CHAPTER 11

The Endocrine System

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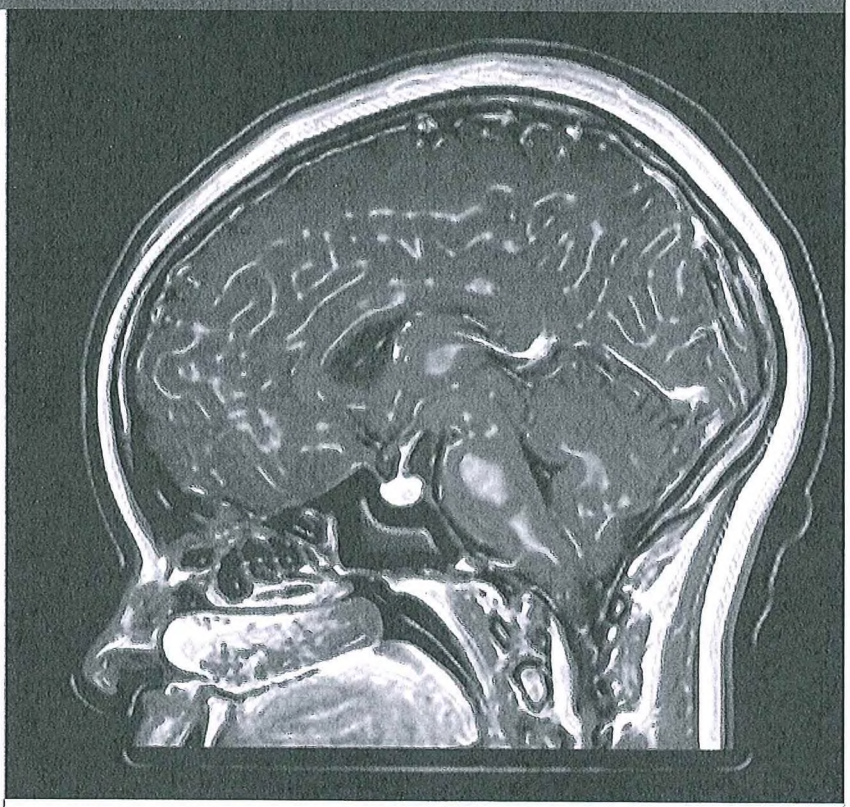
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Sagital MRI of a human brain showing the connection between the hypothalamus, the pituitary stalk, and the pituitary gland (white structures in center of image). Living Art Enterprises/Science Source

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Chapter 11 Clinical Case Study

In Chapters 6–8 and 10, you learned that the nervous system is one of the two major control systems of the body, and now we turn our attention to the other—the endocrine system. The **endocrine system** consists of ductless glands called **endocrine glands** that secrete hormones, as well as hormone-secreting cells located in various organs such as the brain, heart, kidneys, liver, and stomach. You will learn about exocrine (ducted) glands in Chapter 15. **Hormones** are chemical messengers that enter the blood, which carries them from their site of secretion to the cells upon which they act. The cells a particular hormone influences are known as the target cells for that hormone. The aim of this chapter is to first present a detailed overview of endocrinology—that is, a structural and functional analysis of general features of hormones—followed by a more detailed analysis of several important hormonal systems. Before continuing, you should review the principles of ligand-receptor interactions and cell signaling that were described in Chapters 3 and 5— they pertain to the mechanisms by which hormones exert their actions.

Hormones functionally link various organ systems together. As such, several of the general principles of physiology first introduced in Chapter 1 apply to the study of the endocrine system, including the principle that the functions of organ systems are coordinated with each other. This coordination is key to the maintenance of homeostasis, which is important for health and survival, another important general principle of physiology that will be covered in subsequent sections of this chapter. In many cases, the actions of one hormone can be potentiated, inhibited, or counterbalanced by the actions of another. This illustrates the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition, which will be especially relevant in the sections on the endocrine control of metabolism and the control of pituitary gland function. The binding of hormones to their carrier proteins and receptors illustrates the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The anatomy of the connection of the hypothalamus and anterior pituitary demonstrates that structure is a determinant of—and has coevolved with—function (hypothalamic control of anterior pituitary function). The regulated uptake of iodine into the cells of the thyroid gland that synthesize thyroid hormones demonstrates the general principle of physiology that controlled exchange of materials occurs between compartments and across cellular membranes. Finally, this chapter exemplifies the general principle of physiology that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes. ■

General Characteristics of Hormones and Hormonal Control Systems

11.1 Hormones and Endocrine Glands

Endocrine glands are distinguished from another type of gland in the body called exocrine glands. Exocrine glands secrete their products into a duct, from where the secretions either exit the body (as in sweat) or enter the lumen of another organ, such as the intestines. By contrast, endocrine glands are ductless and release hormones into the blood (**Figure 11.1**). Hormones are actually released first into interstitial fluid, from where they diffuse into the blood, but for simplicity we will often omit the interstitial fluid step in our discussion.

Figure 11.2 summarizes most of the endocrine glands and other hormone-secreting organs, the hormones they secrete, and some of the major functions the hormones control. The endocrine system differs from most of the other organ systems of the body in that the various components are not anatomically connected; however, they do form a system in the functional sense. You may be puzzled to see some organs—the heart, for

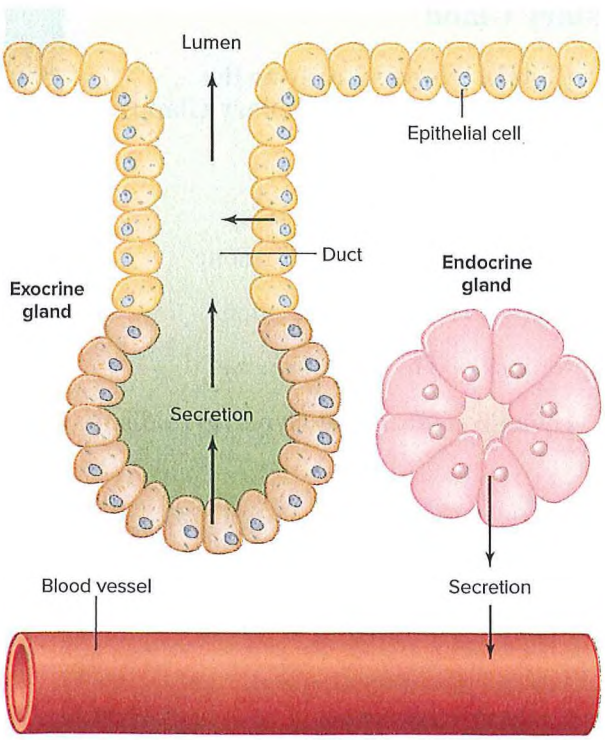


Figure 11.1 APR Exocrine gland secretions enter ducts from where their secretions either exit the body or, as shown here, connect to the lumen of a structure such as the intestines or to the surface of the skin. By contrast, endocrine glands secrete hormones that enter the interstitial fluid and diffuse into the blood, from where they can reach distant target cells.

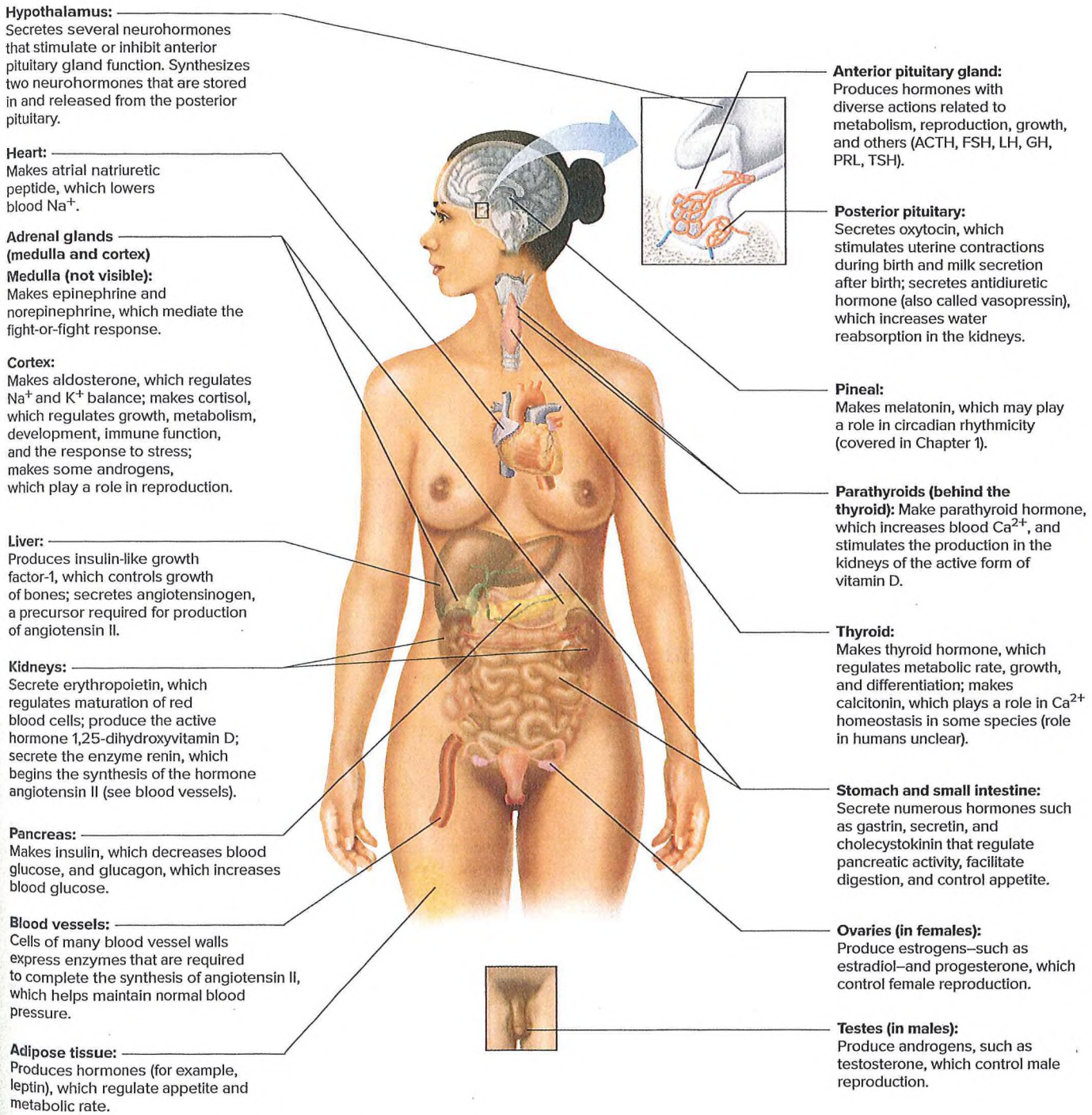


Figure 11.2 Overview of the major hormones and their sites of production, and some of their important functions.

instance—that clearly have other functions yet are listed as part of the endocrine system. The explanation is that, in addition to the cells that carry out other functions, the organ also contains cells that secrete hormones.

Note also in Figure 11.2 that the hypothalamus, a part of the brain, is considered part of the endocrine system. This is because the chemical messengers released by certain axon terminals in both the hypothalamus and its extension, the posterior pituitary, do not function as neurotransmitters affecting adjacent cells but, rather, enter the blood as hormones. The blood then carries these hormones to their sites of action.

Figure 11.2 demonstrates that there are a large number of endocrine glands and hormones. This chapter is not all inclusive. Some of the hormones listed in Figure 11.2 are best considered in the context of the control systems in which they participate. For example, the pancreatic hormones (insulin and glucagon) are

described in Chapter 16 in the context of organic metabolism, and the reproductive hormones are extensively covered in Chapter 17.

Also evident from Figure 11.2 is that a single gland may secrete multiple hormones. The usual pattern in such cases is that a single cell type secretes only one hormone, so that multiple-hormone secretion reflects the presence of different types of endocrine cells in the same gland. In a few cases, however, a single cell may secrete more than one hormone or different forms of the same hormone.

Finally, in some cases, a hormone secreted by an endocrine gland cell may also be secreted by other cell types and serves in these other locations as a neurotransmitter or paracrine or autocrine substance. For example, somatostatin, a hormone produced by neurons in the hypothalamus, is also secreted by cells of the stomach and pancreas, where it has local paracrine actions.

Study and Review 11.1

- **Endocrine glands:** Ductless organs or groups of cells that secrete hormones directly into the blood or other body fluids.
  - A single gland may secrete multiple hormones.

Review Question: *Give an example of an endocrine gland and an exocrine gland and explain the major anatomical feature that distinguishes them. What organ contains both endocrine and exocrine glands?* ***(Answer found in Appendix A.)***

11.2 Hormone Structures and Synthesis

Hormones fall into three major structural classes:

- amines
- peptides and proteins
- steroids

Amine Hormones

The **amine hormones** are derivatives of the amino acid tyrosine. They include the **thyroid hormones** (produced by the thyroid gland) and the catecholamines **epinephrine** and **norepinephrine** (produced by the adrenal medulla) and **dopamine** (produced by the hypothalamus). The structure and synthesis of the iodine-containing thyroid hormones will be described in detail in Section 11.9 of this chapter. For now, their structures are included in **Figure 11.3**. Chapter 6 described the structures of catecholamines and the steps of their synthesis; the structures are reproduced here in Figure 11.3.

There are two adrenal glands, one above each kidney. Each **adrenal gland** is composed of an inner **adrenal medulla,** which secretes catecholamines, and a surrounding **adrenal cortex,** which secretes steroid hormones. The adrenal medulla is really a modified sympathetic ganglion whose cell bodies do not have axons. Instead, they release their secretions into the blood, thereby fulfilling a criterion for an endocrine gland.

The adrenal medulla secretes mainly two catecholamines, epinephrine and norepinephrine. In humans, the adrenal medulla secretes approximately four times more epinephrine than norepinephrine. This is because the adrenal medulla expresses high amounts of an enzyme called phenylethanolamine-N-methyltransferase (PNMT), which catalyzes the reaction that converts norepinephrine to epinephrine (refer back to Figure 6.35). Epinephrine and norepinephrine exert actions similar to those of the sympathetic nerves, which, because they do not express PNMT, make only norepinephrine. These actions are described in various chapters and summarized in Section 11.16 of this chapter.

The other catecholamine hormone, dopamine, is synthesized by neurons in the hypothalamus. Dopamine is released into a special circulatory system called a portal system (see Section 11.8), which carries the hormone to the pituitary gland; there, it acts to inhibit the activity of certain endocrine cells.

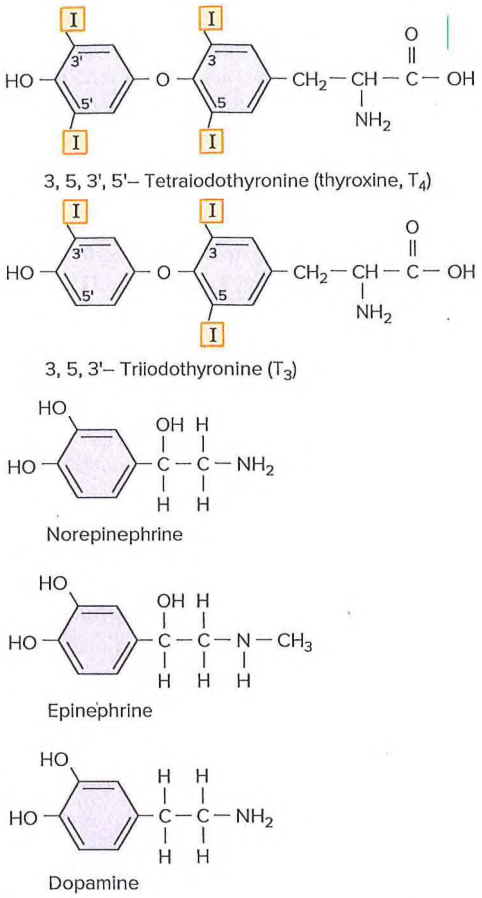


Figure 11.3 Chemical structures of the amine hormones: thyroxine and triiodothyronine (thyroid hormones), and norepinephrine, epinephrine, and dopamine (catecholamines). The two thyroid hormones differ by only one iodine atom, a difference noted in the abbreviations T_3 and T_4. The position of the carbon atoms in the two rings of T_3 and T_4 are numbered; this provides the basis for the complete names of T_3 and T_4 as shown in the figure. T_4 is the primary secretory product of the thyroid gland, but is activated to the much more potent T_3 in target tissue.

Peptide and Protein Hormones

Most hormones are polypeptides. Short polypeptides with a known function are often referred to simply as peptides; longer polypeptides with tertiary structure and a known function are called proteins. Hormones in this class range in size from small peptides having only three amino acids to large proteins, some of which contain carbohydrate and thus are glycoproteins. For convenience, we will simply refer to all these hormones as **peptide hormones.**

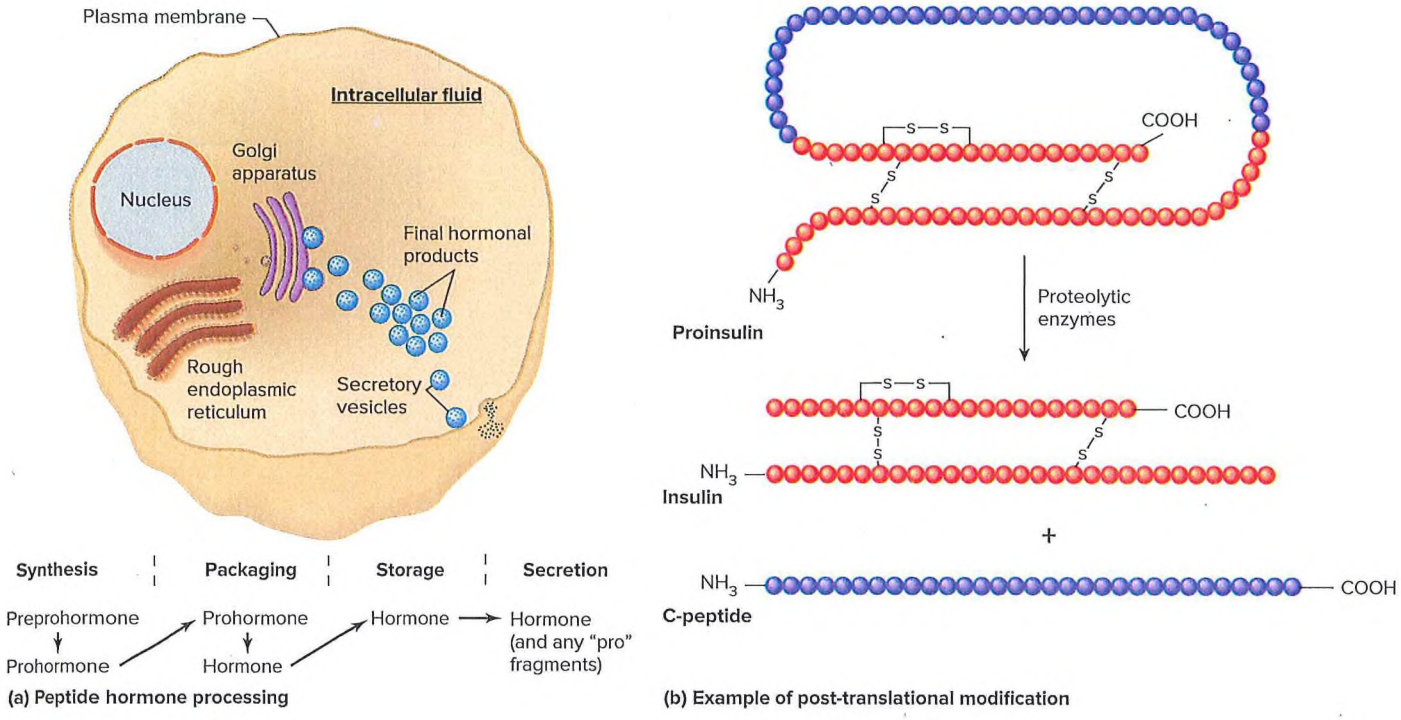


Figure 11.4 APR Typical synthesis and secretion of peptide hormones. (a) Peptide hormones typically are processed by enzymes from preprohormones containing a signal peptide to become prohormones; further processing results in one or more active hormones that are stored in secretory vesicles. Secretion of stored secretory vesicles occurs by the process of exocytosis. (b) An example of peptide hormone synthesis. Insulin is synthesized as a preprohormone (not shown) that is cleaved to the prohormone shown here. Each bead represents an amino acid. The action of proteolytic enzymes cleaves the prohormone into insulin and C-peptide (plus four amino acids that are removed altogether; not shown). Note that this cleavage results in two chains of insulin, which are connected by disulfide bridges.

DIG DEEPER

- What is the advantage of packaging peptide hormones in secretory vesicles?

Answer found in Appendix A.

In many cases, peptide hormones are initially synthesized on the ribosomes of endocrine cells as larger molecules known as preprohormones, which are then cleaved to **prohormones** by proteolytic enzymes in the rough endoplasmic reticulum (**Figure 11.4a**). The prohormone is then packaged into secretory vesicles by the Golgi apparatus. In this process (called **post-translational modification**), the prohormone is cleaved to yield the active hormone and other peptide chains found in the prohormone. Consequently, when the cell is stimulated to release the contents of the secretory vesicles by exocytosis, the other peptides are secreted along with the hormone. In certain cases, these other peptides may also exert hormonal effects. In other words, instead of just one peptide hormone, the cell may secrete multiple peptide hormones—derived from the same prohormone—each of which differs in its effects on target cells. One well-studied example of this is the synthesis of insulin in the pancreas (**Figure 11.4b**). Insulin is synthesized as a polypeptide preprohormone, then processed to the prohormone. Enzymes clip off a portion of the prohormone resulting in insulin and another product called C-peptide. Both insulin and C-peptide are secreted into the circulation in roughly equimolar amounts. Insulin is a key regulator of metabolism, while C-peptide may have several actions on a variety of cell types.

Steroid Hormones

Steroid hormones make up the third family of hormones. **Figure 11.5** shows some examples of steroid hormones; their ringlike structure was described in Chapter 2. Steroid hormones are primarily produced by the adrenal cortex and the **gonads** (testes and ovaries), as well as by the placenta during pregnancy. In addition, vitamin D is enzymatically converted in the body to an active steroid hormone, as you will learn in Section 11.21.

The general process of steroid hormone synthesis is illustrated in **Figure 11.6a**. In both the gonads and the adrenal cortex, the hormone-producing cells are stimulated by the binding of an anterior pituitary gland hormone to its plasma membrane receptor. These receptors are linked to G_s proteins (refer back to Figure 5.6), which activate adenylyl cyclase and cAMP production. The subsequent activation of protein kinase A by cAMP results in phosphorylation of numerous intracellular proteins, which facilitate the subsequent steps in the process.

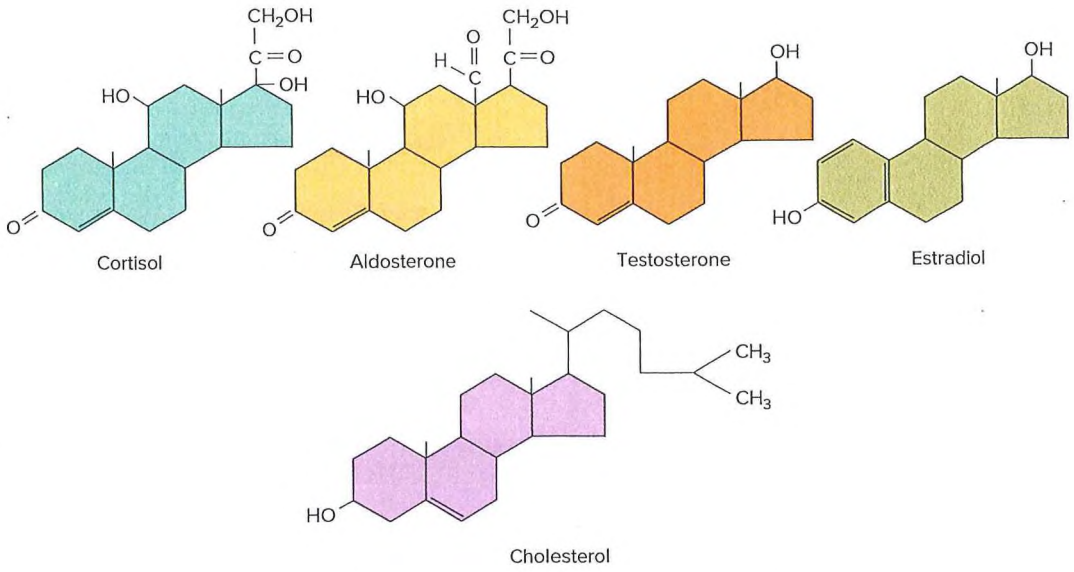


Figure 11.5 Structures of representative steroid hormones and their structural relationship to cholesterol.

All of the steroid hormones are derived from cholesterol, which is either taken up from the extracellular fluid by the cells or synthesized by intracellular enzymes. The final steroid hormone product depends upon the cell type and the types and amounts of the enzymes it expresses. Cells in the ovary, for example, express large amounts of the enzyme needed to convert testosterone to estradiol, whereas cells in the testes do not express significant amounts of this enzyme and therefore make primarily testosterone.

Once formed, steroid hormones are not stored in the cytosol in membrane-bound vesicles, because the lipophilic nature of steroids allows them to freely diffuse across lipid bilayers. As a result, once they are synthesized, steroid hormones diffuse across the plasma membrane into the circulation. Because of their lipid nature, steroid hormones are not highly soluble in blood. Consequently, the majority of steroid hormones are reversibly bound in plasma to carrier proteins such as albumin and various other specific proteins.

The next sections describe the pathways for steroid synthesis in the adrenal cortex and gonads. Those for the placenta are somewhat unusual and are briefly discussed in Chapter 17.

Hormones of the Adrenal Cortex

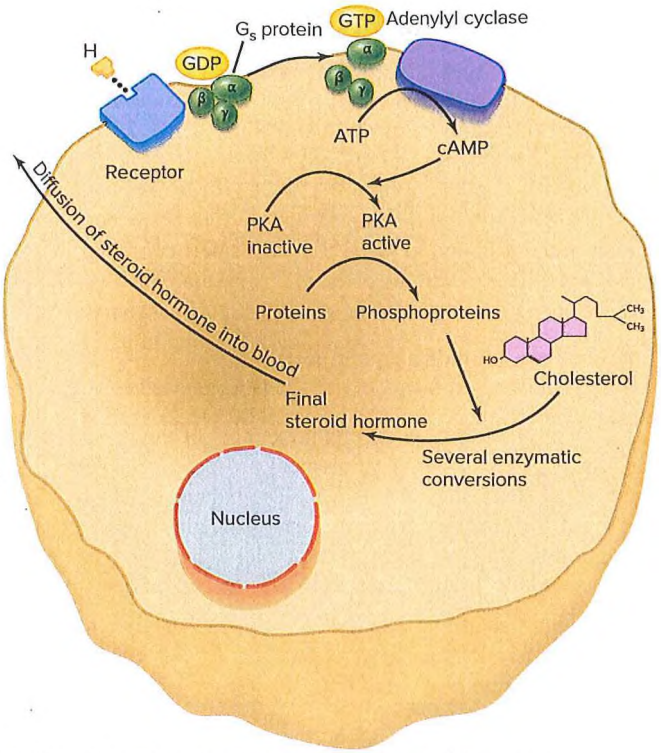
The five major hormones secreted by the adrenal cortex are aldosterone, cortisol, corticosterone, dehydroepiandrosterone (DHEA), and androstenedione (**Figure 11.6b**). **Aldosterone** is known as a **mineralocorticoid** because its effects are on salt (mineral) balance, mainly on the kidneys' handling of sodium, potassium, and hydrogen ions. Its actions are described in detail in Chapter 14. Briefly, production of aldosterone is under the control of another hormone called **angiotensin II,** which binds to plasma membrane receptors in the adrenal cortex to activate the inositol trisphosphate second-messenger pathway (see Chapter 5). This is different from the more common cAMP-mediated mechanism by which most steroid hormones are produced, as previously described. Once synthesized, aldosterone enters the circulation and acts on cells of the kidneys to stimulate Na^+ and H_2O retention, and K^+ and H^+ excretion in the urine.

Cortisol and the related but less functional steroid corticosterone are called **glucocorticoids** because they have important effects on the metabolism of glucose and other organic nutrients. Cortisol is the predominant glucocorticoid in humans and is the only one we will discuss. In addition to its effects on organic metabolism, cortisol exerts many other effects, including facilitation of the body's responses to stress and regulation of the immune system (see Section 11.14).

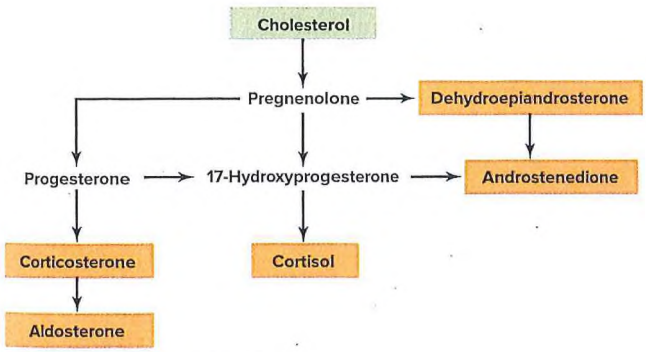
Dehydroepiandrosterone (DHEA) and androstenedione belong to the class of steroid hormones known as **androgens;** this class also includes the major male sex steroid **testosterone,** produced by the testes. The adrenal androgens are much less potent than testosterone, and they are usually of little physiological significance in the adult male. They do, however, have functions in the adult female and in both sexes in the fetus and at **puberty,** as described in Chapter 17.

The adrenal cortex is composed of three distinct layers (**Figure 11.7**). The cells of the outermost layer—the zona glomerulosa—express the enzymes required to synthesize corticosterone and then convert it to aldosterone (see Figure 11.6b) but do *not* express the genes that code for the enzymes required for the formation of cortisol and androgens. Therefore, this layer synthesizes and secretes aldosterone but not the other major adrenocortical hormones. In contrast, the zona fasciculata and zona reticularis have the opposite enzyme profile. They secrete no aldosterone but do secrete cortisol and androgens. In humans, the zona fasciculata primarily produces cortisol and the zona reticularis primarily produces androgens.

In certain diseases, the adrenal cortex may secrete decreased or increased amounts of various steroids. For example, the absence of an enzyme required for the formation of cortisol by the adrenal cortex can result in the shunting of the cortisol precursors into the androgen pathway. (Look at Figure 11.6b to imagine how this might happen.) One example of an inherited disease of this type is ***congenital adrenal hyperplasia* (*CAH*)** (see Chapter 17 for more details). In CAH, the excess adrenal androgen production results



(a) General events of steroid hormone synthesis and secretion



(b) Major adrenal steroid hormones

Figure 11.6 (a) Schematic overview of steps commonly involved in steroid synthesis. (b) The five hormones shown in boxes are the major hormones secreted from the adrenal cortex. Dehydroepiandrosterone (DHEA) and androstenedione are androgens—that is, testosterone-like hormones. Cortisol and corticosterone are glucocorticoids, and aldosterone is a mineralocorticoid that is produced by only one part of the adrenal cortex. *Note:* For simplicity, not all enzymatic steps are indicated.

DIG DEEPER

- Why are steroid hormones not packaged into secretory vesicles, such as those depicted in Figure 11.4?

Answer found in Appendix A.

in virilization of the genitalia of female fetuses; at birth, it may not be obvious whether the baby is phenotypically male or female. Fortunately, the most common form of this disease is routinely screened for at birth in many countries and appropriate therapeutic measures can be initiated immediately.

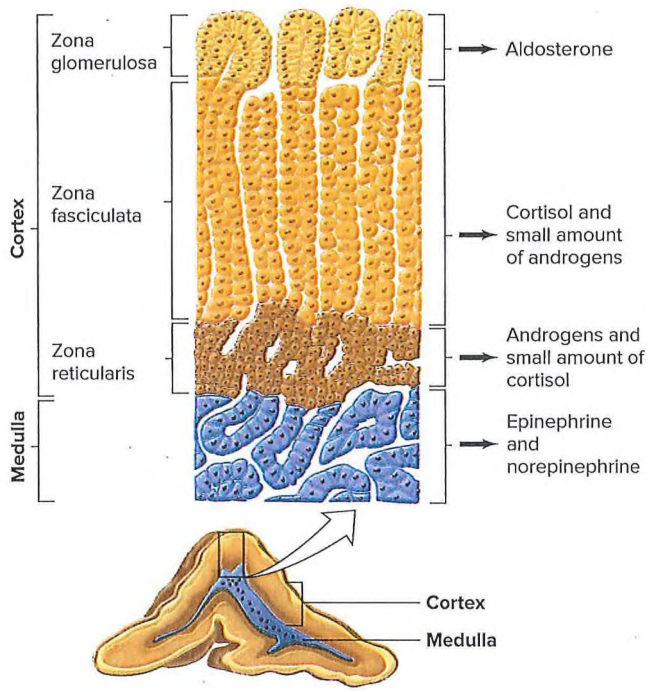


Figure 11.7 APR Section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete.

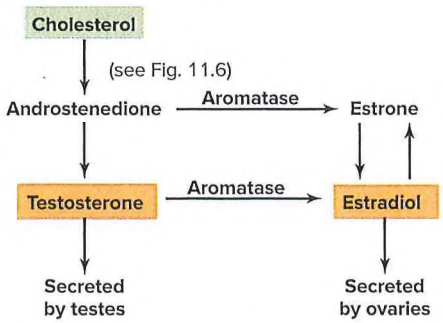


Figure 11.8 Gonadal production of steroids. Only the ovaries have high concentrations of the enzyme (aromatase) required to produce the estrogens estrone and estradiol.

Hormones of the Gonads

Compared to the adrenal cortex, the gonads express different enzymes in their steroid pathways. Endocrine cells in both the testes and the ovaries do not express the enzymes required to produce aldosterone and cortisol. They possess high concentrations of enzymes in the androgen pathways leading to androstenedione, as in the adrenal cortex. In addition, the endocrine cells in the testes express large amounts of an enzyme that converts androstenedione to testosterone, which is the major androgen secreted by the testes (**Figure 11.8**). The ovarian endocrine cells synthesize the female sex hormones, which are collectively known as **estrogens** (primarily estradiol and estrone). **Estradiol** is the predominant estrogen present during a woman's lifetime. The ovarian endocrine cells express large amounts of the enzyme aromatase, which catalyzes the conversion of androgens to estrogens (see Figure 11.8). Consequently, estradiol—rather than testosterone—is the major steroid hormone secreted by the ovaries.

Very small amounts of testosterone do diffuse out of ovarian endocrine cells, however, and very small amounts of estradiol are produced from testosterone in the testes. Moreover, following their release into the blood by the gonads and the adrenal cortex, steroid hormones may undergo further conversion in other organs. For example, testosterone is converted to estradiol in some of its target cells. Consequently, the major male and female sex hormones—testosterone and estradiol, respectively—are not unique to males and females. The ratio of the concentrations of the hormones, however, is very different in the two sexes.

Finally, endocrine cells of the corpus luteum, an ovarian structure that arises following each ovulation, secrete another major steroid hormone, **progesterone.** This steroid is critically important for maintaining a pregnancy (see Chapter 17). Progesterone is also synthesized in other parts of the body—notably, the placenta in pregnant women and the adrenal cortex in both males and females.

Study and Review 11.2

- **Amine hormones:** amino acid derivatives
  - iodine-containing **thyroid hormones**
  - **Catecholamines:** secreted by the adrenal medulla and the hypothalamus
- **Peptides and proteins:** strings of amino acids
  - typically synthesized as larger (inactive) molecules that are cleaved into active fragments by **post-translational modification**
- **Steroid hormones:** produced from cholesterol by the adrenal cortex and the gonads and from steroid precursors by the placenta
  - **Adrenal cortex** produces the mineralocorticoid aldosterone; the glucocorticoid cortisol; and two androgens, DHEA and androstenedione.
  - **Ovaries** produce mainly estradiol and progesterone.
  - **Testes** produce mainly testosterone.

Review Question: What are the three general chemical classes of hormones? Give examples of each and their gland of origin. (Answer found in Appendix A.)

11.3 Hormone Transport in the Blood

Most peptide and all catecholamine hormones are water-soluble. Therefore, with the exception of a few peptides, these hormones are transported simply dissolved in plasma (**Table 11.1**). In contrast, steroid hormones and thyroid hormones are poorly soluble; consequently, they circulate in the blood largely bound to plasma proteins. Even though the steroid and thyroid hormones exist in plasma mainly bound to large proteins, small concentrations of these hormones do exist dissolved in the plasma. The dissolved, or free, hormone is in equilibrium with the bound hormone:

$$\text{Free hormone} + \text{Binding protein} \rightleftharpoons \text{Hormone–protein complex}$$

This reaction is an excellent example of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The balance of this equilibrium will shift to the right as the endocrine gland secretes more free hormone and to the left in the target gland as hormone dissociates from its binding protein in plasma and diffuses into the target gland cell. The total hormone concentration in plasma is the sum of the free and bound hormones. However, only the *free* hormone can diffuse out of capillaries and encounter its target cells. Therefore, the concentration of the free hormone is what is biologically important rather than the concentration of the total hormone, most of which is bound. As we will see next, the degree of protein binding also influences the rate of metabolism and the excretion of the hormone.

Study and Review 11.3

- **Peptide hormones** and **catecholamines:** soluble in plasma
- **Steroid** and **thyroid hormones:** poorly soluble; mostly bound to plasma proteins

Review Question: *Which classes of hormones are carried in the blood mainly as unbound, dissolved hormone? Mainly bound to plasma proteins? What accounts for the differences?* ***(Answer found in Appendix A.)***

TABLE 11.1 Categories of Hormones

Chemical Class	Major Form in Plasma	Location of Receptors	Most Common Signaling Mechanisms*	Rate of Excretion/Metabolism
Peptides and catecholamines	Free (unbound)	Plasma membrane	1. Second messengers (e.g., cAMP, Ca^{2+}, IP_3) 2. Enzyme activation by receptor (e.g., JAK) 3. Intrinsic enzymatic activity of receptor (e.g., tyrosine autophosphorylation)	Fast (minutes)
Steroids and thyroid hormone	Protein-bound	Intracellular	Intracellular receptors directly alter gene transcription	Slow (hours to days)

*The diverse mechanisms of action of chemical messengers such as hormones were discussed in detail in Chapter 5.