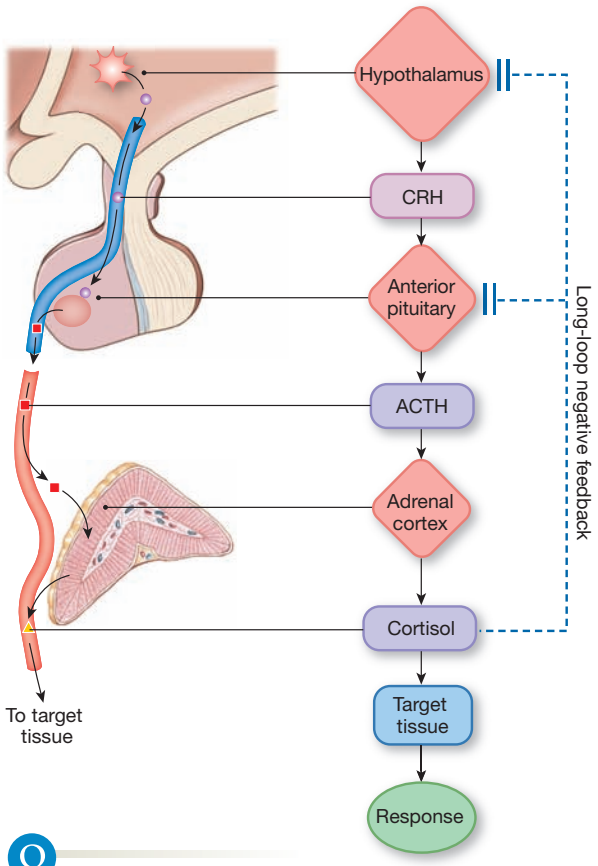


FIGURE QUESTION
Draw in the short-loop negative feedback for this pathway.

Fig. 7.11

Hormone Interactions

One of the most complicated and confusing aspects of endocrinology is the way hormones interact at their target cells. It would be simple if each endocrine reflex were a separate entity and if each cell were under the influence of only a single hormone. In many instances, however, cells and tissues are controlled by multiple hormones that may be present at the same time. Complicating the picture is the fact that multiple hormones acting on a single cell can interact in ways that cannot be predicted by knowing the individual effects of the hormone. In this section, we examine three types of hormone interaction: synergism, permissiveness, and antagonism.

In Synergism, the Effect of Interacting Hormones Is More Than Additive

Sometimes different hormones have the same effect on the body, although they may accomplish that effect through different cellular mechanisms. One example is the hormonal control

of blood glucose levels. Glucagon from the pancreas is the hormone primarily responsible for elevating blood glucose levels, but it is not the only hormone that has that effect. Cortisol raises blood glucose concentration, as does epinephrine.

What happens if two of these hormones are present in a target cell at the same time, or if all three hormones are secreted at the same time? You may expect their effects to be additive. In other words, if a given amount of epinephrine elevates blood glucose 5 mg/100 mL blood, and glucagon elevates blood glucose 10 mg/100 mL blood, you may expect both hormones acting at the same time to elevate blood glucose 15 mg/100 mL blood (5 + 10).

Frequently, however, two (or more) hormones interact at their targets so that the combination yields a result that is greater than additive (1 + 2 > 3). This type of interaction is called **synergism**. For our epinephrine/glucagon example, a synergistic reaction would be:

epinephrine	elevates blood glucose	5 mg/100 mL blood
glucagon	elevates blood glucose	10 mg/100 mL blood
epinephrine + glucagon	elevate blood glucose	22 mg/100 mL blood

In other words, the combined effect of the two hormones is greater than the sum of the effects of the two hormones individually.

An example of synergism involving epinephrine, glucagon, and cortisol is shown in Figure 7.12. The cellular mechanisms that underlie synergistic effects are not always clear, but with peptide hormones, synergism is often linked to overlapping effects on second messenger systems.

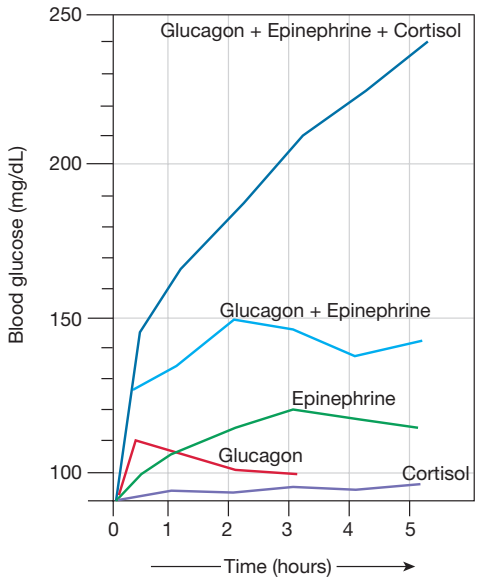


Fig. 7.12 ***Synergism.*** This graph shows the effect of hormone infusions on blood glucose levels. The effects of combined hormones are greater than the summed effects of the individual hormones, indicating synergistic relationships. (Data adapted from Eigler *et al., J. Clin. Invest.* 63: 114, 1979.)

RUNNING PROBLEM

Ben Crenshaw was diagnosed with Graves' disease, one form of hyperthyroidism. The goal of treatment is to reduce thyroid hormone activity, and Ben's physician offered him several alternatives. One treatment involves drugs that prevent the thyroid gland from using iodine. Another treatment is a single dose of radioactive iodine that destroys the thyroid tissue. A third treatment is surgical removal of all or part of the thyroid gland. Ben elected initially to use the thyroid-blocking drug. Several months later he was given radioactive iodine.

Q3: Why is radioactive iodine (rather than some other radioactive element, such as cobalt) used to destroy thyroid tissue?

Synergism is not limited to hormones. It can occur with any two (or more) chemicals in the body. Pharmacologists have developed drugs with synergistic components. For example, the effectiveness of the antibiotic penicillin is enhanced by the presence of clavulanic acid in the same pill.

A Permissive Hormone Allows Another Hormone to Exert Its Full Effect

In **permissiveness,** one hormone cannot fully exert its effects unless a second hormone is present (0 + 2 > 2). For example, maturation of the reproductive system is controlled by gonadotropin-releasing hormone from the hypothalamus, gonadotropins from the anterior pituitary, and steroid hormones from the gonads. However, if thyroid hormone is not present in sufficient amounts, maturation of the reproductive system is delayed. Because thyroid hormone by itself cannot stimulate maturation of the reproductive system, thyroid hormone is considered to have a permissive effect on sexual maturation.

The results of this interaction can be summarized as follows:

thyroid hormone alone	no development of reproductive system
reproductive hormones alone	delayed development of reproductive system
reproductive hormones with adequate thyroid hormone	normal development of reproductive system

The molecular mechanisms responsible for permissiveness are not well understood in most instances.

Antagonistic Hormones Have Opposing Effects

In some situations, two molecules work against each other, one diminishing the effectiveness of the other. This tendency of one substance to oppose the action of another is called *antagonism*. Antagonism may result when two molecules compete for the same receptor. When one molecule binds to the receptor but does not activate it, that molecule acts as a *competitive inhibitor*, or antagonist, to the other molecule. This type of receptor antagonism has been put to use in the development of pharmaceutical compounds, such as the estrogen receptor antagonist *tamoxifen*, which is used to treat breast cancers that are stimulated by estrogen.

In endocrinology, two hormones are considered *functional antagonists* if they have opposing physiological actions. For example, both glucagon and growth hormone raise the concentration of glucose in the blood, and both are antagonistic to insulin, which lowers the concentration of glucose in the blood. Hormones with antagonistic actions do not necessarily compete for the same receptor. Instead, they may act through different metabolic pathways, or one hormone may decrease the number of receptors for the opposing hormone. For example, evidence suggests that growth hormone decreases the number of insulin receptors, providing part of its functional antagonistic effects on blood glucose concentration.

The synergistic, permissive, and antagonistic interactions of hormones make the study of endocrinology both challenging and intriguing. With this brief survey of hormone interactions, you have built a solid foundation for learning more about hormone interactions.

Endocrine Pathologies

As one endocrinologist said, "There are no good or bad hormones. A balance of hormones is important for a healthy life. . . . Unbalance leads to diseases."* We can learn much about the normal functions of a hormone by studying the diseases caused by hormone imbalances. There are three basic patterns of endocrine pathology: hormone excess, hormone deficiency, and abnormal responsiveness of target tissues to a hormone.

To illustrate endocrine pathologies, we will use a single example, that of cortisol production by the adrenal cortex (see Fig. 7.11b). This is a complex reflex pathway that starts with the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates release of adrenocorticotropin (ACTH) from the anterior pituitary. ACTH in turn controls the synthesis and release of cortisol from the adrenal cortex. As in other homeostatic reflex pathways, negative feedback shuts off the pathway. As cortisol increases, it acts as a negative feedback signal, causing the pituitary and hypothalamus to decrease their output of ACTH and CRH, respectively.

*W. König, preface to *Peptide and Protein Hormones,* New York: VCH Publishers, 1993.

Hypersecretion Exaggerates a Hormone's Effects

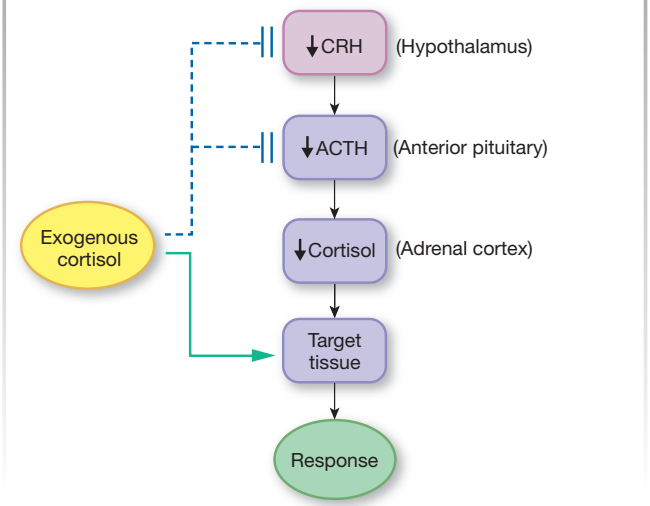
If a hormone is present in excessive amounts, the normal effects of the hormone are exaggerated. Most instances of hormone excess are due to **hypersecretion.** There are numerous causes of hypersecretion, including benign tumors (*adenomas*) and cancerous tumors of the endocrine glands. Occasionally, nonendocrine tumors secrete hormones.

Any substance coming from outside the body is referred to as *exogenous* {*exo-,* outside}, and sometimes a patient may exhibit signs of hypersecretion as the result of medical treatment with an exogenous hormone or agonist. In this case, the condition is said to be *iatrogenic,* or physician-caused {*iatros,* healer + *-gen,* to be born}. It seems simple enough to correct the hormone imbalance by stopping treatment with the exogenous hormone, but this is not always the case.

In our example, exogenous cortisol in the body acts as a negative feedback signal, just as cortisol produced within the body would, shutting off the production of CRH and ACTH (■ Fig. 7.13). Without the trophic "nourishing" influence of ACTH, the body's own cortisol production shuts down. If the pituitary remains suppressed and the adrenal cortex is deprived of ACTH long enough, the cells of both glands shrink and lose their ability to manufacture ACTH and cortisol. The loss of cell mass is known as **atrophy** {*a-,* without + *trophikós,* nourishment}.

If the cells of an endocrine gland atrophy because of exogenous hormone administration, they may be very slow or totally unable to regain normal function when the treatment with exogenous hormone is stopped. As you may know, steroid hormones can be used to treat poison ivy and severe allergies. However, when treatment is complete, the dosage must be tapered off gradually to allow the pituitary and adrenal gland to

Exogenous hormone has the same negative feedback effect as endogenous hormone.



■ **Fig. 7.13**

work back up to normal hormone production. As a result, packages of steroid pills direct patients ending treatment to take six pills one day, five the day after that, and so on. Low-dose, over-the-counter steroid creams usually do not pose a risk of feedback suppression when used as directed.

Hyposecretion Diminishes or Eliminates a Hormone's Effects

Symptoms of hormone deficiency occur when too little hormone is secreted (**hyposecretion**). Hyposecretion may occur anywhere along the endocrine control pathway, in the hypothalamus, pituitary, or other endocrine glands. For example, hyposecretion of thyroid hormone may occur if there is insufficient dietary iodine for the thyroid gland to manufacture the iodinated hormone. The most common cause of hyposecretion pathologies is atrophy of the gland due to some disease process.

Negative feedback pathways are affected in hyposecretion, but in the opposite direction from hypersecretion. The absence of negative feedback causes trophic hormone levels to rise as the trophic hormones attempt to make the defective gland increase its hormone output. For example, if the adrenal cortex atrophies as a result of tuberculosis, cortisol production diminishes. The hypothalamus and anterior pituitary sense that cortisol levels are below normal, so they increase secretion of CRH and ACTH, respectively, in an attempt to stimulate the adrenal gland into making more cortisol.

Receptor or Second Messenger Problems Cause Abnormal Tissue Responsiveness

Endocrine diseases do not always arise from problems with endocrine glands. They may also be triggered by changes in the responsiveness of target tissues to the hormones. In these situations, the target tissues show abnormal responses even though the hormone levels may be within the normal range. Changes in the target tissue response are usually caused by abnormal interactions between the hormone and its receptor or by alterations in signal transduction pathways.

Down-Regulation If hormone secretion is abnormally high for an extended period of time, target cells may *down-regulate* (decrease the number of) their receptors in an effort to diminish their responsiveness to excess hormone. **Hyperinsulinemia** {*hyper-,* elevated + insulin + *-emia,* in the blood} is a classic example of down-regulation in the endocrine system. In this disorder, sustained high levels of insulin in the blood cause target cells to remove insulin receptors from the cell membrane. Patients suffering from hyperinsulinemia may show signs of diabetes despite their high blood insulin levels.

Receptor and Signal Transduction Abnormalities Many forms of inherited endocrine pathologies can be traced to problems with hormone action in the target cell. Endocrinologists once believed that these problems were rare, but they are being recognized more frequently as scientists increase their understanding of receptors and signal transduction mechanisms.

Some pathologies are due to problems with the hormone receptor. If a mutation alters the protein sequence of the receptor, the cellular response to receptor-hormone binding may be altered. In other mutations, the receptors may be absent or completely nonfunctional. For example, in *testicular feminizing syndrome,* androgen receptors are nonfunctional in the male fetus because of a genetic mutation. As a result, androgens produced by the developing fetus are unable to influence development of the genitalia. The result is a child who appears to be female but lacks a uterus and ovaries.

Genetic alterations in signal transduction pathways can lead to symptoms of hormone excess or deficiency. In the disease called *pseudohypoparathyroidism* {*pseudo-,* false + *hypo-,* decreased + parathyroid + *-ism,* condition or state of being}, patients show signs of low parathyroid hormone even though blood levels of the hormone are normal or elevated. These patients have inherited a defect in the G protein that links the hormone receptor to the cAMP amplifier enzyme, adenylyl cyclase. Because the signal transduction pathway does not function, target cells are unable to respond to parathyroid hormone, and signs of hormone deficiency appear.

Diagnosis of Endocrine Pathologies Depends on the Complexity of the Reflex

Diagnosis of endocrine pathologies may be simple or complicated, depending on the complexity of the reflex. For example, consider a simple endocrine reflex, such as that for parathyroid hormone. If there is too much or too little hormone, the problem can arise in only one location: the parathyroid glands (see Figure 7.10). However, with complex hypothalamic-pituitary-endocrine gland reflexes, the diagnosis can be much more difficult.

If a pathology (deficiency or excess) arises in the last endocrine gland in a reflex, the problem is considered to be a **primary pathology**. For example, if a tumor in the adrenal cortex begins to produce excessive amounts of cortisol, the resulting condition is called *primary hypersecretion*. If dysfunction occurs in one of the tissues producing trophic hormones, the problem is a **secondary pathology**. For example, if the pituitary is damaged because of head trauma and ACTH secretion diminishes, the resulting cortisol deficiency is considered to be *secondary hyposecretion* of cortisol.

The diagnosis of pathologies in complex endocrine pathways depends on understanding negative feedback in the control pathway. ■ Figure 7.14 shows three possible causes of excess cortisol secretion. To determine which is the correct *etiology* (cause) of the disease in a particular patient, the clinician must assess the levels of the three hormones in the control pathway.

If cortisol levels are high but levels of both trophic hormones are low, the problem must be a primary disorder (Figure 7.14a). There are two possible explanations: endogenous

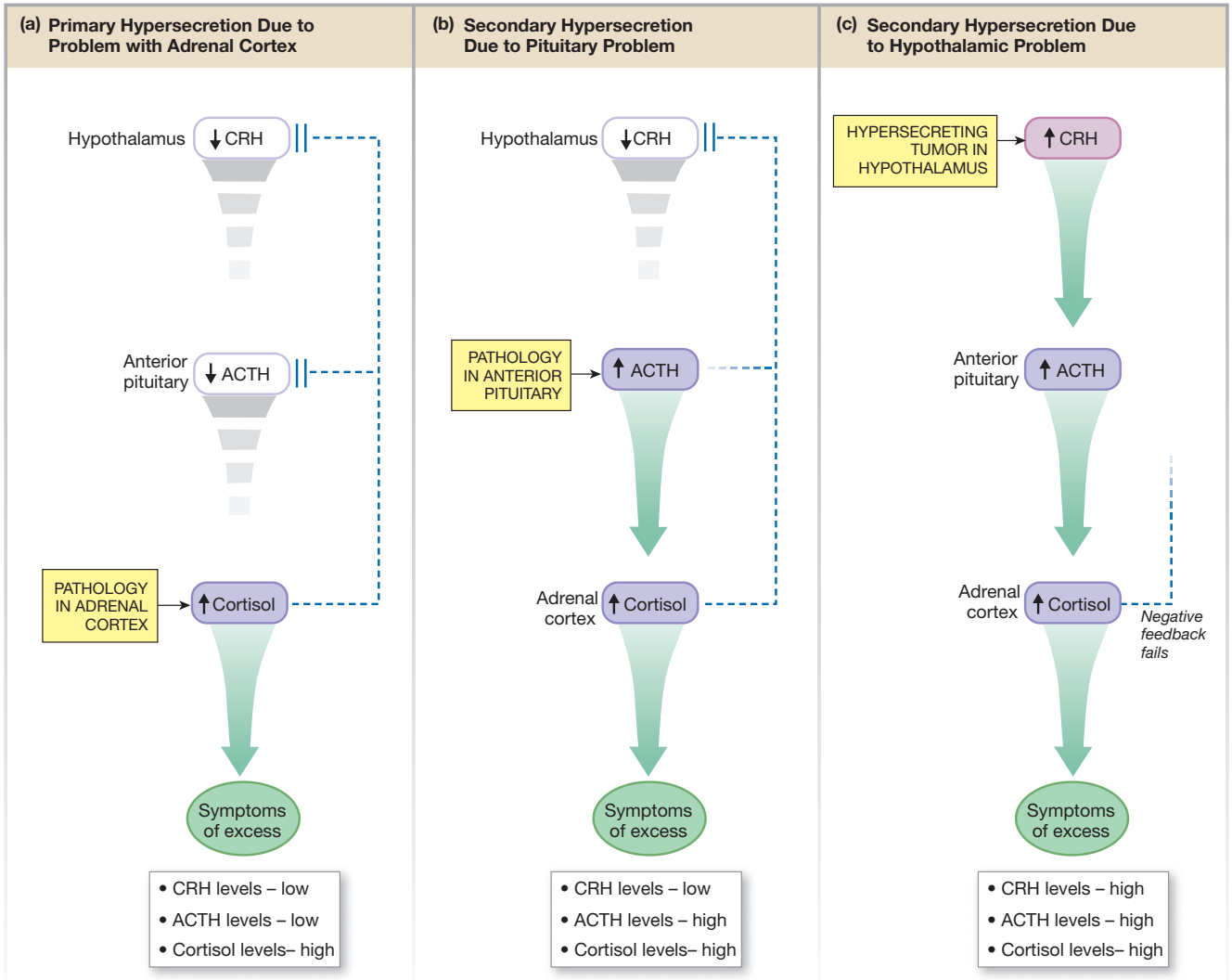


Fig. 7.14 ***Primary and secondary hypersecretion of cortisol.*** When there is a pathology in an endocrine gland, negative feedback fails.

cortisol hypersecretion or the exogenous administration of cortisol for therapeutic reasons (see Figure 7.13). In either case, high levels of cortisol act as a negative feedback signal that shuts off production of CRH and ACTH. The pattern of high cortisol with low trophic hormone levels points to a primary disorder.

When the problem is endogenous—an adrenal tumor that is secreting cortisol in an unregulated fashion—the normal control pathways are totally ineffective. Although negative feedback shuts off production of the trophic hormones, the tumor is not dependent on them for cortisol production, so cortisol secretion continues in their absence. The tumor must be removed or suppressed before cortisol secretion can be controlled.

Figure 7.14b shows a secondary hypersecretion of cortisol due to an ACTH-secreting tumor of the pituitary. The high levels of ACTH cause high cortisol production, but in this example the high

RUNNING PROBLEM

Graves' disease is one form of thyroid gland hyperactivity. For this reason, people with Graves' disease have elevated thyroxine levels in the blood. Their TSH levels are very low.

Q4: If levels of TSH are low and thyroxine levels are high, is Graves' disease a primary disorder or a secondary disorder (one that arises as a result of a problem with the anterior pituitary or the hypothalamus)? Explain your answer.

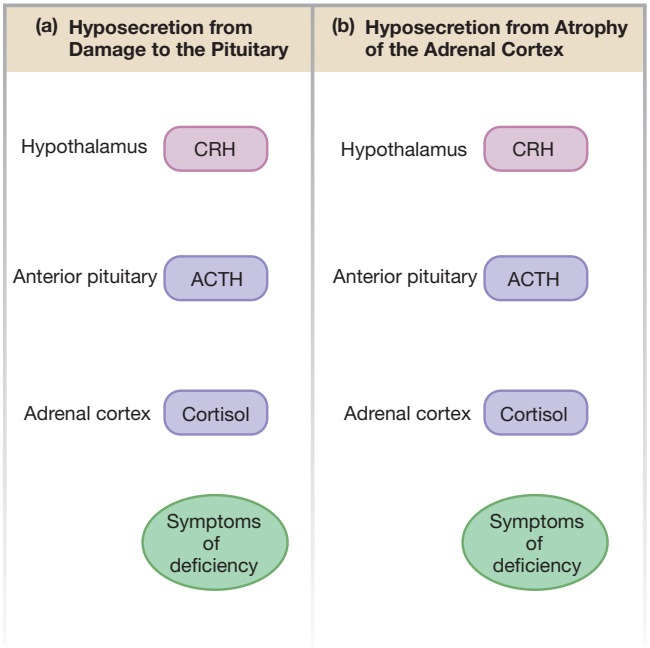


FIGURE QUESTION

For each condition, use arrows to indicate whether levels of the three hormones in the pathway will be increased, decreased, or unchanged. Draw in negative feedback loops where functional.

Fig. 7.15 ***Patterns of hormone secretion in hypocortisolism***

cortisol level has a negative feedback effect on the hypothalamus, decreasing production of CRH. The combination of low CRH and high ACTH isolates the problem to the pituitary. This pathology is responsible for about two-thirds of cortisol hypersecretion *syndromes* {*syn-*, together + *-drome,* running; a combination of symptoms characteristic of a particular pathology}.

If the problem is overproduction of CRH by the hypothalamus (Figure 7.14c) CRH levels are higher than normal. High CRH in turn causes high ACTH, which in turn causes high cortisol. This is therefore secondary hypersecretion arising from a problem in the hypothalamus. In clinical practice, hypothalamic hypersecretion pathologies are rare.

Figure 7.15 shows two possible etiologies for hyposecretion of cortisol. You can apply your understanding of negative feedback in the hypothalamic-pituitary control pathway to predict whether the levels of CRH, ACTH, and cortisol will be high or low in each case.

Hormone Evolution

Chemical signaling is an ancient method for communication and the maintenance of homeostasis. As scientists sequence the genomes of diverse species, they are discovering that in many cases hormone structure and function have changed amazingly little from the most primitive vertebrates through the mammals. In fact, hormone signaling pathways that were once considered exclusive to vertebrates, such as those for thyroid hormones and insulin, have now been shown to play physiological or developmental roles in invertebrates such as echinoderms and insects. This *evolutionary conservation* of hormone function is also demonstrated by the fact that some hormones from other organisms have biological activity when administered to humans. By studying which portions of a hormone molecule do not change from species to species, scientists have acquired important clues to aid in the design of agonist and antagonist drugs.

The ability of nonhuman hormones to work in humans was a critical factor in the birth of endocrinology. When Best and Banting discovered insulin in 1921 and the first diabetic patients were treated with the hormone, the insulin was extracted from cow, pig, or sheep pancreases. Before the mid-1980s slaughterhouses were the major source of insulin for the medical profession. Now, with genetic engineering, the human gene for insulin has been inserted into bacteria, which then synthesize the hormone, providing us with a plentiful source of human insulin.

Although many hormones have the same function in most vertebrates, a few hormones that play a significant role in the physiology of lower vertebrates seem to be evolutionarily "on their way out" in humans. Calcitonin is a good example of such a hormone. Although it plays a role in calcium metabolism in fish, calcitonin apparently has no significant influence on daily calcium balance in adult humans. Neither calcitonin deficiency nor calcitonin excess is associated with any pathological condition or symptom.

Although calcitonin is not a significant hormone in humans, the calcitonin gene does code for a biologically active protein. In the brain, cells process mRNA from the calcitonin gene to make

RUNNING PROBLEM

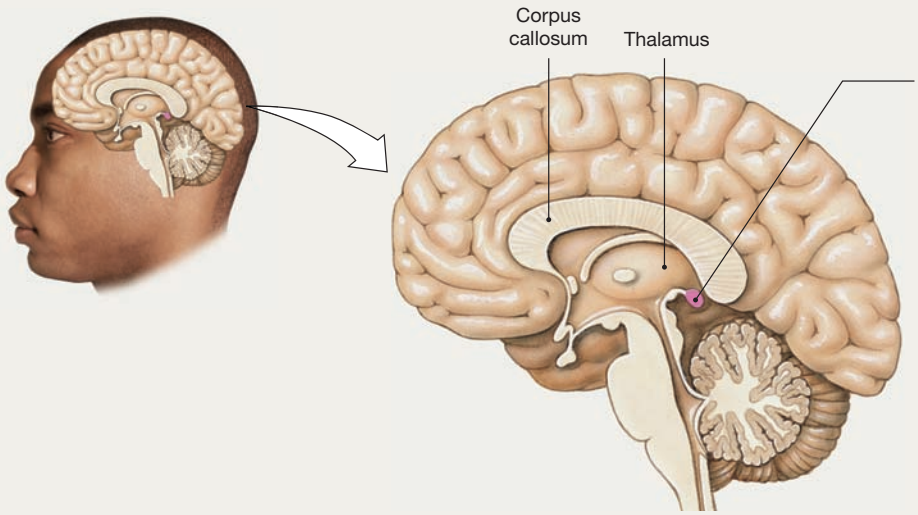
Researchers have learned that Graves' disease is an autoimmune disorder in which the body fails to recognize its own tissue. In this condition, the body produces antibodies that mimic TSH and bind to the TSH receptor, turning it on. This false signal "fools" the thyroid gland into overproducing thyroid hormone. More women than men are diagnosed with Graves' disease, perhaps because of the influence of female hormones on thyroid function. Stress and other environmental factors have also been implicated in hyperthyroidism.

Q5: Antibodies are proteins that bind to the TSH receptor. From that information, what can you conclude about the cellular location of the TSH receptor?

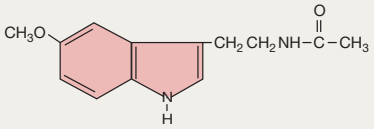
Q6: In Graves' disease, why doesn't negative feedback shut off thyroid hormone production before it becomes excessive?

■ Fig. 7.16 *FOCUS ON ...*

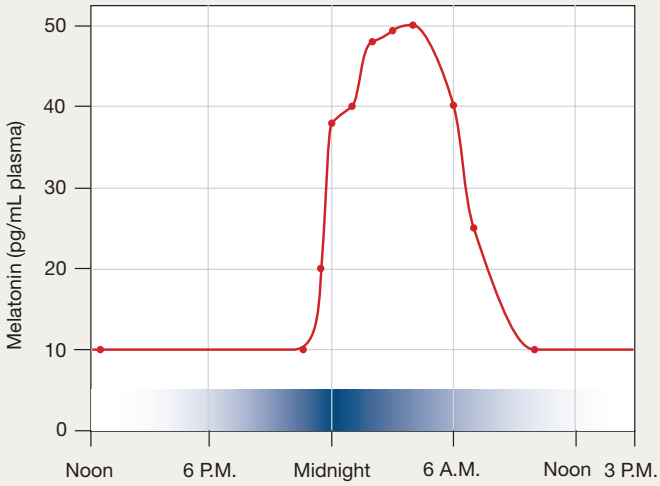
The Pineal Gland



The **pineal gland** is a pea-sized structure buried deep in the brain of humans. Nearly 2000 years ago, this "seat of the soul" was thought to act as a valve that regulated the flow of vital spirits and knowledge into the brain. By 1950, however, scientists had decided that it was a vestigial structure with no known function.



Melatonin is an amino acid–derived hormone made from tryptophan.



Melatonin is the "darkness hormone," secreted at night as we sleep. It is the chemical messenger that transmits information about light-dark cycles to the brain center that governs the body's biological clock.

(Adapted from J. Arendt, *Clin. Endocrinol.* 29:205–229, 1988.)

About 1957 one of the wonderful coincidences of scientific research occurred. An investigator heard about a factor in beef pineal glands that could lighten the skin of amphibians. Using the classical methodology of endocrinology, he obtained pineal glands from a slaughterhouse and started making extracts. His biological assay consisted of dropping pineal extracts into bowls of live tadpoles to see if their skin color blanched. Several years and hundreds of thousands of pineal glands later, he had isolated a small amount of melatonin.

Fifty years later, we are still learning about the functions of melatonin in humans. In addition to its role in sleep-wake cycles and the body's internal clock, scientists have evidence that melatonin is a powerful antioxidant. Some studies using mouse models of Alzheimer's disease suggest that melatonin may help slow the progression of the disease. Melatonin has also been linked to sexual function, the onset of puberty, and depression in the darker winter months (seasonal affective disorder, or SAD). In 2011 there were over 100 active clinical trials in the United States testing the efficacy of melatonin in treating disorders associated with sleep disturbances and depression.

In 2009 European authorities approved the use of a melatonin receptor agonist, *agomelatine*, for treating major depression. The U.S. Food and Drug Administration has been slower to approve the drug, and it is currently being tested in Phase II and Phase III clinical trials in the United States. Phase II trials are usually placebo-controlled, double-blind studies. Phase III trials include more patients and some uncontrolled studies. Some Phase III studies are "open-label," meaning that the patients and healthcare providers know what drug is being administered.

a peptide known as *calcitonin gene-related peptide* (CGRP), which acts as a neurotransmitter. CGRP can act as a powerful dilator of blood vessels, and one recent study found that a CGRP receptor antagonist effectively treated migraine headaches, which occur when cerebral blood vessels dilate (vasodilation). The ability of one gene to produce multiple peptides is one reason research is shifting from genomics to physiology and *proteomics* (the study of the role of proteins in physiological function).

Some endocrine structures that are important in lower vertebrates are *vestigial* {*vestigium,* trace} in humans, meaning that in humans these structures are present as minimally functional glands. For example, *melanocyte-stimulating hormone* (MSH) from the intermediate lobe of the pituitary controls pigmentation in reptiles and amphibians. However, adult humans have only a vestigial intermediate lobe and normally do not have measurable levels of MSH in their blood.

In the research arena, *comparative endocrinology*—the study of endocrinology in nonhuman organisms—has made significant contributions to our quest to understand the human body. Many of our models of human physiology are based on research carried out in fish or frogs or rats, to name a few. For example, the pineal gland hormone *melatonin* (■ Fig. 7.16) was

discovered through research using tadpoles. Many small nonhuman vertebrates have short life cycles that facilitate studying aging or reproductive physiology. Genetically altered mice (transgenic or knockout mice) have provided researchers valuable information about proteomics.

Opponents of animal research argue that scientists should not experiment with animals at all and should use only cell cultures and computer models. Cell cultures and models are valuable tools and can be helpful in the initial stages of medical research, but at some point new drugs and procedures must be tested on intact organisms prior to clinical trials in humans. Responsible scientists follow guidelines for appropriate animal use and limit the number of animals killed to the minimum needed to provide valid data.

In this chapter we have examined how the endocrine system with its hormones helps regulate the slower processes in the body. The nervous system takes care of the more rapid responses needed to maintain homeostasis.

RUNNING PROBLEM CONCLUSION

Graves' Disease

In this running problem, you learned that in Graves' disease, thyroid hormone levels are high because an immune-system protein mimics TSH. You also learned that the thyroid gland concentrates iodine for synthesis of thyroid hormones and that radioactive iodine can concentrate in the gland and destroy the thyroid cells. Ben Crenshaw's treatment for Graves' disease was successful. He went on to win the Masters Tournament for a second time in 1995 and he still plays golf professionally today.

Graves' disease is the most common form of hyperthyroidism. Other famous people who have suffered from it include former U.S. President George H. W. Bush and First Lady Barbara Bush. To learn more about Graves' disease and other thyroid conditions, visit the Endocrine Society's Hormone Foundation web site at *www.hormone.org* or the American Thyroid Association at *www.thyroid.org*. Check your answers to the problem questions by comparing them to the information in the summary table below.

Question	Facts	Integration and Analysis
1a. To which of the three classes of hormones do thyroid hormones belong?	The three classes of hormones are peptides, steroids, and amino-acid derivatives.	Thyroid hormones are made from the amino acid tyrosine; therefore, they are amino-acid derivatives.
1b. If a person's diet is low in iodine, predict what happens to thyroxine production.	The thyroid gland concentrates iodine and combines it with the amino acid tyrosine to make thyroid hormones.	If iodine is lacking in the diet, a person is unable to make thyroid hormones.
2a. In a normal person, when thyroid hormone levels in the blood increase, will negative feedback increase or decrease the secretion of TSH? **2b.** In a person with a hyperactive gland that is producing too much thyroid hormone, would you expect the level of TSH to be higher or lower than in a normal person?	Negative feedback shuts off response loops.	Normally negative feedback decreases TSH secretion. If thyroid hormone is high, you would expect strong negative feedback and even lower levels of TSH.
3. Why is radioactive iodine (rather than some other radioactive element, such as cobalt) used to destroy thyroid tissue?	The thyroid gland concentrates iodine to make thyroid hormones.	Radioactive iodine is concentrated in the thyroid gland and therefore selectively destroys that tissue. Other radioactive elements distribute more widely throughout the body and may harm normal tissues.
4. If levels of TSH are low and thyroxine levels are high, is Graves' disease a primary disorder or a secondary disorder (one that arises as a result of a problem with the anterior pituitary or the hypothalamus)? Explain your answer.	In secondary hypersecretion disorders, you would expect the levels of the hypothalamic and/or anterior pituitary trophic hormones to be elevated.	In Graves' disease, TSH from the anterior pituitary is very low. Therefore, the oversecretion of thyroid hormones is not the result of elevated TSH. This means that Graves' disease is a primary disorder that is caused by a problem in the thyroid gland itself.

RUNNING PROBLEM CONCLUSION *(continued)*

Question	Facts	Integration and Analysis
5. Antibodies are proteins that bind to the TSH receptor. From that information, what can you conclude about the cellular location of the TSH receptor?	Receptors may be membrane receptors or intracellular receptors. Proteins cannot cross the cell membrane.	The TSH receptor is a membrane receptor. It uses the cAMP second messenger pathway for signal transduction.
6. In Graves' disease, why doesn't negative feedback shut off thyroid hormone production before it becomes excessive?	In normal negative feedback, increasing levels of thyroid hormone shut off TSH secretion. Without TSH stimulation, the thyroid stops producing thyroid hormone.	In Graves' disease, high levels of thyroid hormone have shut off endogenous TSH production. However, the thyroid gland still produces hormone in response to the binding of antibody to the TSH receptor. In this situation, negative feedback fails to correct the problem.

Chapter Summary

This chapter introduced you to the endocrine system and the role it plays in *communication* and *control* of physiological processes. As you've seen before, the *compartmentalization of the body* into intracellular and extracellular compartments means that special mechanisms are required to enable signals to pass from one compartment to the other. The chapter also presented basic patterns that you will encounter again as you study various organ systems: differences among the three chemical classes of hormones, reflex pathways for hormones, types of hormone interactions, and endocrine pathologies.

Hormones

iP Endocrine System: Endocrine System Review

1. The specificity of a hormone depends on its receptors and their associated signal transduction pathways.
2. A **hormone** is a chemical secreted by a cell or group of cells into the blood for transport to a distant target, where it is effective at very low concentrations.
3. **Pheromones** are chemical signals secreted into the external environment.
4. Hormones bind to receptors to initiate responses known as the **cellular mechanism of action.**
5. Hormone activity is limited by terminating secretion, removing hormone from the blood, or terminating activity at the target cell.
6. The rate of hormone breakdown is indicated by a hormone's **half-life.**

The Classification of Hormones

iP Endocrine System: Biochemistry, Secretion and Transport of Hormones, and the Actions of Hormones on Target Cells

7. There are three types of hormones: **peptide/protein hormones,** composed of three or more amino acids; **steroid hormones,** derived from cholesterol; and **amino acid–derived hormones,** derived from either tyrosine (e.g., catecholamines and thyroid hormones) or tryptophan (e.g., melatonin). (Tbl. 7.1)
8. Peptide hormones are made as inactive **preprohormones** and processed to **prohormones.** Prohormones are chopped into active hormone and peptide fragments that are co-secreted. (Fig. 7.3)

9. Peptide hormones dissolve in the plasma and have a short half-life. They bind to surface receptors on their target cells and initiate rapid cellular responses through signal transduction. In some instances, peptide hormones also initiate synthesis of new proteins. (Fig. 7.4)
10. Steroid hormones are synthesized as they are needed. They are hydrophobic, and most steroid hormones in the blood are bound to protein carriers. Steroids have an extended half-life. (Fig. 7.5)
11. Traditional steroid receptors are inside the target cell, where they turn genes on or off and direct the synthesis of new proteins. Cell response is slower than with peptide hormones. Steroid hormones may bind to membrane receptors and have nongenomic effects. (Fig. 7.5)
12. Amine hormones may behave like typical peptide hormones or like a combination of a steroid hormone and a peptide hormone. (Fig. 7.6)

Control of Hormone Release

iP Endocrine System: The Hypothalamic-Pituitary Axis

13. Classic endocrine cells act as both sensor and integrating center in the simple reflex pathway. (Fig. 7.7)
14. Many endocrine reflexes involve the nervous system, either through **neurohormones** or through neurons that influence hormone release.
15. The pituitary gland is composed of the anterior pituitary (a true endocrine gland) and the posterior pituitary (an extension of the brain). (Fig. 7.8a)
16. The posterior pituitary releases two neurohormones, oxytocin and vasopressin, that are made in the hypothalamus. (Fig. 7.8c)
17. **Trophic hormones** control the secretion of other hormones.
18. Hypothalamic releasing hormones and inhibiting hormones control the secretion of anterior pituitary hormones. (Fig. 7.9)
19. The hypothalamic trophic hormones reach the pituitary through the **hypothalamic-hypophyseal portal system.** (Fig. 7.9)
20. There are six anterior pituitary hormones: prolactin, growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and adrenocorticotrophic hormone. (Fig. 7.9)
21. In complex endocrine reflexes, hormones of the pathway act as negative feedback signals. (Fig. 7.11)

Hormone Interactions

22. If the combination of two or more hormones yields a result that is greater than additive, the interaction is **synergism.** (Fig. 7.12)
23. If one hormone cannot exert its effects fully unless a second hormone is present, the second hormone is said to be **permissive** to the first.
24. If one hormone opposes the action of another, the two are **antagonistic** to each other.

Endocrine Pathologies

25. Diseases of hormone excess are usually due to **hypersecretion**. Symptoms of hormone deficiency occur when too little hormone is secreted (**hyposecretion**). **Abnormal tissue responsiveness** may result from problems with hormone receptors or signal transduction pathways.
26. **Primary pathologies** arise in the last endocrine gland in a reflex. A **secondary pathology** is a problem with one of the tissues producing trophic hormones. (Fig. 7.14)

Hormone Evolution

27. Many human hormones are similar to hormones found in other vertebrate animals.

Questions

Level One Reviewing Facts and Terms

1. The study of hormones is called _____.
2. List the three basic ways hormones act on their target cells.
3. List five endocrine glands, and name one hormone secreted by each. Give one effect of each hormone you listed.
4. Match the following researchers with their experiments:

(a) Lower	1. isolated trophic hormones from the hypothalami of pigs and sheep
(b) Berthold	2. claimed sexual rejuvenation after injections of testicular extracts
(c) Guillemin and Shalley	3. isolated insulin
(d) Brown-Séquard	4. accurately described the function of the pituitary gland
(e) Banting and Best	5. studied comb development in castrated roosters

5. Put the following steps for identifying an endocrine gland in order:
   (a) Purify the extracts and separate the active substances.
   (b) Perform replacement therapy with the gland or its extracts and see if the abnormalities disappear.
   (c) Implant the gland or administer the extract from the gland to a normal animal and see if symptoms characteristic of hormone excess appear.
   (d) Put the subject into a state of hormone deficiency by removing the suspected gland, and monitor the development of abnormalities.
6. For a chemical to be defined as a hormone, it must be secreted into the _____ for transport to a(n) _____ and take effect at _____ concentrations.
7. What is meant by the term *half-life* in connection with the activity of hormone molecules?
8. Metabolites are inactivated hormone molecules, broken down by enzymes found primarily in the _____ and _____, to be excreted in the _____ and _____, respectively.

9. Candidate hormones often have the word _____ as part of their name.
10. List and define the three chemical classes of hormones. Name one hormone in each class.
11. Decide if each of the following characteristics applies best to peptide hormones, steroid hormones, both classes, or neither class.
    (a) are lipophobic and must use a signal transduction system
    (b) have a short half-life, measured in minutes
    (c) often have a lag time of 90 minutes before effects are noticeable
    (d) are water-soluble, and thus easily dissolve in the extracellular fluid for transport
    (e) most hormones belong to this class
    (f) are all derived from cholesterol
    (g) consist of three or more amino acids linked together
    (h) are released into the blood to travel to a distant target organ
    (i) are transported in the blood bound to protein carrier molecules
    (j) are all lipophilic, so diffuse easily across membranes
12. Why do steroid hormones usually take so much longer to act than peptide hormones?
13. When steroid hormones act on a cell nucleus, the hormone-receptor complex acts as a(n) _____ factor, binds to DNA, and activates one or more _____, which create mRNA to direct the synthesis of new _____.
14. Researchers have discovered that some cells have additional steroid hormone receptors on their _____, enabling a faster response.
15. Melatonin is made from the amino acid _____, and the catecholamines and thyroid hormones are made from the amino acid _____.
16. A hormone that controls the secretion of another hormone is known as a(n) _____ hormone.
17. In reflex control pathways involving trophic hormones and multiple integrating centers, the hormones themselves act as _____ _____ signals, suppressing trophic hormone secretion earlier in the reflex.
18. What characteristic defines neurohormones?
19. List the two hormones secreted by the posterior pituitary gland. To what chemical class do they belong?
20. What is the hypothalamic-hypophyseal portal system? Why is it important?
21. List the six hormones of the anterior pituitary gland; give an action of each. Which ones are trophic hormones?
22. How do long-loop negative feedback and short-loop negative feedback differ? Give an example of each type in the body's endocrine system.
23. When two hormones work together to create a result that is greater than additive, that interaction is called _____. When two hormones must both be present to achieve full expression of an effect, that interaction is called _____. When hormone activities oppose each other, that effect is called _____.

Level Two Reviewing Concepts

24. Compare and contrast the terms in each of the following sets:
    (a) paracrine, hormone, cytokine
    (b) primary and secondary endocrine pathologies
    (c) hypersecretion and hyposecretion
    (d) anterior and posterior pituitary
25. Compare and contrast the three chemical classes of hormones.
26. Map the following groups of terms. Add terms if you like.

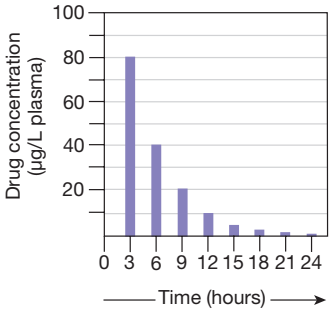
List 1	List 2
co-secretion	ACTH
endoplasmic reticulum	anterior pituitary
exocytosis	blood
Golgi complex	endocrine cell
hormone receptor	gonadotropins
peptide hormone	growth hormone
preprohormone	hypothalamus
prohormone	inhibiting hormone
secretory vesicle	neurohormone
signal sequence	neuron
synthesis	oxytocin
target cell response	peptide/protein
	portal system
	posterior pituitary
	prolactin
	releasing hormone
	trophic hormone
	TSH
	vasopressin

Level Three Problem Solving

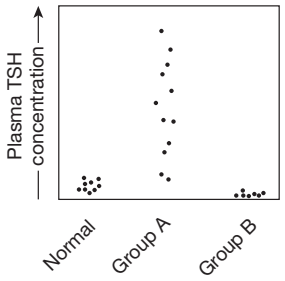
27. The terms *specificity, receptors,* and *down-regulation* can be applied to many physiological situations. Do their meanings change when applied to the endocrine system? What chemical and physical characteristics do hormones, enzymes, transport proteins, and receptors have in common that makes specificity important?
28. Dexamethasone is a drug used to suppress the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. Two patients with hypersecretion of cortisol are given dexamethasone. Patient A's cortisol secretion falls to normal as a result, but patient B's cortisol secretion remains elevated. Draw maps of the reflex pathways for these two patients (see Fig. 7.11b for a template) and use the maps to determine which patient has primary hypercortisolism. Explain your reasoning.
29. Some early experiments for male birth control pills used drugs that suppressed gonadotropin (FSH and LH) release. However, men given these drugs stopped taking them because the drugs decreased testosterone secretion, which decreased the men's sex drive and caused impotence.
    (a) Use the information given in Figure 7.9 to draw the GnRH-FSH/LH-testosterone reflex pathway. Use the pathway to show how suppressing gonadotropins decreases sperm production and testosterone secretion.
    (b) Researchers subsequently suggested that a better treatment would be to give men extra testosterone. Draw another copy of the reflex pathway to show how testosterone could suppress sperm production without the side effect of impotence.

Level Four Quantitative Problems

30. The following graph represents the disappearance of a drug from the blood as the drug is metabolized and excreted. Based on the graph, what is the half-life of the drug?



31. The following graph shows plasma TSH concentration in three groups of subjects. Which pattern would be consistent with the following pathologies? Explain your reasoning.
    (a) primary hypothyroidism
    (b) primary hyperthyroidism
    (c) secondary hyperthyroidism



32. Based on what you have learned about the pathway for insulin secretion, draw and label a graph showing the effect of plasma glucose concentration on insulin secretion.

Answers

Answers to Concept Check Questions

1. Glucose enters cells by facilitated diffusion (GLUT transporters).
2. The suffix *-ase* indicates an enzyme. A *peptidase* digests peptides.
3. A hormone is a chemical that is secreted into the blood and acts on a distant target in very low concentrations.
4. A steroid-producing cell would have extensive smooth endoplasmic reticulum; a protein-producing cell would have lots of rough endoplasmic reticulum and secretory vesicles.
5. The three chemical classes of hormones are peptide, steroid, and amino acid–derived.
6. The short half-life suggests that aldosterone is not bound to plasma proteins as much as other steroid hormones are.
7. Increased blood glucose is the stimulus. Insulin secretion is the efferent pathway; decrease in blood glucose is the response.
8. Insulin release by blood glucose is a simple endocrine reflex. Insulin release in response to a digestive hormone is the complex endocrine reflex. Insulin release triggered by a neural signal following a meal is the neural-endocrine reflex.
9. Stimulus: decreased blood glucose; sensor/integrating center: pancreatic endocrine cells; efferent path: glucagon; target: multiple target tissues; response: increased blood glucose.
10. Catecholamines are amino acid–derived hormones.
11. Microtubules of the cytoskeleton move secretory vesicles.
12. Contents of secretory vesicles are released by exocytosis.
13. (a) pathway 4; (b) pathway 4 for GH acting directly on targets, and pathway 5 for GH acting on the liver.
14. The target is endocrine cells of the anterior pituitary.

Answers to Figure Questions

Figure 7.6: The conversion of tyrosine to dopamine adds a hydroxyl (−OH) group to the 6-carbon ring and changes the carboxyl (−COOH) group to a hydrogen. Norepinephrine is made from dopamine by changing one hydrogen to a hydroxyl group. Epinephrine is made from norepinephrine by changing one hydrogen attached to the nitrogen to a methyl ($-CH_3$) group.

Figure 7.7: The pathway begun by eating a meal shuts off when the stretch stimulus disappears as the meal is digested and absorbed from the digestive tract.

Figure 7.11: In short-loop negative feedback, ACTH feeds back to inhibit hypothalamic release of CRH.

Figure 7.15: (a) CRH high, ACTH low, cortisol low. No negative feedback loops are functioning. (b) CRH normal/high, ACTH high, cortisol low. Absence of negative feedback by cortisol increases trophic hormones. Short-loop negative feedback from ACTH may keep CRH within the normal range.

Answers to Review Questions

Level One Reviewing Facts and Terms

1. *endocrinology*
2. Alter the rate of enzymatic reactions, control transport of molecules into and out of cells, or change gene expression and protein synthesis in target cells.
3. See Figure 7.2.
4. (a) 4, (b) 5, (c) 1, (d) 2, (e) 3
5. (d) , (b) , (c) , (a)
6. *blood; distant target; very low*
7. the time required for half a dose of hormone to disappear from the blood
8. *kidneys* and *liver; urine* and *bile*
9. *factor*
10. Peptides—three or more amino acids; example: insulin. Steroids—derived from cholesterol; example: estrogen. Amino acid–derived—made from single amino acids; example: thyroid hormone
11. (a) peptide (b) peptide (c) steroid (d) peptide (e) peptide (f) steroid (g) peptide (h) all classes (i) steroid (j) steroid
12. Steroid hormones usually initiate new protein synthesis, which takes time. Peptides modify existing proteins.
13. *transcription* factor; *genes; proteins*
14. *cell membrane*
15. *tryptophan; tyrosine*
16. *trophic*
17. *negative feedback*
18. synthesized by and secreted from neurons
19. oxytocin and vasopressin, both peptide neurohormones
20. The portal system is composed of hypothalamic capillaries that take up hormones and deliver them directly to capillaries in the anterior pituitary. The direct connection allows very small amounts of hypothalamic hormone to control the anterior pituitary endocrine cells.
21. See Figure 7.9.
22. Long-loop—hormone from peripheral endocrine gland turns off pituitary and hypothalamic hormone secretion. Short-loop—anterior pituitary hormone turns off hypothalamus.
23. *synergism; permissiveness; antagonistic*

Level Two Reviewing Concepts

24. (a) Paracrines—local; cytokines—local or long distance; hormones—long distance. Cytokines—peptides; hormones—peptides, steroids, or amines. Cytokines—made on demand; peptides—made in advance and stored. (b) Primary pathology arises in the last endocrine gland of the pathway. Secondary pathology arises in a gland secreting a trophic hormone. (c) Hypersecretion—too much hormone; hyposecretion—too little hormone. (d) Both secrete peptide hormones. Anterior pituitary gland—true endocrine gland; posterior pituitary—neural tissue.
25. See Table 7.1.
26. Use Figure. 7.3 for List 1 and Figures. 7.8 and 7.9 for List 2.

Level Three Problem Solving

27. The meanings do not change significantly. Enzymes, hormone receptors, transport proteins, and receptors are all proteins that bind ligands.
28. Patient A—cortisol hypersecretion results from ACTH hypersecretion. When dexamethasone suppresses ACTH secretion, the adrenal gland is no longer stimulated. Cortisol secretion decreases as a result. Patient B—problem in the adrenal gland. His normal negative feedback pathways do not operate, and the adrenal gland continues oversecreting cortisol even though ACTH secretion has been suppressed by dexamethasone.
29. (b) Both LH and testosterone needed for gamete formation. Testosterone does not directly suppress gamete formation, but it does have a negative feedback effect and shuts off LH secretion. LH is needed for gamete production, so its absence would suppress gamete synthesis.

Level Four Quantitative Problems

30. Half-life is 3 hours.
31. (a) Group A (b) Group B (c) Group A
32. *x*-axis—plasma glucose; *y*-axis—insulin secretion. As *X* increases, *Y* increases.

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