CHAPTER 34

The Adrenal Gland

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CHAPTER OUTLINE

KEY CONCEPTS

1. The adrenal gland is comprised of an outer cortex surrounding an inner medulla. The cortex contains three histologically distinct zones (from outside to inside): the zona glomerulosa, zona fasciculata, and zona reticularis.
2. Hormones secreted by the adrenal cortex include glucocorticoids, aldosterone, and adrenal androgens.
3. The glucocorticoids cortisol and corticosterone are synthesized in the zona fasciculata and zona reticularis of the adrenal cortex.
4. The mineralocorticoid aldosterone is synthesized in the zona glomerulosa of the adrenal cortex.
5. Cholesterol, used in the synthesis of the adrenal cortical hormones, comes from cholesterol esters stored in the cells. Stored cholesterol is derived mainly from low-density lipoprotein particles circulating in the blood, but it can also be synthesized *de novo* from acetate within the adrenal gland.
6. The conversion of cholesterol to pregnenolone in mitochondria is the common first step in the synthesis of all adrenal steroids and occurs in all three zones of the cortex.
7. The liver is the main site for the metabolism of adrenal steroids, which are conjugated to glucuronic acid and excreted in the urine.
8. ACTH increases glucocorticoid and androgen synthesis in adrenal cortical cells in the zona fasciculata and zona reticularis by increasing intracellular cAMP. ACTH also has a trophic effect on these cells.
9. Angiotensin II and angiotensin III stimulate aldosterone synthesis in the cells of the zona glomerulosa by increasing cytosolic calcium and activating protein kinase C.
10. Glucocorticoids bind to glucocorticoid receptors in the cytosol of target cells. The glucocorticoid-bound receptor translocates to the nucleus and then binds to glucocorticoid response elements in the DNA to increase or decrease the transcription of specific genes.
11. Glucocorticoids are essential to the adaptation of the body to fasting, injury, and stress.
12. The catecholamines epinephrine and norepinephrine are synthesized and secreted by the chromaffin cells of the adrenal medulla.
13. Catecholamines interact with four adrenergic receptors (α_1, α_2, β_1, and β_2) that mediate the cellular effects of the hormones.
14. Stimuli such as injury, anger, pain, cold, strenuous exercise, and hypoglycemia generate impulses in the cholinergic preganglionic fibers innervating the chromaffin cells, resulting in the secretion of catecholamines.
15. To counteract hypoglycemia, catecholamines stimulate glucose production in the liver, lactate release from muscle, and lipolysis in adipose tissue.

To remain alive, the organs and tissues of the human body must have a finely regulated extracellular environment. This environment must contain the correct concentrations of ions to maintain body fluid volume and to enable excitable cells to function. The extracellular environment must also have an adequate supply of metabolic substrates for cells to generate ATP. Salts, water, and other organic substances are continually lost from the body as a result of perspiration, respiration, and excretion. Metabolic substrates are constantly used by cells. Under normal conditions, these critical constituents of the body's extracellular environment are replenished by the intake of food and liquids. However, a person can survive for weeks on little else but water because the body has a remarkable capacity for adjusting the functions of its organs and tissues to preserve body fluid volume and composition.

The adrenal glands play a key role in making these adjustments. This is readily apparent from the fact that an adrenalectomized animal, unlike its normal counterpart, cannot survive prolonged fasting. Its blood glucose supply diminishes, ATP generation by the cells becomes inadequate to support life, and the animal eventually dies. Even

when fed a normal diet, an adrenalectomized animal typically loses body sodium and water over time, and eventually dies of circulatory collapse. Its death is caused by a lack of certain steroid hormones that are produced and secreted by the cortex of the adrenal gland.

The glucocorticoid hormones, **cortisol** and **corticosterone**, play essential roles in adjusting the metabolism of carbohydrates, lipids, and proteins in liver, muscle, and adipose tissues during fasting, which assures an adequate supply of glucose and fatty acids for energy metabolism despite the absence of food. The mineralocorticoid hormone **aldosterone**, another steroid hormone produced by the adrenal cortex, stimulates the kidneys to conserve sodium and, hence, body fluid volume.

The glucocorticoids also enable the body to cope with physical and emotional traumas or stresses. The physiological importance of this action of the glucocorticoids is emphasized by the fact that adrenalectomized animals lose their ability to cope with physical or emotional stresses. Even when given an appropriate diet to prevent blood glucose and body sodium depletion, an adrenalectomized animal may die when exposed to traumas that are not fatal to normal animals.

Hormones produced by the other endocrine component of the adrenal gland, the medulla, are also involved in compensatory reactions of the body to trauma or life-threatening situations. These hormones are the catecholamines, **epinephrine** and **norepinephrine**, which have widespread effects on the cardiovascular system and muscular system and on carbohydrate and lipid metabolism in liver, muscle, and adipose tissues.

FUNCTIONAL ANATOMY OF THE ADRENAL GLAND

The human adrenal glands are paired, pyramid-shaped organs located on the upper poles of each kidney. The adrenal gland is actually a composite of two separate endocrine organs, one inside the other, each secreting separate hormones and each regulated by different mechanisms. The outer portion or **cortex** of the adrenal gland completely surrounds the inner portion or **medulla** and makes up most of the gland. During embryonic development, the cortex forms from mesoderm; the medulla arises from neural ectoderm.

The Adrenal Cortex Consists of Three Distinct Zones

In the adult human, the adrenal cortex consists of three histologically distinct zones or layers (Fig. 34.1). The outer zone, which lies immediately under the capsule of the gland, is called the **zona glomerulosa** and consists of small clumps of cells that produce the mineralocorticoid aldosterone. The **zona fasciculata** is the middle and thickest layer of the cortex and consists of cords of cells oriented radial to the center of the gland. The inner layer is comprised of interlaced strands of cells called the **zona reticularis**. The zona fasciculata and zona reticularis both produce the physiologically important glucocorticoids, cortisol and corticosterone. These layers of the cortex also produce the

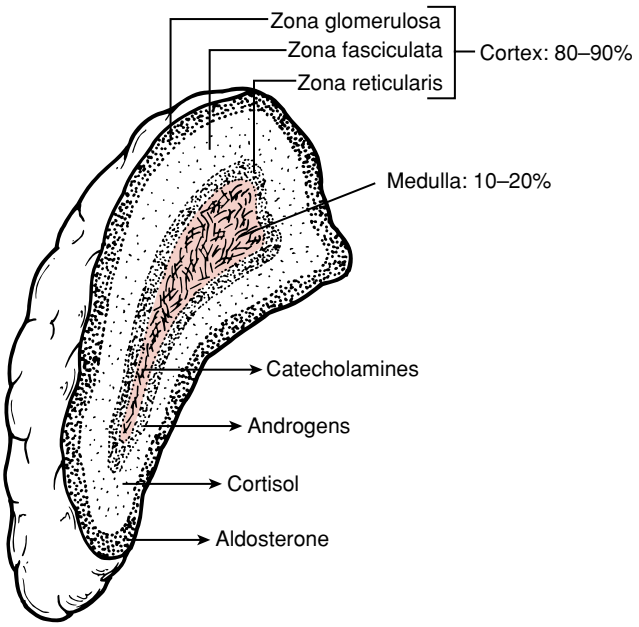


FIGURE 34.1 **The three zones of the adrenal cortex and corresponding hormone secretion.**

androgen **dehydroepiandrosterone**, which is related chemically to the male sex hormone **testosterone**. The molecular structures of these hormones are shown in Figure 34.2.

Like all endocrine organs, the adrenal cortex is highly vascularized. Many small arteries branch from the aorta and renal arteries and enter the cortex. These vessels give rise to capillaries that course radially through the cortex and terminate in venous sinuses in the zona reticularis and adrenal medulla; therefore, the hormones produced by the cells of the cortex have ready access to the circulation.

The cells of the adrenal cortex contain abundant lipid droplets. This stored lipid is functionally significant because cholesterol esters present in the droplets are an important source of the cholesterol used as a precursor for the synthesis of steroid hormones.

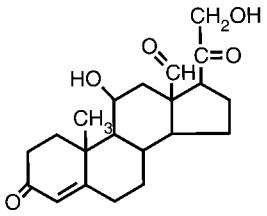
The Adrenal Medulla Is a Modified Sympathetic Ganglion

The adrenal medulla can be considered a modified sympathetic ganglion. The medulla consists of clumps and strands of **chromaffin cells** interspersed with venous sinuses. Chromaffin cells, like the modified postganglionic neurons that receive sympathetic preganglionic cholinergic innervation from the splanchnic nerves, produce catecholamine hormones, principally epinephrine and norepinephrine. Epinephrine and NE are stored in granules in chromaffin cells and discharged into venous sinuses of the adrenal medulla when the adrenal branches of splanchnic nerves are stimulated (see Fig. 6.5).

HORMONES OF THE ADRENAL CORTEX

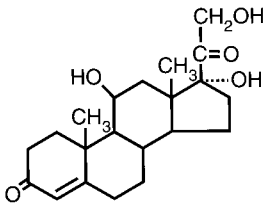
Only small amounts of the glucocorticoids, aldosterone, and adrenal androgens are found in adrenal cortical cells at

Zona glomerulosa

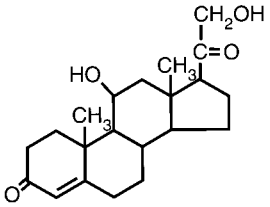


Aldosterone

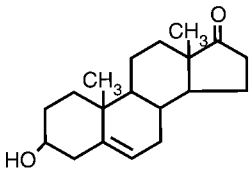
Zona fasciculata and zona reticularis



Cortisol



Corticosterone



Dehydroepiandrosterone

FIGURE 34.2 **Molecular structures of the important hormones secreted by the adrenal cortex.**

a given time because those cells produce and secrete these hormones on demand, rather than storing them. Table 34.1 shows the daily production of adrenal cortex hormones in a healthy adult under resting (unstimulated) conditions. Because the molecular weights of these substances do not vary greatly, comparing the amounts secreted indicates the relative number of molecules of each hormone produced daily. Humans secrete about 10 times more cortisol than corticosterone during an average day, and corticosterone has only one fifth of the glucocorticoid activity of cortisol (Table 34.2). Cortisol is considered the physiologically important glucocorticoid in humans. Compared with the glucocorticoids, a much smaller amount of aldosterone is secreted each day.

Because of similarities in their structures, the glucocorticoids and aldosterone have overlapping actions. For example, cortisol and corticosterone have some mineralocorticoid activity; conversely, aldosterone has some glucocorticoid activity. However, given the amounts of these hormones secreted under normal circumstances and their relative activities, glucocorticoids are not physiologically important mineralocorticoids, nor does aldosterone function physiologically as a glucocorticoid.

As discussed in detail later, the amounts of glucocorticoids and aldosterone secreted by an individual can vary greatly from those given in Table 34.1. The amount secreted depends on the person's physiological state. For example, in an individual subjected to severe physical or emotional trauma, the rate of cortisol secretion may be 10 times greater than the resting rate shown in Table 34.1. Certain diseases of the adrenal cortex that involve steroid hormone biosynthesis can significantly increase or decrease the amount of hormones produced.

The adrenal cortex also produces and secretes substantial amounts of androgenic steroids. Dehydroepiandrosterone (DHEA) in both the free form and the sulfated form (DHEAS) is the main androgen secreted by the adrenal cortex of both men and women (see Table 34.1). Lesser amounts of other androgens are also produced. The adrenal cortex is the main source of androgens in the blood in human females. In the human male, however, androgens produced by the testes and adrenal cortex contribute to the male sex hormones circulating in the blood. Adrenal androgens normally have little physiological effect other than a role in development before the start of puberty in both girls and boys. This is because the male sex hormone activity of the adrenal androgens is weak. Exceptions occur in individuals who produce inappropriately large amounts of certain adrenal androgens as a result of diseases affecting the pathways of steroid biosynthesis in the adrenal cortex.

TABLE 34.1 **The Average Daily Production of Hormones by the Adrenal Cortex**

Hormone	Amount Produced (mg/day)
Cortisol	20
Corticosterone	2
Aldosterone	0.1
Dehydroepiandrosterone	30

TABLE 34.2 **Comparison of Shared Activities of Adrenal Cortical Hormones**

Hormone	Glucocorticoid Activity[a]	Mineralocorticoid Activity[b]
Cortisol	100	0.25
Corticosterone	20	0.5
Aldosterone	10	100

[a]Percentage activity, with cortisol being 100%
[b]Percentage activity, with aldosterone being 100%

Adrenal Steroid Hormones Are Synthesized From Cholesterol

Cholesterol is the starting material for the synthesis of steroid hormones. A cholesterol molecule consists of four interconnected rings of carbon atoms and a side chain of eight carbon atoms extending from one ring (Fig. 34.3). In all, there are 27 carbon atoms in cholesterol, numbered as shown in the figure.

Sources of Cholesterol. The immediate source of cholesterol used in the biosynthesis of steroid hormones is the abundant lipid droplets in adrenal cortical cells. The cho-

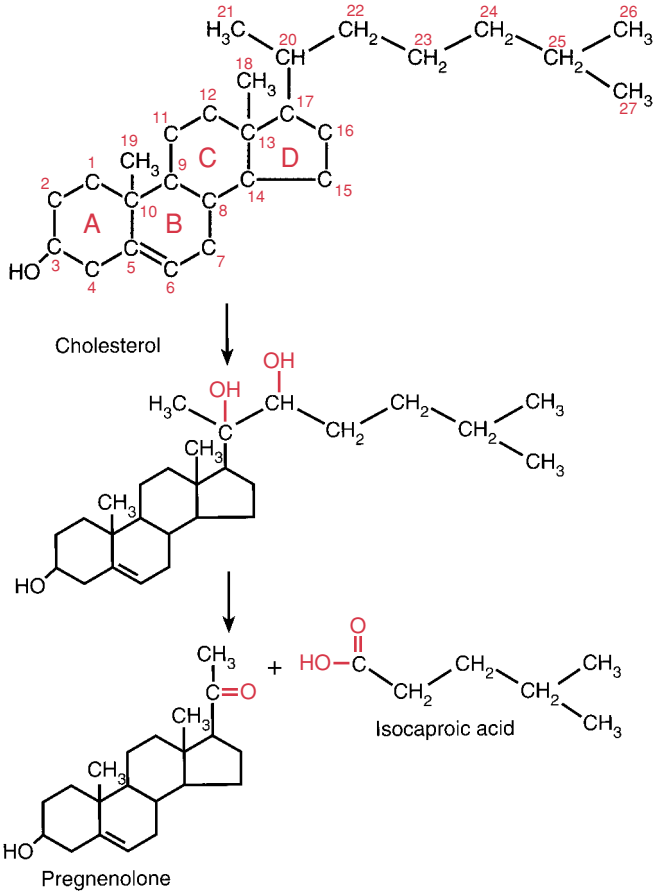


FIGURE 34.3 The formation of pregnenolone from cholesterol by the action of cholesterol side-chain cleavage enzyme (CYP11A1). Note the chemical structure of cholesterol, how the four rings are lettered (A to D), and how the carbons are numbered. The hydrogen atoms on the carbons composing the rings are omitted from the figure.

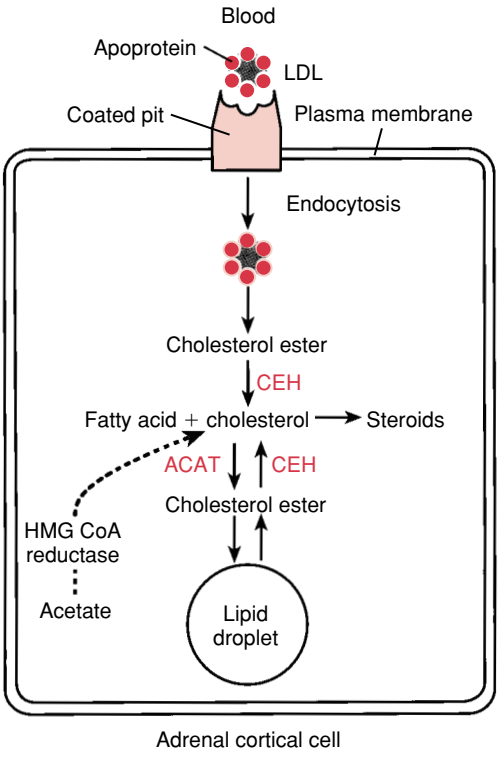


FIGURE 34.4 Sources of cholesterol for steroid biosynthesis by the adrenal cortex. Most cholesterol comes from low-density lipoprotein (LDL) particles in the blood, which bind to receptors in the plasma membrane and are taken up by endocytosis. The cholesterol in the LDL particle is used directly for steroidogenesis or stored in lipid droplets for later use. Some cholesterol is synthesized directly from acetate. CEH, cholesterol ester hydrolase; ACAT, acyl-CoA:cholesterol acyltransferase; HMG, 3-hydroxy-3-methylglutaryl.

lesterol present in these lipid droplets is mainly in the form of **cholesterol esters**, single molecules of cholesterol esterified to single fatty acid molecules. The free cholesterol used in steroid biosynthesis is generated from these cholesterol esters by the action of **cholesterol esterase** (**cholesterol ester hydrolase** [**CEH**]), which hydrolyzes the ester bond. The free cholesterol generated by that cleavage enters mitochondria located in close proximity to the lipid droplet. The process of remodeling the cholesterol molecule into steroid hormones is then initiated.

The cholesterol that has been removed from the lipid droplets for steroid hormone biosynthesis is replenished in two ways (Fig. 34.4). Most of the cholesterol converted to steroid hormones by the human adrenal gland comes from cholesterol esters contained in **low-density lipoprotein** (LDL) particles circulating in the blood. The LDL particles consist of a core of cholesterol esters surrounded by a coat of cholesterol and phospholipids. A 400-kDa protein molecule called **apoprotein B_{100}** is also present on the surface of the LDL particle; it is recognized by LDL receptors localized to coated pits on the plasma membrane of adrenal cortical cells (see Fig. 34.4). The apoprotein binds to the LDL receptor, and both the LDL particle and the receptor are taken up by the cell through endocytosis. The endocytic vesicle containing the LDL particles fuses with a lysosome and the particle is degraded. The cholesterol esters in the core of the particle are hydrolyzed to free cholesterol and fatty acid by the action of CEH.

Any cholesterol not immediately used by the cell is converted again to cholesterol esters by the action of the enzyme **acyl-CoA:cholesterol acyltransferase** (**ACAT**). The esters are then stored in the lipid droplets of the cell to be used later.

When steroid biosynthesis is proceeding at a high rate, cholesterol delivered to the adrenal cell may be diverted directly to mitochondria for steroid production rather than reesterified and stored. Accumulating evidence suggests that **high-density lipoprotein** (HDL) cholesterol may also be used as a substrate for adrenal steroidogenesis.

In humans, cholesterol that has been synthesized *de novo* from acetate by the adrenal glands is a significant but minor source of cholesterol for steroid hormone formation. The rate-limiting step in this process is catalyzed by the enzyme **3-hydroxy-3-methylglutaryl CoA reductase** (**HMG CoA reductase**). The newly synthesized cholesterol is then incorporated into cellular structures, such as membranes, or

converted to cholesterol esters through the action of ACAT and stored in lipid droplets (see Fig. 34.4).

Pathways for the Synthesis of Steroid Hormones. Adrenal steroid hormones are synthesized by four CYP enzymes. The CYPs are a large family of oxidative enzymes with a 450 nm absorbance maximum when complexed with carbon monoxide; hence, these molecules were once referred to as cytochrome P450 enzymes. The adrenal CYPs are more commonly known by their trivial names, which denote their function in steroid biosynthesis (see Table 34.3).

The conversion of cholesterol into steroid hormones begins with the formation of free cholesterol from the cholesterol esters stored in intracellular lipid droplets. Free cholesterol molecules enter the mitochondria, which are located close to the lipid droplets, by a mechanism that is not well understood. Evidence indicates that free cholesterol associates with a small protein called **sterol carrier protein 2**, which facilitates its entry into the mitochondrion in some manner. Several other proteins, as well as cAMP, appear to be involved in cholesterol transport into mitochondria, but the process is still unclear.

Once inside a mitochondrion, single cholesterol molecules bind to the **cholesterol side-chain cleavage enzyme** (CYP11A1), embedded in the inner mitochondrial membrane. This enzyme catalyzes the first and rate-limiting reaction in steroidogenesis, which remodels the cholesterol molecule into a 21-carbon steroid intermediate called **pregnenolone**. The reaction occurs in three steps, as shown in Figure 34.3. The first two steps consist of the hydroxylation of carbons 20 and 22 by cholesterol side-chain cleavage enzyme. Then the enzyme cleaves the side chain of cholesterol between carbons 20 and 22, yielding pregnenolone and **isocaproic acid**.

Once formed, pregnenolone molecules dissociate from cholesterol side-chain cleavage enzyme, leave the mitochondrion, and enter the smooth ER nearby. This mechanism is not understood. At this point, the further remodeling of pregnenolone into steroid hormones can vary, depending on whether the process occurs in the zona fasciculata and zona reticularis or the zona glomerulosa. We first consider what occurs in the zona fasciculata and zona reticularis. These biosynthetic events are summarized in Figure 34.5.

TABLE 34.3 Nomenclature for the Steroidogenic Enzymes

Common Name	Previous Form	Current Form	Gene
Cholesterol side-chain cleavage enzyme	$P450_{SCC}$	CYP11A1	*CYP11A1*
3β-Hydroxysteroid dehydrogenase	3β-HSD	3β-HSD II	*HSD3B2*
17α-Hydroxylase	$P450_{C17}$	CYP17	*CYP17*
21-Hydroxylase	$P450_{C21}$	CYP21A2	*CYP21A2*
11β-Hydroxylase	$P450_{C11}$	CYP11B1	*CYP11B1*
Aldosterone synthase	$P450_{C11AS}$	CYP11B2	*CYP11B2*

In cells of the zona fasciculata and zona reticularis, most of the pregnenolone is converted to cortisol and the main adrenal androgen dehydroepiandrosterone (DHEA). Pregnenolone molecules bind to the enzyme **17α-hydroxylase** (CYP17), embedded in the ER membrane, which hydroxylates pregnenolone at carbon 17. The product formed by this reaction is **17α-hydroxypregnenolone** (see Fig. 34.5).

The 17α-hydroxylase has an additional enzymatic action that becomes important at this step in the steroidogenic process. Once the enzyme has hydroxylated carbon 17 of pregnenolone to form 17α-hydroxypregnenolone, it has the ability to lyse or cleave the carbon 20–21 side chain from the steroid structure. Some molecules of 17α-hydroxypregnenolone undergo this reaction and are converted to the 19-carbon steroid DHEA. This action of 17α-hydroxylase is essential for the formation of androgens (19 carbon steroids) and estrogens (18 carbon steroids), which lack the carbon 20–21 side chain. Therefore, this **lyase** activity of 17α-hydroxylase is important in the gonads, where androgens and estrogens are primarily made. 17α-hydroxylase does not exert significant lyase activity in children before age 7 or 8. As a result, young boys and girls do not secrete significant amounts of adrenal androgens. The appearance of significant adrenal androgen secretion in children of both sexes is termed **adrenarche**. It is not related to the onset of puberty, since it normally occurs before the activation of the hypothalamic-pituitary-gonad axis, which initiates puberty. The adrenal androgens produced as a result of adrenarche are a stimulus for the growth of pubic and axillary hair.

Those molecules of 17α-hydroxypregnenolone that dissociate as such from 17α-hydroxylase bind next to another ER enzyme, **3β-hydroxysteroid dehydrogenase** (3β-HSD II). This enzyme acts on 17α-hydroxypregnenolone to isomerize the double bond in ring B to ring A and to dehydrogenate the 3β-hydroxy group, forming a 3-keto group. The product formed is **17α-hydroxyprogesterone** (see Fig. 34.5). This intermediate then binds to another enzyme, **21-hydroxylase** (CYP21A2), which hydroxylates it at carbon 21. The mechanism of this hydroxylation is similar to that performed by the 17α-hydroxylase. The product formed is **11-deoxycortisol**, which is the immediate precursor for cortisol.

To be converted to cortisol, 11-deoxycortisol molecules must be transferred back into the mitochondrion to be acted on by **11β-hydroxylase** (CYP11B1) embedded in the inner mitochondrial membrane. This enzyme hydroxylates 11-deoxycortisol on carbon 11, converting it into cortisol. The 11β-hydroxyl group is the molecular feature that confers glucocorticoid activity on the steroid. Cortisol is then secreted into the bloodstream.

Some of the pregnenolone molecules generated in cells of the zona fasciculata and zona reticularis first bind to 3β-hydroxysteroid dehydrogenase when they enter the endoplasmic reticulum. As a result, they are converted to **progesterone**. Some of these progesterone molecules are hydroxylated by 21-hydroxylase to form the mineralocorticoid **11-deoxycorticosterone** (DOC) (see Fig. 34.5). The 11-deoxycorticosterone formed may be either secreted or transferred back into the mitochondrion. There it is acted on by 11β-hydroxylase to form corticosterone, which is then secreted into the circulation.

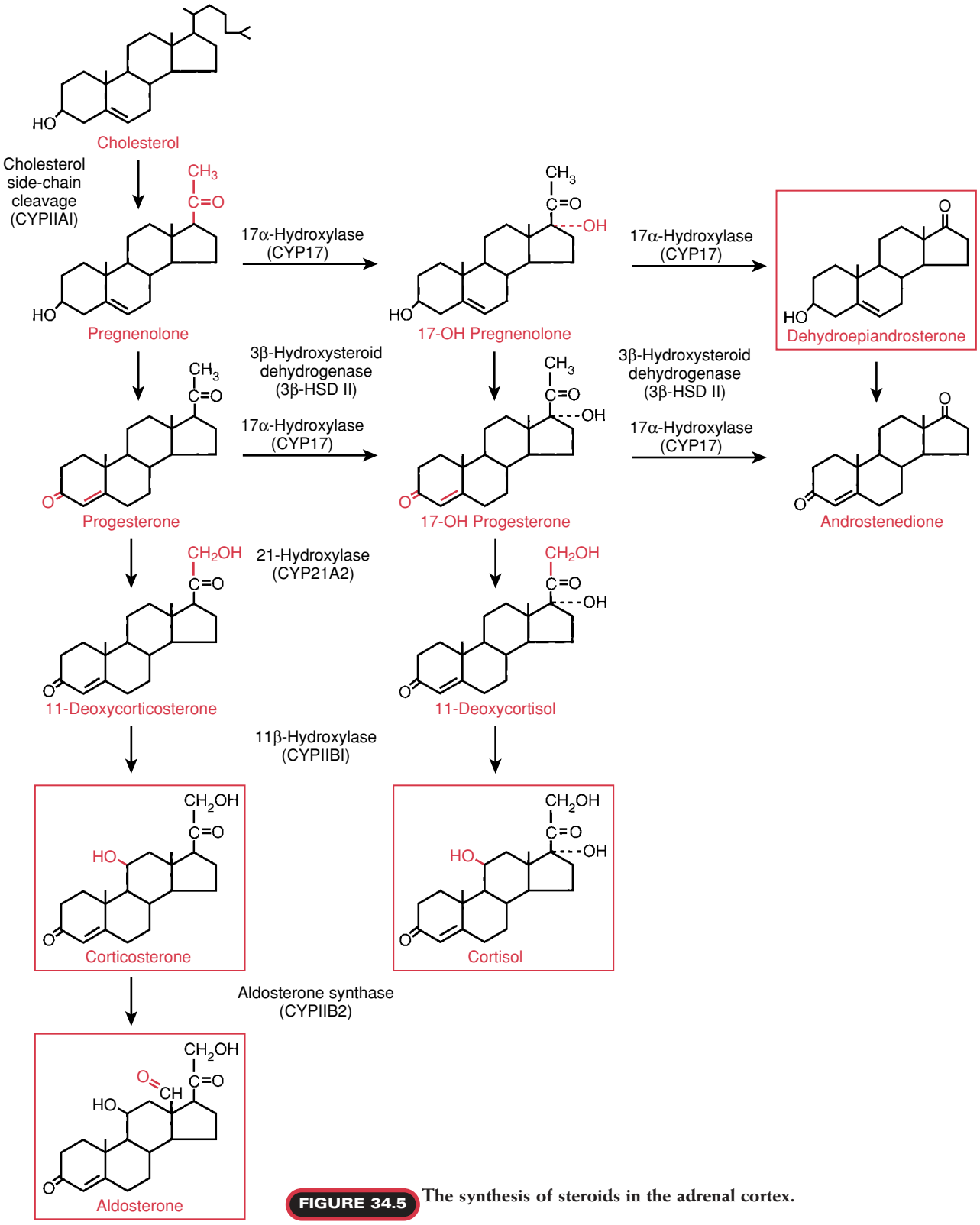


FIGURE 34.5 **The synthesis of steroids in the adrenal cortex.**

Progesterone may also undergo 17α-hydroxylation in the zona fasciculata and zona reticularis. It is then converted to either cortisol or the adrenal androgen **androstenedione**.

The 17α-hydroxylase is not present in cells of the zona glomerulosa; therefore, pregnenolone does not undergo 17α-hydroxylation in these cells, and cortisol and adrenal androgens are not formed by these cells. Instead, the enzymatic pathway leading to the formation of aldosterone is followed (see Fig. 34.5). Pregnenolone is converted by enzymes in the endoplasmic reticulum to progesterone and 11-deoxycorticosterone. The latter compound then moves

into the mitochondrion, where it is converted to aldosterone. This conversion involves three steps: the hydroxylation of carbon 11 to form corticosterone, the hydroxylation of carbon 18 to form 18-hydroxycorticosterone, and the oxidation of the 18-hydroxymethyl group to form aldosterone. In humans, these three reactions are catalyzed by a single enzyme, **aldosterone synthase** (CYP11B2), an isozyme of 11β-hydroxylase (CYP11B1), expressed only in glomerulosa cells. The 11β-hydroxylase enzyme, which is expressed in the zona fasciculata and zona reticularis, although closely related to aldosterone synthase, cannot catalyze all three reactions involved in the conversion of 11-deoxycorticosterone to aldosterone; therefore, aldosterone is not synthesized in the zona fasciculata and zona reticularis of the adrenal cortex.

Genetic Defects in Adrenal Steroidogenesis. Inherited genetic defects can cause relative or absolute deficiencies in the enzymes involved in the steroid hormone biosynthetic pathways. The immediate consequences of these defects are changes in the types and amounts of steroid hormones secreted by the adrenal cortex. The end result is disease.

Most of the genetic defects affecting the steroidogenic enzymes impair the formation of cortisol. As discussed in Chapter 32, a drop in cortisol concentration in the blood stimulates the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary. The consequent rise in ACTH in the blood exerts a trophic (growth-promoting) effect on the adrenal cortex, resulting in adrenal hypertrophy. Because of this mechanism, individuals with genetic defects affecting adrenal steroidogenesis usually have hypertrophied adrenal glands. These diseases are collectively called **congenital adrenal hyperplasia**.

In humans, inherited genetic defects occur that affect cholesterol side-chain cleavage enzyme, 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase, 21-hydroxylase, 11β-hydroxylase, and aldosterone synthase. The most common defect involves mutations in the gene for 21-hydroxylase and occurs in 1 of 7,000 people. The gene for 21-hydroxylase may be deleted entirely, or mutant genes may code for forms of 21-hydroxylase with impaired enzyme activity. The consequent reduction in the amount of active 21-hydroxylase in the adrenal cortex interferes with the formation of cortisol, corticosterone, and aldosterone, all of which are hydroxylated at carbon 21. Because of the reduction of cortisol (and corticosterone) secretion in these individuals, ACTH secretion is stimulated. This, in turn, causes hypertrophy of the adrenal glands and stimulates the glands to produce steroids.

Because 21-hydroxylation is impaired, the ACTH stimulus causes pregnenolone to be converted to adrenal androgens in inappropriately high amounts. Thus, women afflicted with 21-hydroxylase deficiency exhibit **virilization** from the masculinizing effects of excessive adrenal androgen secretion. In severe cases, the deficiency in aldosterone production can lead to sodium depletion, dehydration, vascular collapse, and death, if appropriate hormone therapy is not given.

Addison's Disease. Glucocorticoid and aldosterone deficiency also occur as a result of pathological destruction of the adrenal glands by microorganisms or autoimmune disease. This disorder is called **Addison's disease**. If sufficient adrenal cortical tissue is lost, the resulting decrease in aldosterone production can lead to vascular collapse and death, unless hormone therapy is given (see Clinical Focus Box 34.1).

Transport of Adrenal Steroids in Blood. As noted earlier, steroid hormones are not stored to any extent by cells of the adrenal cortex but are continually synthesized and secreted. The rate of secretion may change dramatically, however, depending on stimuli received by the adrenal cortical cells. The process by which steroid hormones are secreted is not well studied. It has been assumed that the accumulation of the final products of the steroidogenic pathways creates a concentration gradient for steroid hormone between cells and blood. This gradient is thought to be the driving force for diffusion of the lipid-soluble steroids through cellular membranes and into the circulation.

A large fraction of the adrenal steroids that enter the bloodstream become bound noncovalently to certain plasma proteins. One of these is **corticosteroid-binding globulin** (CBG), a glycoprotein produced by the liver. CBG binds glucocorticoids and aldosterone, but has a greater affinity for the glucocorticoids. **Serum albumin** also binds steroid molecules. Albumin has a high capacity for binding steroids, but its interaction with steroids is weak. The binding of a steroid hormone to a circulating protein molecule prevents it from being taken up by cells or being excreted in the urine.

Circulating steroid hormone molecules not bound to plasma proteins are free to interact with receptors on cells and, therefore, are cleared from the blood. As this occurs, bound hormone dissociates from its binding protein and replenishes the circulating pool of free hormone. Because of this process, adrenal steroid hormones have long half-lives in the body, ranging from many minutes to hours.

Metabolism of Adrenal Steroids in the Liver. Adrenal steroid hormones are eliminated from the body primarily by excretion in the urine after they have been structurally modified to destroy their hormone activity and increase their water solubility. Although many cells are capable of carrying out these modifications, they primarily occur in the liver.

The most common structural modifications made in adrenal steroids involve reduction of the double bond in ring A and conjugation of the resultant hydroxyl group formed on carbon 3 with glucuronic acid. Figure 34.6 shows how cortisol is modified in this manner to produce a major excretable metabolite, **tetrahydrocortisol glucuronide**. Cortisol, and other 21-carbon steroids with a 17α-hydroxyl group and a 20-keto group, may undergo lysis of the carbon 20–21 side chain as well. The resultant metabolite, with a keto group on carbon 17, appears as one of the **17-ketosteroids** in the urine. Adrenal androgens are also 17-ketosteroids. They are usually conjugated with sulfuric acid or glucuronic acid before being excreted and normally comprise the bulk of the 17-ketosteroids in the urine. Before the development of specific methods to measure androgens and 17α-hydroxycorticosteroids in body fluids, the amount of 17-ketosteroids in urine was used clinically as a crude in-

CLINICAL FOCUS BOX 34.1

Primary Adrenal Insufficiency: Addison's Disease

Adrenal insufficiency may be caused by destruction of the adrenal cortex (primary adrenal insufficiency), low pituitary ACTH secretion (secondary adrenal insufficiency), or deficient hypothalamic release of CRH (tertiary adrenal insufficiency). **Addison's disease** (primary adrenal insufficiency) results from the destruction of the adrenal gland by microorganisms or autoimmune disease. When Addison's first described primary adrenal insufficiency in the mid-1800s, bilateral adrenal destruction by tuberculosis was the most common cause of the disease. Today, autoimmune destruction accounts for 70 to 90% of all cases, with the remainder the resulting from infection, cancer, or adrenal hemorrhage. The prevalence of primary adrenal insufficiency is about 40 to 110 cases per 1 million adults, with an incidence of about 6 cases per 1 million adults per year.

In primary adrenal insufficiency, all three zones of the adrenal cortex are usually involved. The result is inadequate secretion of glucocorticoids, mineralocorticoids, and androgens. Major symptoms are not usually detected until 90% of the gland has been destroyed. The initial symptoms generally have a gradual onset, with only a partial glucocorticoid deficiency resulting in inadequate cortisol increase in response to stress. Mineralocorticoid deficiency may only appear as a mild postural hypotension. Progression to complete glucocorticoid deficiency results in a decreased sense of well-being and abnormal glucose metabolism. Lack of mineralocorticoid leads to decreased renal potassium secretion and reduced sodium retention, the loss of which results in hypotension and dehydration. The combined lack of glucocorticoid and mineralocorticoid can lead to vascular collapse, shock, and death. Adrenal androgen deficiency is observed in women only (men derive most of their androgen from the testes) as decreased pubic and axillary hair and decreased libido.

Antibodies that react with all three zones of the adrenal cortex have been identified in autoimmune adrenalitis and are more common in women than in men. The presence of antibodies appears to precede the development of adrenal insufficiency by several years. Antiadrenal antibodies are mainly directed to the steroidogenic enzymes cholesterol side-chain cleavage enzyme (CYP11A1), 17α-hydroxylase (CYP17) and 21-hydroxylase (CYP21A2), although antibodies to other steroidogenic enzymes may also be present. In the initial stages of the disease, the adrenal glands may be enlarged with extensive lymphocyte infiltration. Genetic susceptibility to autoimmune adrenal insufficiency is strongly linked with the HLA-B8, HLA-DR3, and HLA-DR4 alleles of human leukocyte antigen (HLA). The earliest sign of adrenal insufficiency is an increase in plasma renin activity, with a low or normal aldosterone level, which suggests that the zona glomerulosa is affected first during disease progression.

Treatment for acute adrenal insufficiency should be directed at reversal of the hypotension and electrolyte abnormalities. Large volumes of 0.9% saline or 5% dextrose in saline should be infused as quickly as possible. Dexamethasone or a soluble form of injectable cortisol should also be given. Daily glucocorticoid and mineralocorticoid replacement allows the patient to lead a normal active life.

Reference

Orth DN, Kovacs WJ. The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams Textbook of Endocrinology. 9th Ed. Philadelphia: WB Saunders, 1998;517–664.

dicator of the production of these substances by the adrenal gland.

ACTH Regulates the Synthesis of Adrenal Steroids

Adrenocorticotropic hormone (ACTH) is the physiological regulator of the synthesis and secretion of glucocorticoids and androgens by the zona fasciculata and zona reticularis. It has a very rapid stimulatory effect on steroidogenesis in these cells, which can result in a great rise in blood glucocorticoids within seconds. It also exerts several long-term trophic effects on these cells, all directed toward maintaining the cellular machinery necessary to carry out steroidogenesis at a high, sustained rate. These actions of ACTH are summarized in Figure 34.7.

Role of cAMP. When the level of ACTH in the blood rises, increased numbers of ACTH molecules interact with receptors on the plasma membranes of adrenal cortical cells. These ACTH receptors are coupled to the enzyme adenylyl cyclase by stimulatory guanine nucleotide-binding proteins (G_s proteins). The production of cAMP from ATP greatly increases, and the concentration of cAMP rises in the cell. cAMP activates protein kinase A (PKA), which phosphorylates proteins that regulate steroidogenesis.

The rapid rise in cAMP produced by ACTH stimulates the mechanism that transfers cholesterol into the inner mitochondrial membrane. This action provides abundant cholesterol for side-chain cleavage enzyme, which carries out the rate-limiting step in steroidogenesis. As a result, the rates of steroid hormone formation and secretion rise greatly.

Gene Expression for Steroidogenic Enzymes. Adrenocorticotropic hormone maintains the capacity of the cells of the zona fasciculata and zona reticularis to produce steroid hormones by stimulating the transcription of the genes for many of the enzymes involved in steroidogenesis. For example, transcription of the genes for side-chain cleavage enzyme, 17α-hydroxylase, 21-hydroxylase, and 11β-hydroxylase, is increased several hours after adrenal cortical cells have been stimulated by ACTH. Because normal individuals are continually exposed to episodes of ACTH secretion (see Fig. 32.7), the mRNA for these enzymes is well maintained in the cells. Again, this long-term or maintenance effect of ACTH is due to its ability to increase cAMP in the cells (see Fig. 34.7).

The importance of ACTH in gene transcription be-

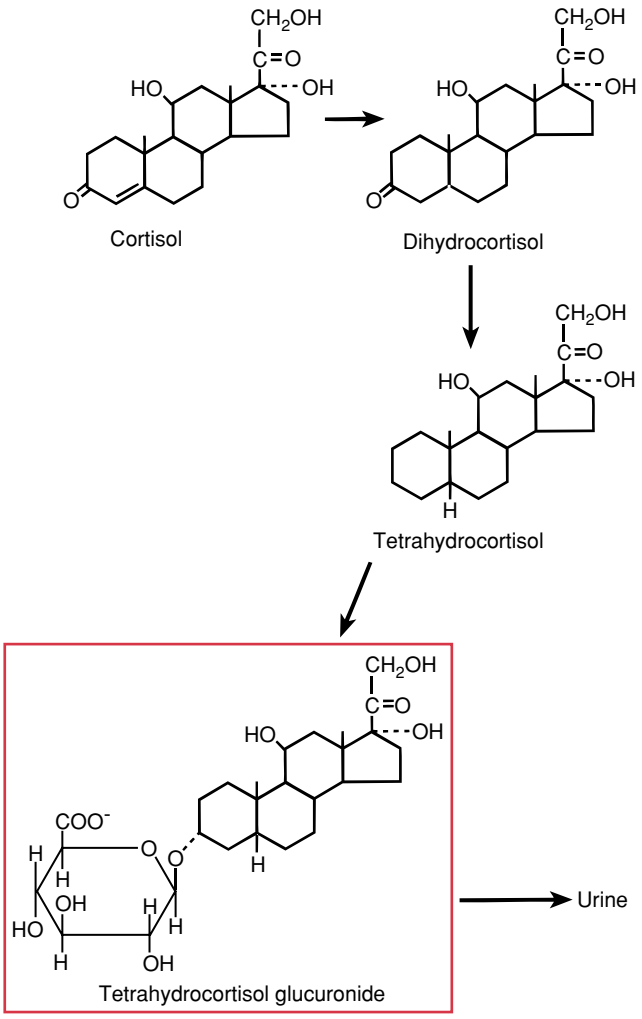


FIGURE 34.6 **The metabolism of cortisol to tetrahydrocortisol glucuronide in the liver.** The reduced and conjugated steroid is inactive. Because it is more water-soluble than cortisol, it is easily excreted in the urine.

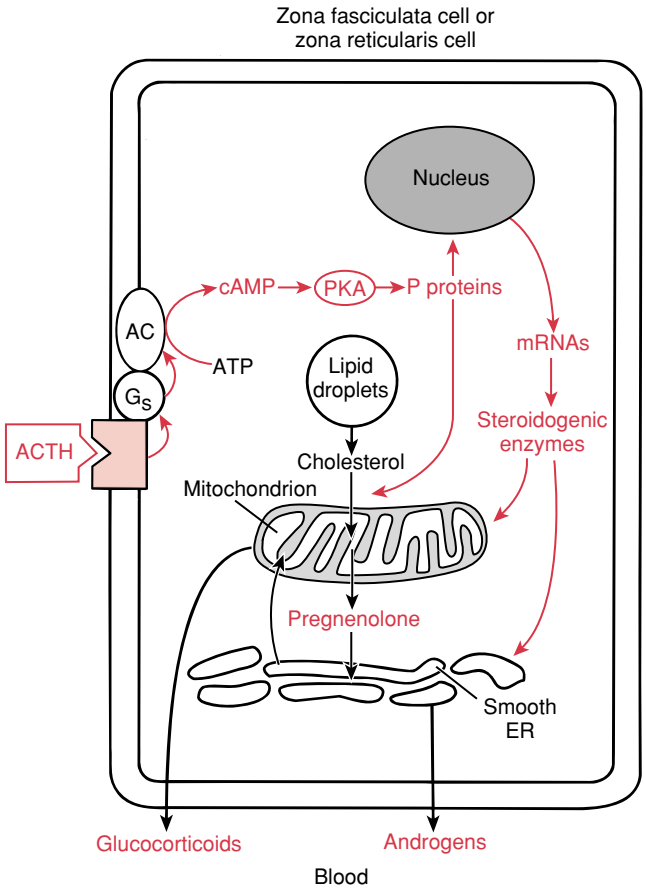


FIGURE 34.7 **The main actions of ACTH on steroidogenesis.** ACTH binds to plasma membrane receptors, which are coupled to adenylyl cyclase (AC) by stimulatory G proteins (G_s). cAMP rises in the cells and activates protein kinase A (PKA), which then phosphorylates certain proteins (P-Proteins). These proteins presumably initiate steroidogenesis and stimulate the expression of genes for steroidogenic enzymes.

comes evident in hypophysectomized animals or humans with ACTH deficiency. An example of the latter is a human treated chronically with large doses of cortisol or related steroids, which causes prolonged suppression of ACTH secretion by the anterior pituitary. The chronic lack of ACTH decreases the transcription of the genes for steroidogenic enzymes, causing a deficiency in these enzymes in the adrenals. As a result, the administration of ACTH to such an individual does not cause a marked increase in glucocorticoid secretion. Chronic exposure to ACTH is required to restore mRNA levels for the steroidogenic enzymes and, hence, the enzymes themselves, to obtain normal steroidogenic responses to ACTH. A patient receiving long-term treatment with glucocorticoid may suffer serious glucocorticoid deficiency if hormone therapy is halted abruptly; withdrawing glucocorticoid therapy gradually allows time for endogenous ACTH to restore steroidogenic enzyme levels to normal.

Effects on Cholesterol Metabolism. ACTH has several long-term effects on cholesterol metabolism that support steroidogenesis in the zona fasciculata and zona reticularis. It increases the abundance of LDL receptors and the activity of the enzyme HMG-CoA reductase in these cells. These actions increase the availability of cholesterol for steroidogenesis. It is not clear whether ACTH exerts these effects directly. The abundance of LDL receptors in the plasma membrane and the activity of HMG-CoA reductase in most cells are inversely related to the amount of cellular cholesterol. By stimulating steroidogenesis, ACTH reduces the amount of cholesterol in adrenal cells; therefore, the increased abundance of LDL receptors and high HMG-CoA reductase activity in ACTH-stimulated cells may merely result from the normal compensatory mechanisms that function to maintain cell cholesterol levels.

ACTH also stimulates the activity of cholesterol esterase in adrenal cells, which promotes the hydrolysis of the cholesterol esters stored in the lipid droplets of these cells, making free cholesterol available for steroidogenesis. The cholesterol esterase in the adrenal cortex appears to be identical to hormone-sensitive lipase, which is activated when it is phosphorylated by a cAMP-dependent protein

kinase. The rise in cAMP concentration produced by ACTH might account for its effect on the enzyme.

Trophic Action on Adrenal Cortical Cell Size. ACTH maintains the size of the two inner zones of the adrenal cortex, presumably by stimulating the synthesis of structural elements of the cells; however, it does not affect the size of the cells of the zona glomerulosa. The trophic effect of ACTH is clearly evident in states of ACTH deficiency or excess. In hypophysectomized or ACTH-deficient individuals, the cells of the two inner zones atrophy. Chronic stimulation of these cells with ACTH causes them to hypertrophy. The mechanisms involved in this trophic action of ACTH are unclear.

ACTH and Aldosterone Production. The cells of the zona glomerulosa have ACTH receptors, which are coupled to adenylyl cyclase. In these cells, cAMP increases in response to ACTH, resulting in some increase in aldosterone secretion. However, angiotensin II is the important physiological regulator of aldosterone secretion, not ACTH. Other factors, such as an increase in serum potassium, can also stimulate aldosterone secretion, but normally, they play only a secondary role.

Formation of Angiotensin II. Angiotensin II is a short peptide consisting of eight amino acid residues. It is formed in the bloodstream by the proteolysis of the α_2-globulin **angiotensinogen**, which is secreted by the liver. The formation of angiotensin II occurs in two stages (Fig. 34.8). Angiotensinogen is first cleaved at its N-terminal end by the circulating protease **renin**, releasing the inactive decapeptide **angiotensin I**. Renin is produced and secreted by granular (juxtaglomerular) cells in the kidneys (see Chapter 23). A dipeptide is then removed from the C-terminal end of angiotensin I, producing angiotensin II. This cleavage is performed by the protease **angiotensin-converting enzyme** present on the endothelial cells lining the vasculature. This step usually occurs as angiotensin I molecules traverse the pulmonary circulation. The rate-limiting factor for the formation of angiotensin II is the renin concentration of the blood.

Cleavage of the N-terminal aspartate from angiotensin II results in the formation of angiotensin III, which circulates at a concentration of 20% that of angiotensin II. Angiotensin III is as potent a stimulator of aldosterone secretion as angiotensin II.

Action of Angiotensin II on Aldosterone Secretion. Angiotensin II stimulates aldosterone synthesis by promoting the rate-limiting step in steroidogenesis (i.e., the movement of cholesterol into the inner mitochondrial membrane and its conversion to pregnenolone). The primary mechanism is shown in Figure 34.9.

The stimulation of aldosterone synthesis is initiated when angiotensin II binds to its receptors on the plasma membranes of zona glomerulosa cells. The signal generated by the interaction of angiotensin II with its receptors is transmitted to phospholipase C (PLC) by a G protein, and the enzyme becomes activated. The PLC then hydrolyzes phosphatidylinositol 4,5 bisphosphate (PIP_2) in the plasma membrane, producing the intracellular second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG). The IP_3 mobilizes calcium, which is bound to intracellular structures, increasing the calcium concentration in the cytosol. This increase in intracellular calcium and DAG activates protein kinase C (PKC). The rise in intracellular calcium also activates **calmodulin-dependent protein kinase** (CMK). These enzymes phosphorylate proteins, which then become involved in initiating steroidogenesis.

Signals for Increased Angiotensin II Formation. Although angiotensin II is the final mediator in the physiological regulation of aldosterone secretion, its formation from angiotensinogen is dependent on the secretion of renin by the kidneys. The rate of renin secretion ultimately determines the rate of aldosterone secretion. Renin is secreted by the granular cells in the walls of the afferent arterioles of renal glomeruli. These cells are stimulated to secrete renin by three signals that indicate a possible loss of body fluid: a fall in blood pressure in the afferent arterioles of the glomeruli, a drop in sodium chloride concentration in renal tubular fluid at the macula densa, and an increase in renal sympathetic nerve activity (see Chapters 23 and 24).

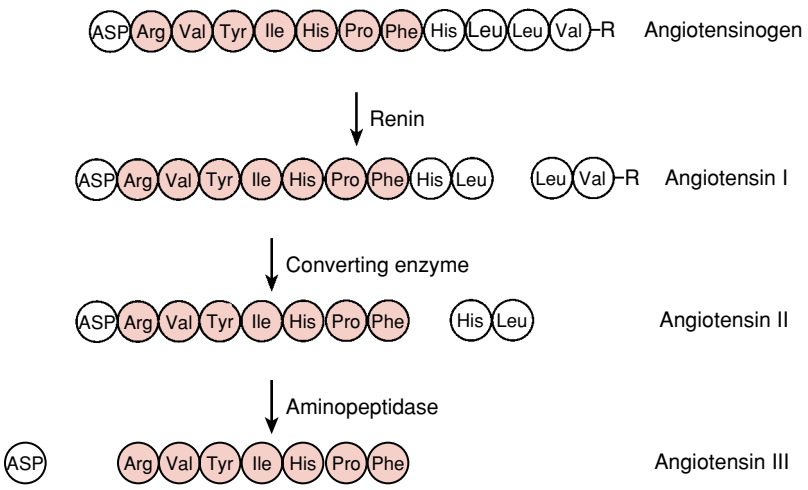


FIGURE 34.8 **The formation of angiotensins I, II, and III from angiotensinogen.**

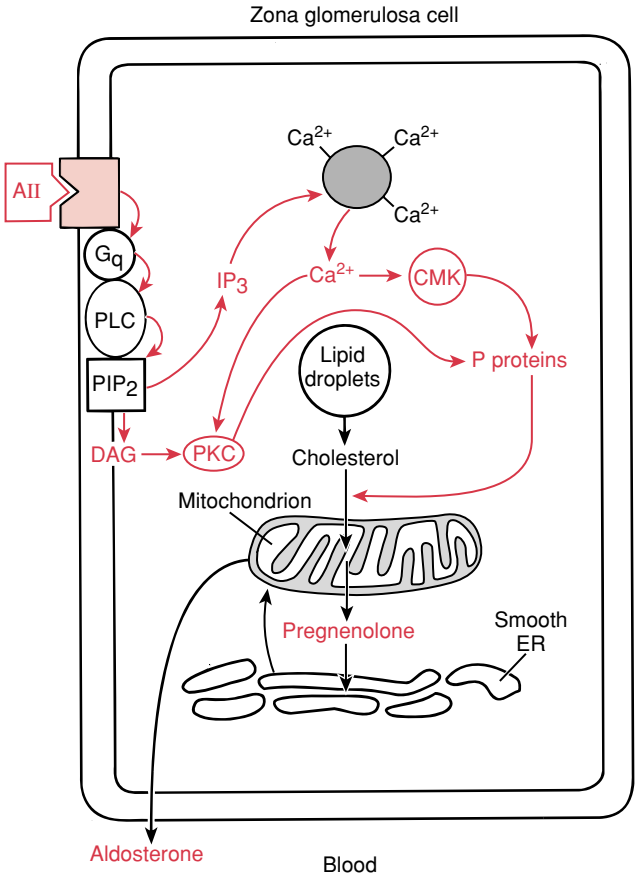


FIGURE 34.9 The action of angiotensin II on aldosterone synthesis. Angiotensin II (AII) binds to receptors on the plasma membrane of zona glomerulosa cells. This activates phospholipase C (PLC), which is coupled to the angiotensin II receptor by G proteins (G_q). PLC hydrolyzes phosphatidylinositol 4,5 bisphosphate (PIP_2) in the plasma membrane, producing inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes intracellularly bound Ca^{2+}. The rise in Ca^{2+} and DAG activates protein kinase C (PKC) and calmodulin-dependent protein kinase (CMK). These enzymes phosphorylate proteins (P-Proteins) involved in initiating aldosterone synthesis.

Increased renin secretion results in an increase in angiotensin II formation in the blood, thereby stimulating aldosterone secretion by the zona glomerulosa. This series of events tends to conserve body fluid volume because aldosterone stimulates sodium reabsorption by the kidneys.

Extracellular Potassium Concentration and Aldosterone Secretion. Aldosterone secretion is also stimulated by an increase in the potassium concentration in extracellular fluid, caused by a direct effect of potassium on zona glomerulosa cells. Glomerulosa cells are sensitive to this effect of extracellular potassium and, therefore, increase their rate of aldosterone secretion in response to small increases in blood and interstitial fluid potassium concentration. This signal for aldosterone secretion is appropriate from a physiological point of view because aldosterone promotes the renal excretion of potassium (see Chapter 24).

A rise in extracellular potassium depolarizes glomerulosa cell membranes, activating voltage-dependent calcium channels in the membranes. The consequent rise in cytosolic calcium is thought to stimulate aldosterone synthesis by the mechanisms described above for the action of angiotensin II.

Aldosterone and Sodium Reabsorption by Kidney Tubules. The physiological action of aldosterone is to stimulate sodium reabsorption in the kidneys by the distal tubule and collecting duct of the nephron and to promote the excretion of potassium and hydrogen ions. The mechanism of action of aldosterone on the kidneys and its role in water and electrolyte balance are discussed in Chapter 24.

Glucocorticoids Play a Role in the Reactions to Fasting, Injury, and Stress

Glucocorticoids widely influence physiological processes. In fact, most cells have receptors for glucocorticoids and are potential targets for their actions. Consequently, glucocorticoids have been used extensively as therapeutic agents, and much is known about their pharmacological effects.

Actions on Transcription. Unlike many other hormones, glucocorticoids influence physiological processes slowly, sometimes taking hours to produce their effects. Glucocorticoids that are free in the blood diffuse through the plasma membranes of target cells; once inside, they bind tightly but noncovalently to receptor proteins present in the cytoplasm. The interaction between the glucocorticoid molecule and its receptor molecule produces an activated glucocorticoid-receptor complex, which translocates into the nucleus.

These complexes then bind to specific regions of DNA called **glucocorticoid response elements** (GREs), which are near glucocorticoid-sensitive target genes. The binding triggers events that either stimulate or inhibit the transcription of the target gene. As a result of the change in transcription, amounts of mRNA for certain proteins are either increased or decreased. This, in turn, affects the abundance of these proteins in the cell, which produces the physiological effects of the glucocorticoids. The apparent slowness of glucocorticoid action is due to the time required by the mechanism to change the protein composition of a target cell.

Glucocorticoids and the Metabolic Response to Fasting. During the fasting periods between food intake in humans, metabolic adaptations prevent hypoglycemia. The maintenance of sufficient blood glucose is necessary because the brain depends on glucose for its energy needs. Many of the adaptations that prevent hypoglycemia are not fully expressed in the course of daily life because the individual eats before they fully develop. Full expression of these changes is seen only after many days to weeks of fasting. Glucocorticoids are necessary for the metabolic adaptation to fasting.

At the onset of a prolonged fast, there is a gradual decline in the concentration of glucose in the blood. Within 1 to 2 days, the blood glucose level stabilizes at a concentration of 60 to 70 mg/dL, where it remains even if the fast is prolonged for many days (Fig. 34.10). The blood glucose

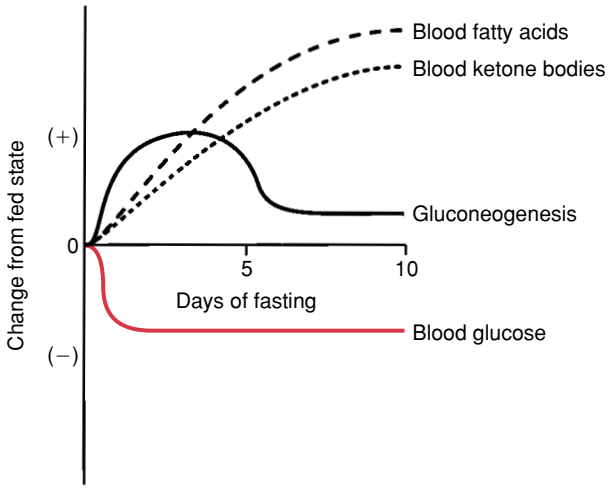


FIGURE 34.10 **Metabolic adaptations during fasting.** This graphs shows the changes in the concentrations of blood glucose, fatty acids, and ketone bodies and the rate of gluconeogenesis during the course of a prolonged fast. Only the *direction* of change over time is indicated: increase (+) or decrease (−).

level is stabilized by the production of glucose by the body and the restriction of its use by tissues other than the brain. Although a limited supply of glucose is available from glycogen stored in the liver, the more important source of blood glucose during the first days of a fast is gluconeogenesis in the liver and, to some extent, in the kidneys.

Gluconeogenesis begins several hours after the start of a fast. Amino acids derived from tissue protein are the main substrates. Fasting results in protein breakdown in the skeletal muscle and accelerated release of amino acids into the bloodstream. Protein breakdown and protein accretion in adult humans are regulated by two opposing hormones, insulin and glucocorticoids. During fasting, insulin secretion is suppressed and the inhibitory effect of insulin on protein breakdown is lost. As proteins are broken down, glucocorticoids inhibit the reuse of amino acids derived from tissue proteins for new protein synthesis, promoting the release of these amino acids from the muscle. Amino acids released into the blood by the skeletal muscle are extracted from the blood at an accelerated rate by the liver and kidneys. The amino acids then undergo metabolic transformations in these tissues, leading to the synthesis of glucose. The newly synthesized glucose is then delivered to the bloodstream.

The glucocorticoids are essential for the acceleration of gluconeogenesis during fasting. They play a permissive role in this process by maintaining gene expression and, therefore, the intracellular concentrations of many of the enzymes needed to carry out gluconeogenesis in the liver and kidneys. For example, glucocorticoids maintain the amounts of transaminases, pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, fructose-6-phosphatase, and glucose-6-phosphatase needed to carry out gluconeogenesis at an accelerated rate. In an untreated, glucocorticoid-deficient individual, the amounts of these enzymes in the liver are greatly reduced. As a consequence, the individual cannot respond to fasting with accelerated gluconeogenesis and will die from hypoglycemia. In essence, the glucocorticoids maintain the liver and kidney in a state that enables them to carry out accelerated gluconeogenesis should the need arise.

The other important metabolic adaptation that occurs during fasting involves the mobilization and use of stored fat. Within the first few hours of the start of a fast, the concentration of free fatty acids rises in the blood (see Fig. 34.10). This action is due to the acceleration of lipolysis in the fat depots, as a result of the activation of **hormone-sensitive lipase** (HSL). HSL hydrolyzes the stored triglyceride to free fatty acids and glycerol, which are released into the blood.

HSL is activated when it is phosphorylated by a cAMP-dependent protein kinase. As the level of insulin falls in the blood during fasting, the inhibitory effect of insulin on cAMP accumulation in the fat cell diminishes. There is a rise in the cellular level of cAMP, and HSL is activated. The glucocorticoids are essential for maintaining fat cells in an enzymatic state that permits lipolysis to occur during a fast. This is evident from the fact that accelerated lipolysis does not occur when a glucocorticoid-deficient individual fasts.

The abundant fatty acids produced by lipolysis are taken up by many tissues. The fatty acids enter mitochondria, undergo β-oxidation to acetyl CoA, and become the substrate for ATP synthesis. The enhanced use of fatty acids for energy metabolism spares the blood glucose supply. There is also significant gluconeogenesis in liver from the glycerol released from triglyceride by lipolysis. In prolonged fasting, when the rate of glucose production from body protein has declined, a significant fraction of blood glucose is derived from triglyceride glycerol.

Within a few hours of the start of a fast, the increased delivery to and oxidation of fatty acids in the liver results in the production of the ketone bodies. As a result of these events in the liver, a gradual rise in ketone bodies occurs in the blood as a fast continues over many days (Fig. 34.10). Ketone bodies become the principal energy source used by the CNS during the later stages of fasting.

The increased use of fatty acids for energy metabolism by skeletal muscle results in less use of glucose in this tissue, sparing blood glucose for use by the CNS. Two products resulting from the breakdown of fatty acids, acetyl CoA and citrate, inhibit glycolysis. As a result, the uptake and use of glucose from the blood is reduced.

In summary, the strategy behind the metabolic adaptation to fasting is to provide the body with glucose produced primarily from protein until the ketone bodies become abundant enough in the blood to be a principal source of energy for the brain. From that point on, the body uses mainly fat for energy metabolism, and it can survive until the fat depots are exhausted. Glucocorticoids do not trigger the metabolic adaptations to fasting but only provide the metabolic machinery necessary for the adaptations to occur.

Cushing's Disease. When present in excessive amounts, glucocorticoids can trigger many of the metabolic adaptations to the fasting state. **Cushing's disease** is the name of such pathological hypercortisolic states. Cushing's disease

may be ACTH-dependent or ACTH-independent. One type of ACTH-dependent syndrome (actually called **Cushing's disease**) is caused by a corticotroph adenoma, which secretes excessive ACTH and stimulates the adrenal cortex to produce large amounts of cortisol. ACTH-independent Cushing's syndrome is usually due toa result of an adrenocortical adenoma that secretes large amounts of cortisol. Whatever the cause, prolonged exposure of the body to large amounts of glucocorticoids causes the breakdown of skeletal muscle protein, increased glucose production by the liver, and mobilization of lipid from the fat depots. Despite the increased mobilization of lipid, there is also an abnormal deposition of fat in the abdominal region, between the shoulders, and in the face. The increased mobilization of lipid provides abundant fatty acids for metabolism and the increased oxidation of fatty acids by tissues reduces their ability to use glucose. The underutilization of glucose by skeletal muscle, coupled with increased glucose production by the liver, results in hyperglycemia, which, in turn, stimulates the pancreas to secrete insulin. In this instance, however, the rise in insulin is not effective in reducing the blood glucose concentration because glucose uptake and use are decreased in the skeletal muscle and adipose tissue. Evidence also indicates that excessive glucocorticoids decrease the affinity of insulin receptors for insulin. The net result is that the individual becomes insensitive or resistant to the action of insulin and little glucose is removed from the blood, despite the high level of circulating insulin. The persisting hyperglycemia continually stimulates the pancreas to secrete insulin. The result is a form of "diabetes" similar to Type 2 diabetes mellitus (see Chapter 35).

The opposite situation occurs in the glucocorticoid-deficient individual. Little lipid mobilization and use occur, so there is little restriction on the rate of glucose use by tissues. The glucocorticoid-deficient individual is sensitive to insulin in that a given concentration of blood insulin is more effective in clearing the blood of glucose than it is in a healthy person. The administration of even small doses of insulin to such individuals may produce hypoglycemia.

The Anti-inflammatory Action of Glucocorticoids. Tissue injury triggers a complex mechanism called **inflammation** that precedes the actual repair of damaged tissue. A host of chemical mediators are released into the damaged area by neighboring cells, adjacent vasculature, and phagocytic cells that migrate to the damaged site. Mediators released under these circumstances include **prostaglandins, leukotrienes, kinins, histamine, serotonin,** and **lymphokines**. These substances exert a multitude of actions at the site of injury and directly or indirectly promote the local vasodilation, increased capillary permeability, and edema formation that characterize the inflammatory response (see Chapter 11).

Because glucocorticoids inhibit the inflammatory response to injury, they are used extensively as therapeutic anti-inflammatory agents; however, the mechanisms are not clear. Their regulation of the production of prostaglandins and leukotrienes is the best understood. These substances play a major role in mediating the inflammatory reaction. They are synthesized from the unsaturated fatty acid arachidonic acid, which is released from plasma membrane phospholipids by the hydrolytic action of **phospholipase A_2**. Glucocorticoids stimulate the synthesis of a family of proteins called **lipocortins** in their target cells. Lipocortins inhibit the activity of phospholipase A_2, reducing the amount of arachidonic acid available for conversion to prostaglandins and leukotrienes.

Effects on the Immune System. Glucocorticoids have little influence on the human immune system under normal physiological conditions. When administered in large doses over a prolonged period, however, they can suppress antibody formation and interfere with cell-mediated immunity. Glucocorticoid therapy, therefore, is used to suppress the rejection of surgically transplanted organs and tissues.

Immature T cells in the thymus and immature B cells and T cells in lymph nodes can be killed by exposure to high concentrations of glucocorticoids, decreasing the number of circulating lymphocytes. The destruction of immature T and B cells by glucocorticoids also causes some reduction in the size of the thymus and lymph nodes.

Maintenance of the Vascular Response to Norepinephrine. Glucocorticoids are required for the normal responses of vascular smooth muscle to the vasoconstrictor action of norepinephrine. NE is much less active on vascular smooth muscle in the absence of glucocorticoids and is another example of the permissive action of glucocorticoids.

Glucocorticoids and Stress. Perhaps the most interesting, but least understood, of all glucocorticoid action is the ability to protect the body against stress. All that is really known is that the body cannot cope successfully with even mild stresses in the absence of glucocorticoids. One must presume that the processes that enable the body to defend itself against physical or emotional trauma require glucocorticoids. This, again, emphasizes the permissive role they play in physiological processes.

Stress stimulates the secretion of ACTH, which increases the secretion of glucocorticoids by the adrenal cortex (see Chapter 32). In humans, this increase in glucocorticoid secretion during stress appears to be important for the appropriate defense mechanisms to be put into place. It is well known, for example, that glucocorticoid-deficient individuals receiving replacement therapy require larger doses of glucocorticoid to maintain their well-being during periods of stress.

Regulation of Glucocorticoid Secretion. An important physiological action of glucocorticoids is the ability to regulate their own secretion. This effect is achieved by a negative-feedback mechanism of glucocorticoids on the secretion of corticotropin-releasing hormone (CRH) and ACTH and on proopiomelanocortin (POMC) gene expression (see Chapter 32).

PRODUCTS OF THE ADRENAL MEDULLA

The catecholamines, epinephrine and norepinephrine, are the two hormones synthesized by the chromaffin cells of the adrenal medulla. The human adrenal medulla produces

and secretes about 4 times more epinephrine than norepinephrine. Postganglionic sympathetic neurons also produce and release NE from their nerve terminals but do not produce epinephrine.

Epinephrine and NE are formed in the chromaffin cells from the amino acid tyrosine. The pathway for the synthesis of catecholamines is illustrated in Figure 3.18.

Trauma, Exercise, and Hypoglycemia Stimulate the Medulla to Release Catecholamines

Epinephrine and some NE are released from chromaffin cells by the fusion of secretory granules with the plasma membrane. The contents of the granules are extruded into the interstitial fluid. The catecholamines diffuse into capillaries and are transported in the bloodstream.

Neural stimulation of the cholinergic preganglionic fibers that innervate chromaffin cells triggers the secretion of catecholamines. Stimuli such as injury, anger, anxiety, pain, cold, strenuous exercise, and hypoglycemia generate impulses in these fibers, causing a rapid discharge of the catecholamines into the bloodstream.

Catecholamines Have Rapid, Widespread Effects

Most cells of the body have receptors for catecholamines and, thus, are their target cells. There are four structurally related forms of catecholamine receptors, all of which are transmembrane proteins: α_1, α_2, β_1, and β_2. All can bind epinephrine or NE, to varying extents (see Chapter 3).

Fight-or-Flight Response. Epinephrine and NE produce widespread effects on the cardiovascular system, muscular system, and carbohydrate and lipid metabolism in liver, muscle, and adipose tissues. In response to a sudden rise in catecholamines in the blood, the heart rate accelerates, coronary blood vessels dilate, and blood flow to the skeletal muscles is increased as a result of vasodilation (but vasoconstriction occurs in the skin). Smooth muscles in the airways of the lungs, gastrointestinal tract, and urinary bladder relax. Muscles in the hair follicles contract, causing piloerection. Blood glucose level also rises. This overall reaction to the sudden release of catecholamines is known as the fight-or-flight response (see Chapter 6).

Catecholamines and the Metabolic Response to Hypoglycemia. Catecholamines secreted by the adrenal medulla and NE released from sympathetic postganglionic nerve terminals are key agents in the body's defense against hypoglycemia. Catecholamine release usually starts when the blood glucose concentration falls to the low end of the physiological range (60 to 70 mg/dL). A further decline in blood glucose concentration into the hypoglycemic range produces marked catecholamine release. Hypoglycemia can result from a variety of situations, such as insulin overdosing, catecholamine antagonists, or drugs that block fatty acid oxidation. Hypoglycemia is always a dangerous condition because the CNS will die of ATP deprivation in extended cases. The length of time profound hypoglycemia can be tolerated depends on its severity and the individual's sensitivity.

When the blood glucose concentration drops toward the hypoglycemic range, CNS receptors monitoring blood glucose are activated, stimulating the neural pathway leading to the fibers innervating the chromaffin cells. As a result, the adrenal medulla discharges catecholamines. Sympathetic postganglionic nerve terminals also release norepinephrine.

Catecholamines act on the liver to stimulate glucose production. They activate glycogen phosphorylase, resulting in the hydrolysis of stored glycogen, and stimulate gluconeogenesis from lactate and amino acids. Catecholamines also activate glycogen phosphorylase in skeletal muscle and adipose cells by interacting with β receptors, activating adenylyl cyclase and increasing cAMP in the cells. The elevated cAMP activates glycogen phosphorylase. The glucose 6-phosphate generated in these cells is metabolized, although glucose is not released into the blood, since the cells lack glucose-6-phosphatase. The glucose 6-phosphate in muscle is converted by glycolysis to lactate, much of which is released into the blood. The lactate taken up by the liver is converted to glucose via gluconeogenesis and returned to the blood.

In adipose cells, the rise in cAMP produced by catecholamines activates hormone-sensitive lipase, causing the hydrolysis of triglycerides and the release of fatty acids and glycerol into the bloodstream. These fatty acids provide an alternative substrate for energy metabolism in other tissues, primarily skeletal muscle, and block the phosphorylation and metabolism of glucose.

During profound hypoglycemia, the rapid rise in blood catecholamine levels triggers some of the same metabolic adjustments that occur more slowly during fasting. During fasting, these adjustments are triggered mainly in response to the gradual rise in the ratio of glucagon to insulin in the blood. The ratio also rises during profound hypoglycemia, reinforcing the actions of the catecholamines on glycogenolysis, gluconeogenesis, and lipolysis. The catecholamines released during hypoglycemia are thought to be partly responsible for the rise in the glucagon-to-insulin ratio by directly influencing the secretion of these hormones by the pancreas. Catecholamines stimulate the secretion of glucagon by the alpha cells and inhibit the secretion of insulin by beta cells (see Chapter 35). These catecholamine-mediated responses to hypoglycemia are summarized in Table 34.4.

TABLE 34.4 Catecholamine-Mediated Responses to Hypoglycemia

Liver	Stimulation of glycogenolysis
	Stimulation of gluconeogenesis
Skeletal muscle	Simulation of glycogenolysis
Adipose tissue	Simulation of glycogenolysis
	Stimulation of triglyceride lipolysis
Pancreatic islets	Inhibition of insulin secretion by beta cells
	Stimulation of glucagon secretion by alpha cells

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is the BEST in each case.

1. Which of the following sources of cholesterol is most important for sustaining adrenal steroidogenesis when it occurs at a high rate for a long time?
   (A) *De novo* synthesis of cholesterol from acetate
   (B) Cholesterol in LDL particles
   (C) Cholesterol in the plasma membrane
   (D) Cholesterol in lipid droplets within adrenal cortical cells
   (E) Cholesterol from the endoplasmic reticulum
   (F) Cholesterol in lipid droplets within adrenal medullary cells
2. A 7-year-old boy comes to the pediatric endocrine unit for evaluation of excess body weight. Review of his growth charts indicates substantial weight gain over the previous 3 years but little increase in height. To differentiate between the development of obesity and Cushing's disease, blood and urine samples are taken. Which of the following would be most diagnostic of Cushing's disease?
   (A) Increased serum ACTH, decreased serum cortisol, and increased urinary free cortisol
   (B) Decreased serum ACTH, increased serum cortisol, and increased serum insulin
   (C) Increased serum ACTH, increased serum cortisol, and increased serum insulin
   (D) Increased serum ACTH, decreased serum cortisol, and decreased serum insulin
   (E) Increased serum ACTH, decreased serum cortisol, and decreased urinary free cortisol
   (F) Decreased serum ACTH, decreased serum cortisol, and increased serum insulin
3. Congenital adrenal hyperplasia is most likely a result of
   (A) Defects in adrenal steroidogenic enzymes
   (B) Addison's disease
   (C) Defects in ACTH secretion
   (D) Defects in corticosteroid-binding globulin
   (E) Cushing's disease
   (F) Defects in aldosterone synthase
4. What is the mechanism through which catecholamines stabilize blood glucose concentration in response to hypoglycemia?
   (A) Catecholamines stimulate glycogen phosphorylase to release glucose from muscle
   (B) Catecholamines inhibit glycogenolysis in the liver
   (C) Catecholamines stimulate the release of insulin from the pancreas
   (D) Catecholamines inhibit the release of fatty acids from adipose tissue
   (E) Catecholamines stimulate gluconeogenesis in the liver
   (F) Catecholamines inhibit the release of lactate from muscle
5. A patient receiving long-term glucocorticoid therapy plans to undergo hip replacement surgery. What would the physician recommend prior to surgery and why?
   (A) Glucocorticoids should be decreased to prevent serious hypoglycemia during recovery
   (B) Glucocorticoids should be increased to stimulate immune function and prevent possible infection
   (C) Glucocorticoids should be decreased to minimize potential interactions with anesthetics
   (D) Glucocorticoids should be increased to stimulate ACTH secretion during surgery to promote wound healing
   (E) Glucocorticoids should be decreased to prevent inadequate vascular response to catecholamines during recovery
   (F) Glucocorticoids should be increased to compensate for the increased stress associated with surgery
6. Which of the following is most likely to result in a decreased rate of aldosterone release?
   (A) An increase in renin secretion by the kidney
   (B) A rise in serum potassium
   (C) A fall in blood pressure in the kidney
   (D) A decrease in tubule fluid sodium concentration at the macula densa
   (E) An increase in renal sympathetic nerve activity
   (F) A decrease in IP_3 in cells of the zona glomerulosa
7. The rate-limiting step in the synthesis of cortisol is catalyzed by
   (A) 21-Hydroxylase
   (B) 3β-Hydroxysteroid dehydrogenase
   (C) Cholesterol side-chain cleavage enzyme
   (D) 11β-Hydroxylase
   (E) 3-Hydroxy-3-methylglutaryl CoA reductase
   (F) 17α-Hydroxylase
8. A patient complains of generalized weakness and fatigue, anorexia, and weight loss associated with gastrointestinal symptoms (nausea, vomiting). Physical examination notes hyperpigmentation and hypotension. Laboratory findings include hyponatremia (low plasma sodium) and hyperkalemia (high plasma potassium). The most likely diagnosis is
   (A) Cushing's disease
   (B) Addison's disease
   (C) Primary hypoaldosteronism
   (D) Congenital adrenal hyperplasia
   (E) Hypopituitarism
   (F) Glucocorticoid-suppressible hyperaldosteronism
9. Through what "permissive action" do glucocorticoids accelerate gluconeogenesis during fasting?
   (A) Glucocorticoids stimulate the secretion of insulin, which activates gluconeogenic enzymes in the liver
   (B) Glucocorticoids inhibit the use of glucose by skeletal muscle
   (C) Glucocorticoids maintain the vascular response to norepinephrine
   (D) Glucocorticoids inhibit glycogenolysis
   (E) Glucocorticoids maintain the intracellular concentrations of many of the enzymes needed to carry out gluconeogenesis through effects on transcription
   (F) Glucocorticoids inhibit the release of fatty acids from adipose tissue

SUGGESTED READING

Bornstein SR, Chrousos GP. Clinical review 104. Adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: Neural and immune inputs. J Clin Endocrinol Metab 1999;84:1729–1736.

Lumbers ER. Angiotensin and aldosterone. Regul Pept 1999;80:91–100.

Miller WL: Early steps in androgen biosynthesis: From cholesterol to DHEA. Baillieres Clin Endocrinol Metab 1998;12:67–81.

Nordenstrom A, Thilen A, Hagenfeldt L, Larsson A, Wedell A. Genotyping is a valuable diagnostic complement to neonatal screening for congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency. J Clin Endocrinol Metab 1999;84:1505–1509.

(continued)

Orth DN, Kovacs WJ. The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams Textbook of Endocrinology. 9th Ed. Philadelphia: WB Saunders, 1998.

Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21:55–89.

Young JB, Landsberg L. Catecholamines and the adrenal medulla. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds: Williams Textbook of Endocrinology. 9th Ed. Philadelphia: WB Saunders, 1998.