43
The Adrenal Gland

LEARNING OBJECTIVES

Upon completion of this chapter, you should be able to answer the following questions:

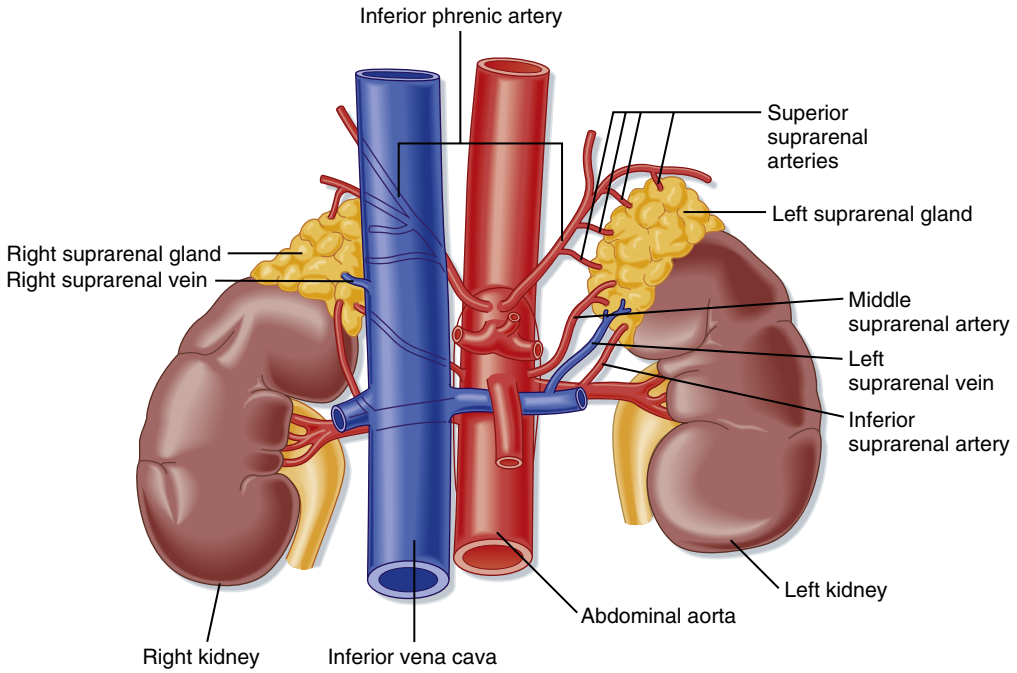
1. Describe the anatomy and microscopic anatomy of the adrenal gland, including the chromaffin cells of the adrenal medulla and the three zones of the adrenal cortex.
2. Explain the enzymatic reactions involved in generating norepinephrine and epinephrine and integrate those reactions with the regulation of epinephrine synthesis and secretion by the adrenal medulla.
3. Utilize the specific actions of catecholamines to explain an overall sympathetic response to a stress imposed on the body.
4. Describe the first two common reactions of the steroidogenic pathway, and their subcellular locations, and the function of StAR protein in the first reaction.
5. Compare the steroidogenic pathways within the zona glomerulosa, zona fasciculata, and zona reticularis with respect to common and zona-specific reactions.
6. Describe the mechanism of action of glucocorticoids and mineralocorticoids, including the cross-reactivity of cortisol with the mineralocorticoid receptor, and the mechanism to prevent this.
7. Integrate the multiple actions of cortisol throughout the body to explain the hormone's role during normal development and physiology, and to describe the multiple aspects of the pathophysiology of Addison's disease and Cushing's syndrome.
8. Map out the hypothalamic-pituitary-adrenal axis, including the "loophole" in the feedback mechanisms that leads to excessive androgen production (e.g., in congenital adrenal hyperplasia) in the face of an enzyme deficiency specific to the zona fasciculata and cortisol synthesis.
9. Review the regulation and actions of aldosterone.

In adults the adrenal glands emerge as fairly complex endocrine structures that produce two structurally distinct classes of hormones: steroids and catecholamines. The catecholamine hormone **epinephrine** acts as a rapid responder to stresses such as hypoglycemia and exercise to regulate multiple parameters of physiology, including energy metabolism and cardiac output. Stress is also a major secretagogue of the longer-acting steroid hormone **cortisol,** which regulates glucose utilization, immune and inflammatory homeostasis, and numerous other processes. In addition, the adrenal glands regulate salt and volume homeostasis through the steroid hormone **aldosterone.** Finally, the adrenal gland secretes large amounts of the androgen precursor **dehydroepiandrosterone sulfate (DHEAS),** which plays a major role in fetoplacental estrogen synthesis and as a substrate for peripheral androgen synthesis in women.

Anatomy

The **adrenal glands** are bilateral structures located immediately above the kidneys (*ad,* near; *renal,* kidney) (Fig. 43.1). In humans they are also referred to as the **suprarenal glands** because they sit on the superior pole of each kidney. The adrenal glands are similar to the pituitary in that they are derived from both neuronal tissue and epithelial (or epithelial-like) tissue. The outer portion of the adrenal gland, called the **adrenal cortex** (Fig. 43.2), develops from mesodermal cells in the vicinity of the superior pole of the developing kidney. These cells form cords of epithelial endocrine cells. The cells of the cortex develop into steroidogenic cells (see Chapter 38). In adults the adrenal cortex is composed of three zones—the **zona glomerulosa,** the **zona fasciculata,** and the **zona reticularis**—that produce mineralocorticoids, glucocorticoids, and adrenal androgens, respectively (see Fig. 43.2B).

Soon after the cortex forms, neural crest–derived cells associated with the sympathetic ganglia, called **chromaffin cells,** migrate into the cortex and become encapsulated by cortical cells. Thus, the chromaffin cells establish the inner portion of the adrenal gland, which is called the **adrenal medulla** (see Fig. 43.2B). The chromaffin cells of the adrenal medulla are innervated by cholinergic preganglionic sympathetic neurons and can synthesize the catecholamine neurotransmitter **norepinephrine** from tyrosine. However, high levels of cortisol that drain into the medulla from the adrenal cortex induce expression of the enzyme **phenylethanolamine *N*-methyl transferase** (**PNMT**), which transfers a methyl group onto norepinephrine to produce the catecholamine hormone, **epinephrine,** the primary hormonal product of the adrenal medulla (see Fig. 43.2B).



• **Fig. 43.1** The adrenal glands sit on the superior poles of the kidneys and receive a rich arterial supply from the inferior, middle, and superior suprarenal arteries. The adrenals are drained by a single suprarenal vein. (Modified from Drake RL, Vogl W, Mitchell AWM. *Gray's Anatomy for Students.* Philadelphia: Churchill Livingstone; 2005.)

Adrenal Medulla

Instead of being secreted near a target organ and acting as neurotransmitters, adrenomedullary catecholamines are secreted into blood and act as hormones. About 80% of the cells of the adrenal medulla secrete **epinephrine,** and the remaining 20% secrete **norepinephrine.** Although circulating epinephrine is derived entirely from the adrenal medulla, only about 30% of the circulating norepinephrine comes from the medulla. The remaining 70% is released from postganglionic sympathetic nerve terminals and diffuses into the vascular system. Because the adrenal medulla is not the sole source of catecholamine production, this tissue is not essential for life.

Synthesis of Epinephrine

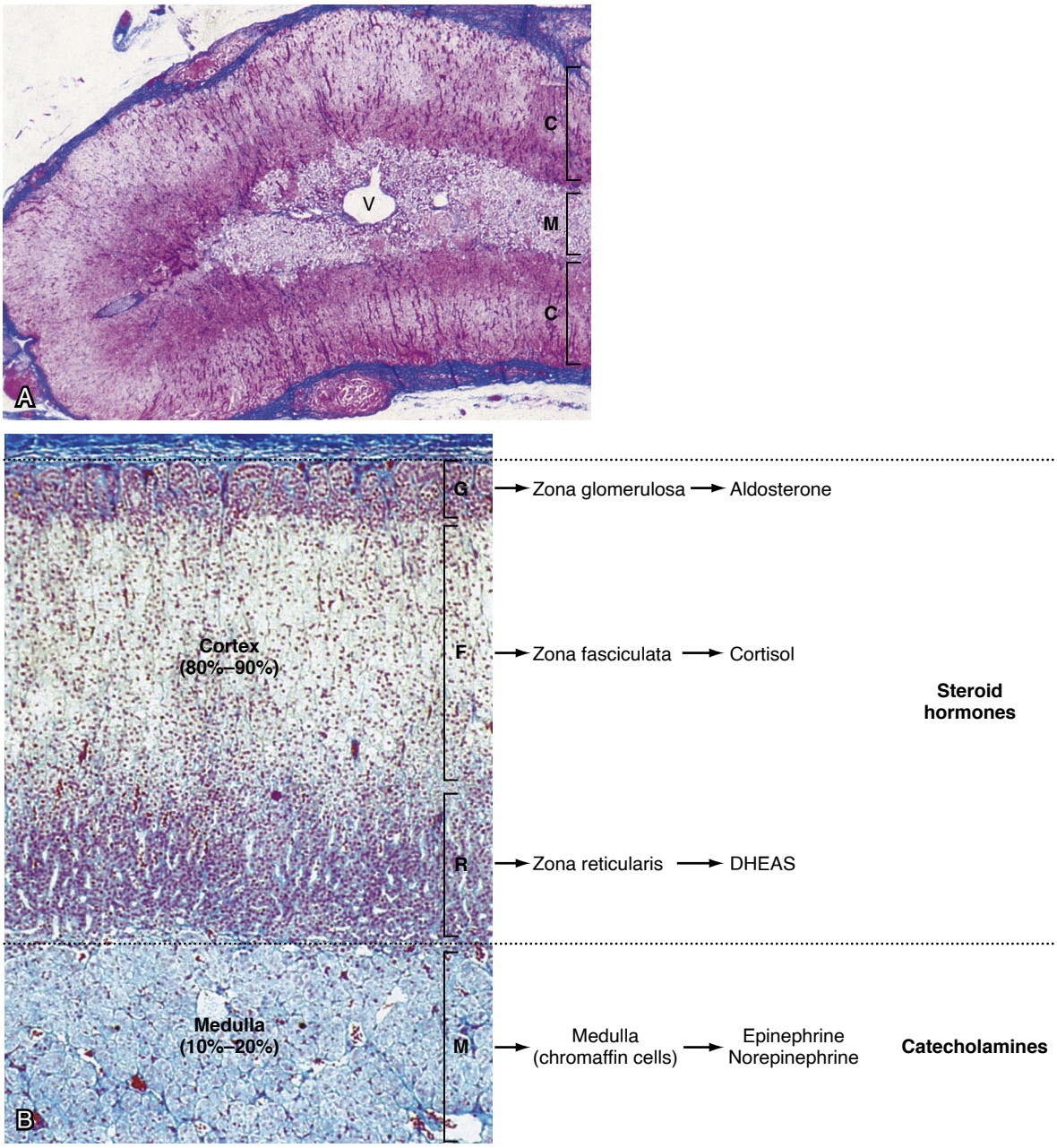
The enzymatic steps in epinephrine synthesis are shown in Fig. 43.4. Synthesis begins with transport of the amino acid **tyrosine** into the chromaffin cell cytoplasm and subsequent hydroxylation of tyrosine by the rate-limiting enzyme **tyrosine hydroxylase** to produce **dihydroxyphenylalanine (DOPA).** DOPA is converted to **dopamine** by a cytoplasmic enzyme, aromatic amino acid decarboxylase, and is then transported into the secretory vesicle (also called the **chromaffin granule**). Within the granule, all dopamine is completely converted to **norepinephrine** by the enzyme dopamine β-hydroxylase. In most adrenomedullary cells, essentially all of the norepinephrine diffuses out of the chromaffin granule by facilitated transport and is methylated by the cytoplasmic enzyme **PNMT** to form epinephrine.

AT THE CELLULAR LEVEL

The high local concentration of cortisol in the medulla is maintained by the vascular configuration within the adrenal gland. The outer connective tissue capsule of the adrenal gland is penetrated by a rich arterial supply coming from three main arterial branches: the inferior, middle, and superior suprarenal arteries (see Fig. 43.1). These give rise to two types of blood vessels that carry blood from the cortex to the medulla (Fig. 43.3): (1) relatively few medullary arterioles, which provide high oxygen- and nutrient-laden blood directly to the medullary chromaffin cells, and (2) relatively numerous cortical sinusoids into which cortical cells secrete steroid hormones (including cortisol). Both vessel types fuse to give rise to the medullary plexus of vessels that ultimately drains into a single suprarenal vein. Thus, secretions of the adrenal cortex percolate through the chromaffin cells and bathe them in high concentrations of cortisol before leaving the gland and entering the inferior vena cava. Cortisol inhibits neuronal differentiation of the medullary cells, so they fail to form dendrites and axons. Additionally, cortisol induces expression of the enzyme **PNMT,** which converts norepinephrine to epinephrine (Fig. 43.4). Glucocorticoid receptor–knockout mice have an enlarged cortex, but the size of the medulla is decreased and PNMT activity is undetectable.

Epinephrine is then transported back into the granule for storage and to undergo regulated exocytosis.

Secretion of epinephrine and norepinephrine from the adrenal medulla is regulated primarily by descending sympathetic signals in response to various forms of stress, including exercise, hypoglycemia, and hemorrhagic hypovolemia



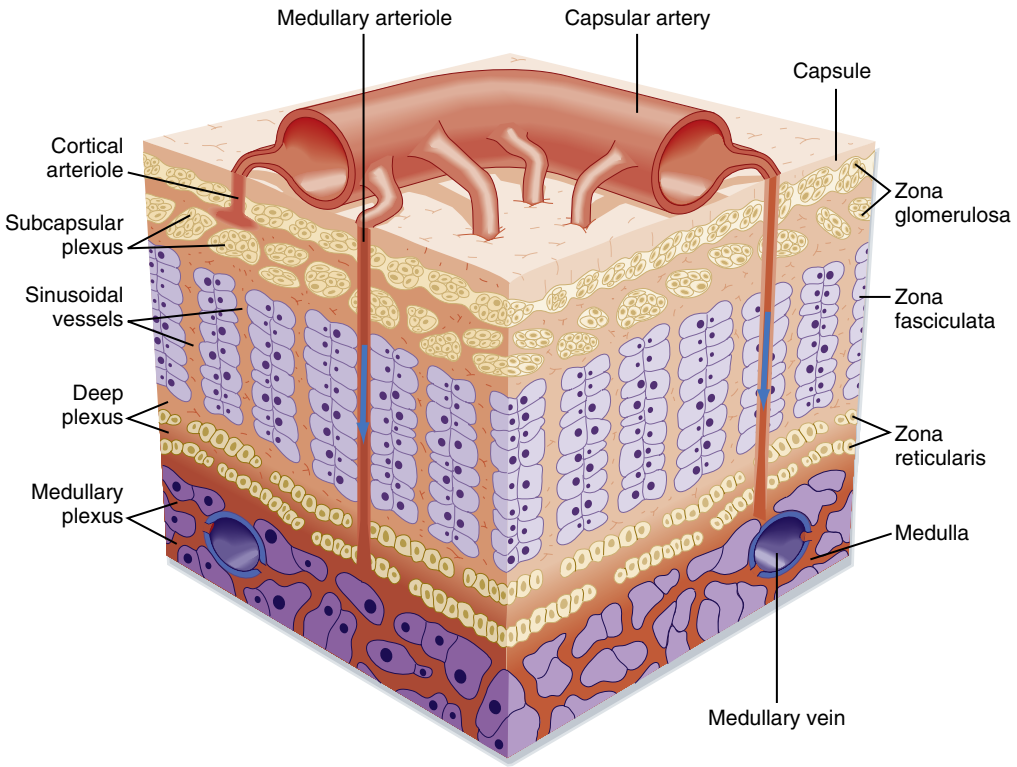
• **Fig. 43.2** Histology of the adrenal gland. **A,** Low magnification illustrating the outer cortex *(C)* and inner medulla (*M*; note the central vein *[V]*). **B,** Higher magnification clearly illustrating the zonation of the cortex. The corresponding endocrine function and the different zones of the cortex and the medulla are noted. *DHEAS*, Dehydroepiandrosterone sulfate. (From Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology.* 5th ed. Philadelphia: Churchill Livingstone; 2006.)

(Fig. 43.5). The primary autonomic centers that initiate sympathetic responses reside in the hypothalamus and brainstem, and they receive input from the cerebral cortex, the limbic system, and other regions of the hypothalamus and brainstem.

The chemical signal for secretion of catecholamine from the adrenal medulla is **acetylcholine (ACh),** which is secreted from **preganglionic sympathetic neurons** and binds to **nicotinic receptors** on chromaffin cells (see Fig. 43.5). ACh increases the activity of the rate-limiting enzyme tyrosine hydroxylase in chromaffin cells (see Fig. 43.4). It also increases the activity of dopamine β-hydroxylase and stimulates exocytosis of secretory granules from chromaffin cells. Synthesis of epinephrine and norepinephrine is closely coupled to secretion so that levels of intracellular catecholamines do not change significantly even in the face of changing sympathetic activity.

Mechanism of Action of Catecholamines

Adrenergic receptors are generally classified as α- and β-**adrenergic receptors,** with the α-adrenergic receptors



• **Fig. 43.3** Blood flow through the adrenal gland. Capsular arteries give rise to sinusoidal vessels that carry blood centripetally through the cortex to the medulla. (Modified from Young B, Lowe JS, Stevens A, Heath JW, Deakin PJ. *Wheater's Functional Histology.* 5th ed. Philadelphia: Churchill Livingstone; 2006.)

further divided into α_1 and α_2 **receptors** and the β-adrenergic receptors divided into β_1, β_2, and β_3 **receptors** (Table 43.1). These receptors can be characterized according to:

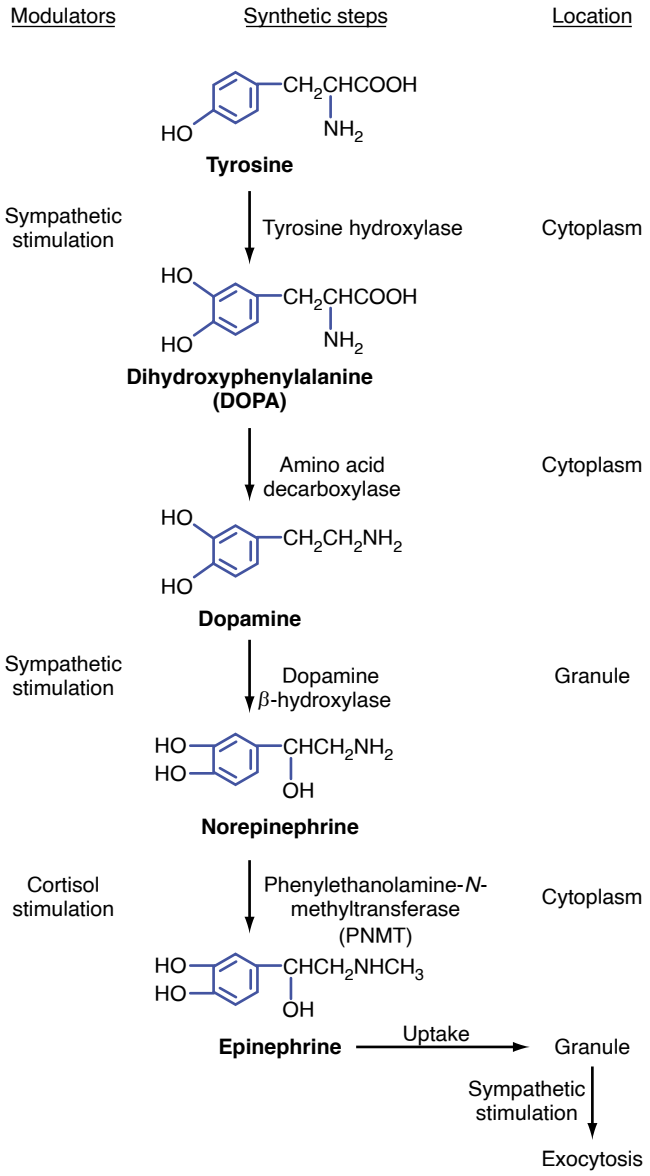
1. Relative potency of endogenous and pharmacological agonists and antagonists. Epinephrine and norepinephrine are potent agonists for α receptors and for β_1 and β_3 receptors, whereas epinephrine is more potent than norepinephrine for β_2 receptors. A large number of synthetic selective and nonselective adrenergic agonists and antagonists now exist.
2. Downstream signaling pathways. Table 43.1 shows the primary pathways that are coupled to the different adrenergic receptors. This is an oversimplification, because differences in signaling pathways for a given receptor have been linked to the duration of agonist exposure and cell type.
3. Location and relative density of receptors. Importantly, different receptor types predominate in different tissues. For example, although both α and β receptors are expressed by pancreatic islet beta cells, the predominant response to a sympathetic discharge is mediated by α_2 receptors.

Physiological Actions of Adrenomedullary Catecholamines

Because the adrenal medulla is directly innervated by the autonomic nervous system, adrenomedullary responses are very rapid. Furthermore, because of the involvement of several centers in the central nervous system (CNS), most notably the cerebral cortex, adrenomedullary responses can precede onset of the actual stress (i.e., they can be anticipated) (see Fig. 43.5). In many cases the adrenomedullary output, which is primarily epinephrine, is coordinated with sympathetic nervous activity as determined by the release of norepinephrine from postganglionic sympathetic neurons. However, some stimuli (e.g., hypoglycemia) evoke a stronger adrenomedullary than sympathetic nervous response and vice versa.

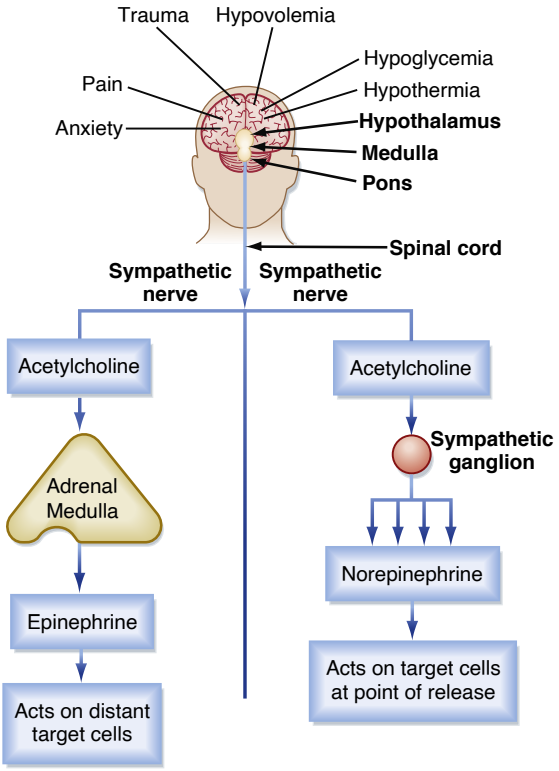
Many organs and tissues are affected by a sympathoadrenal response (Table 43.2). An informative example of the major physiological roles of catecholamines is the sympathoadrenal response to exercise. Exercise is similar to the **"fight-or-flight" response** but without the subjective element of fear, and it involves a greater adrenomedullary response (i.e., endocrine role of epinephrine) than a sympathetic nervous response (i.e., neurotransmitter role of norepinephrine). The overall goal of the sympathoadrenal system during exercise is to meet the increased energy demands of skeletal and cardiac muscle while maintaining sufficient oxygen and glucose supply to the brain. The response to exercise includes the following major physiological actions of epinephrine (Fig. 43.6):

1. Increased blood flow to muscles is achieved by the integrated action of norepinephrine and epinephrine on the heart, veins and lymphatics, and nonmuscular (e.g., splanchnic) and muscular arteriolar beds.



• **Fig. 43.4** Steps in synthesis and secretion of catecholamines from adrenal medullary chromaffin cells.

2. Epinephrine promotes glycogenolysis in muscle. Exercising muscle can also utilize free fatty acids (FFAs), and epinephrine and norepinephrine promote lipolysis in adipose tissue. Epinephrine increases blood glucose by increasing hepatic glycogenolysis and gluconeogenesis. The promotion of lipolysis in adipose tissue is also coordinated with an epinephrine-induced increase in hepatic ketogenesis. Finally, the effects of catecholamines on metabolism are reinforced by the fact that they stimulate glucagon secretion (β_2 receptors) and inhibit insulin secretion (α_2 receptors). Efficient production of adenosine triphosphate (ATP) during normal exercise



• **Fig. 43.5** Stimuli that enhance catecholamine secretion.

TABLE 43.1 Adrenergic Receptors

Receptor Type	Primary Mechanism of Action	Examples of Tissue Distribution	Examples of Action
α_1	↑ IP3 and Ca^{++}, DAG	Sympathetic postsynaptic nerve terminals	Increase vascular smooth muscle contraction
α_2	↓ cAMP	Sympathetic presynaptic nerve terminals, beta cell of pancreatic islets	Inhibit norepinephrine release, inhibit insulin release
β_1	↑ cAMP	Heart	Increase cardiac output
β_2	↑ cAMP	Liver; smooth muscle of vasculature, bronchioles, and uterus	Increase hepatic glucose output; decrease contraction of blood vessels, bronchioles, and uterus
β_3	↑ cAMP	Liver, adipose tissue	Increase hepatic glucose output, increase lipolysis

cAMP, Cyclic adenosine monophosphate; *DAG*, diacylglycerol.

TABLE 43.2 Some Actions of Catecholamine Hormones

β: Epinephrine > Norepinephrine	α: Norepinephrine > Epinephrine
↑ Glycogenolysis	↑ Gluconeogenesis (α_1)
↑ Gluconeogenesis (β_2)	↑ Glycogenolysis (α_1)
↑ Lipolysis (β_3) (β_2)	
↑ Calorigenesis (β_1)	
↓ Glucose utilization	
↑ Insulin secretion (β_2)	↓ Insulin secretion (α_2)
↑ Glucagon secretion (β_2)	
↑ Muscle K^+ uptake (β_2)	↑ Cardiac contractility (α_1)
↑ Cardiac contractility (β_1)	
↑ Heart rate (β_1)	
↑ Conduction velocity (β_1)	
↑ Arteriolar dilation: ↓ BP (β_2) (muscle)	↑ Arteriolar vasoconstriction; ↑ BP (α_1) (splanchnic, renal, cutaneous, genital)
↑ Muscle relaxation (β_2)	↑ Sphincter contraction (α_1)
Gastrointestinal	Gastrointestinal
Urinary	Urinary
Bronchial	↑ Platelet aggregation (α_2)
	↑ Sweating ("adrenergic")
	↑ Dilation of pupils (α_1)

BP, Blood pressure.

(i.e., a 1-hour workout) also requires efficient exchange of gases with an adequate supply of oxygen to exercising muscle. Catecholamines promote this by relaxation of bronchiolar smooth muscle.

3. Catecholamines decrease energy demand by visceral smooth muscle. In general, a sympathoadrenal response decreases overall motility of the smooth muscle in the gastrointestinal (GI) and urinary tracts, thereby conserving energy where it is not immediately needed.

Metabolism of Catecholamines

Two primary enzymes are involved in the degradation of catecholamines: **monoamine oxidase (MAO)** and **catechol-*O*-methyltransferase (COMT)**. The neurotransmitter norepinephrine is degraded by MAO and COMT after uptake into the presynaptic terminal. This mechanism is also involved in the catabolism of circulating adrenal catecholamines. However, the predominant fate of adrenal catecholamines is methylation by COMT in nonneuronal tissues such as the liver and kidney. Urinary **vanillylmandelic acid (VMA)** and **metanephrine** are sometimes used clinically to assess the level of catecholamine production in a patient. Much of the urinary VMA and metanephrine is derived from neuronal rather than adrenal catecholamines.

IN THE CLINIC

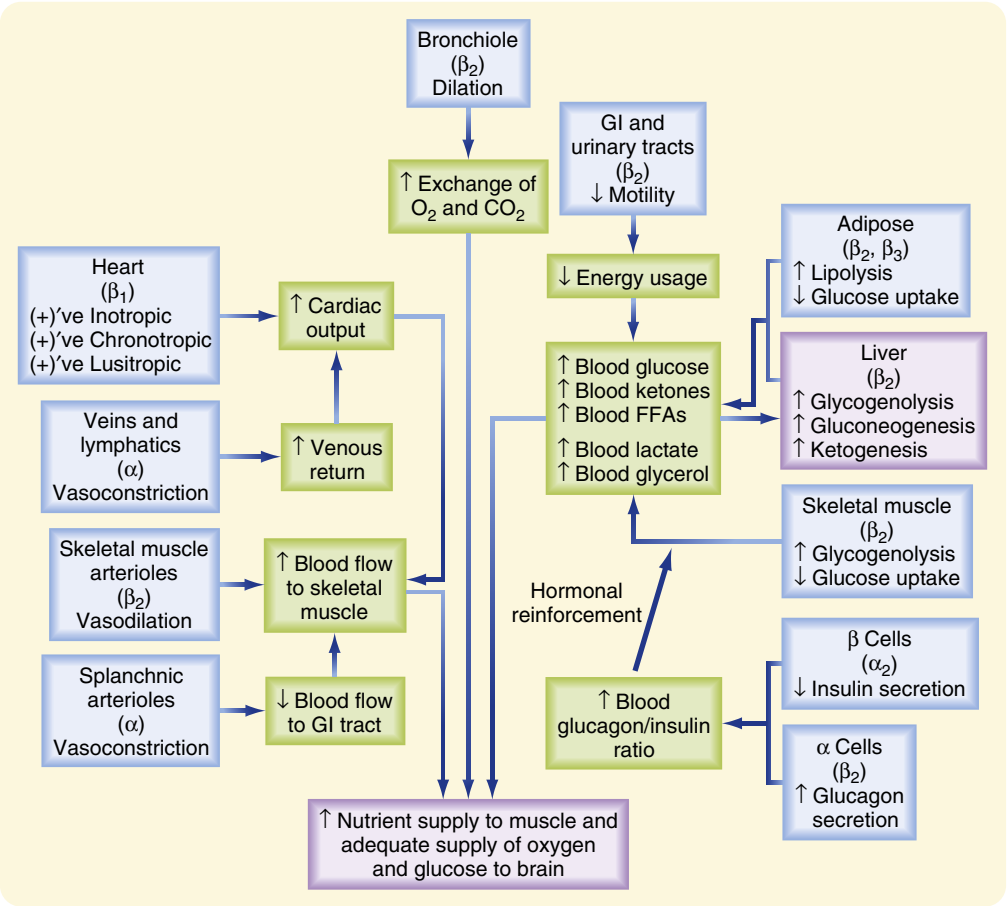
Pheochromocytoma is a tumor of chromaffin tissue that produces excessive quantities of catecholamines. These are commonly adrenal medullary tumors, but they can occur in other chromaffin cells of the autonomic nervous system. Although pheochromocytomas are not common tumors, they are the most common cause of hyperfunctioning of the adrenal medulla. The catecholamine most frequently elevated in pheochromocytoma is norepinephrine. For unknown reasons, the symptoms of excessive catecholamine secretion are often sporadic rather than continuous. Symptoms include hypertension, headaches (from hypertension), sweating, anxiety, palpitations, and chest pain. In addition, patients with this disorder may show orthostatic hypotension (despite the tendency for hypertension). This occurs because hypersecretion of catecholamines can decrease the postsynaptic response to norepinephrine as a result of downregulation of the receptors (see Chapter 3). Consequently, the baroreceptor response to blood shifts that occurs on standing is blunted.

Adrenal Cortex

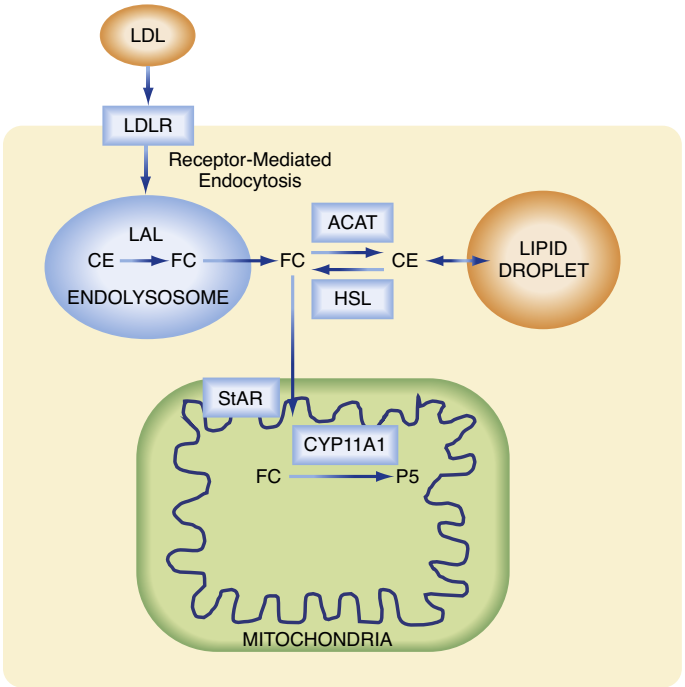
Zona Fasciculata

The zona fasciculata produces the glucocorticoid hormone **cortisol.** This zone is an actively steroidogenic tissue composed of straight cords of large cells. These cells have a "foamy" cytoplasm because they are filled with lipid droplets that represent stored cholesterol esters (CEs). These cells make some cholesterol de novo but import a significant amount of cholesterol from the blood in the form of low-density lipoprotein (LDL; see Chapter 39). LDL particles bind to their receptor (LDLR) and are endocytosed. Within endolysosomes, free cholesterol (FC) is released from CEs by a lysosomal lipase, and the FC is transported out of the endolysosome by Niemann-Pick C (NPC) proteins. FC is stored in lipid droplets in the cytoplasm after esterification by acyl CoA-cholesterol acyltransferase (ACAT) (Fig. 43.7). The stored cholesterol is continually turned back into FC by **hormone-sensitive lipase (HSL),** a process that is increased in response to adrenocorticotropic hormone (ACTH; see Regulation of Cortisol Production).

All steroid hormone synthesis begins in the mitochondria, where the first enzyme, CYP11A1, is attached to the inner mitochondrial membrane. CYP11A1 (also called "P450 side-chain cleavage") converts cholesterol to pregnenolone (P5). P5 can then exit the mitochondria and, through a multistep enzymatic pathway, ultimately be converted to cortisol. Since cortisol is not a substrate itself for any enzyme, its levels will increase and cortisol will diffuse out of the cell and into the circulation.



• **Fig. 43.6** Some of the individual actions of catecholamines that contribute to the integrated sympathoadrenal response to exercise. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)



• **Fig. 43.7** Events involved in the first two reactions in the steroidogenic pathway: conversion of cholesterol to pregnenolone; conversion of pregnenolone (P5) to progesterone (P4) in zona fasciculata cells. *ACAT*, Acyl CoA:cholesterol acyltransferase; *CE*, cholesterol esters; *CYP11A1* also called *P450 side-chain cleavage enzyme; FC*, free cholesterol; *HSL*, hormone-sensitive lipase; *LAL*, lysosomal acid hydrolase; *LDL*, low-density lipoprotein; *LDLR*, low-density lipoprotein receptor; *P5*, pregnenolone; *StAR*, steroidogenic acute regulatory protein. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

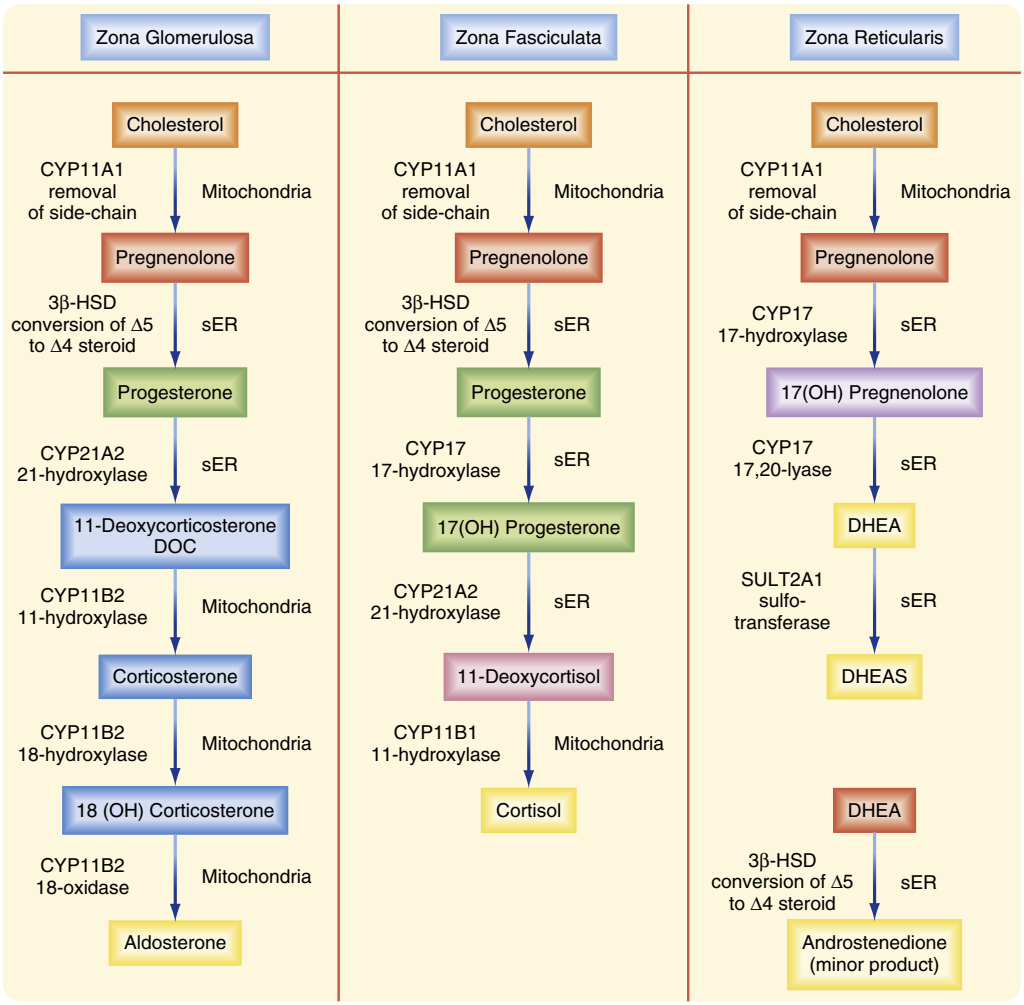
IN THE CLINIC

The protein, **steroidogenic acute regulatory protein (StAR protein),** is indispensable in the transfer of FC into the inner mitochondrial matrix (see Fig. 43.7). StAR protein is short-lived and rapidly activated post-translationally (phosphorylation) and transcriptionally by pituitary tropic hormones. In patients with inactivating mutations in StAR protein, cells of the zona fasciculata become excessively laden with lipid ("lipoid") because cholesterol cannot be accessed by CYP11A1 within the mitochondria and used for cortisol synthesis. In these newborns or infants, cortisol is low and pituitary ACTH levels are high (see Chapter 41), leading to overstimulation of the zona fasciculata and increased LDLR expression and cholesterol uptake. This condition is called "congenital lipoid adrenal hyperplasia." Patients are treated with replacement cortisol.

In the zona fasciculata, cholesterol is converted sequentially to pregnenolone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, and cortisol (Figs. 43.8 and 43.9). A parallel pathway in the zona fasciculata involves a pathway that bypasses 17-hydroxylation, in which progesterone is converted to 11-deoxycorticosterone (DOC) and then to corticosterone (see Fig. 43.9*C*). This pathway is minor in humans, but in the absence of active CYP11B1 (11-hydroxylase activity), the production of DOC is significant. Because DOC acts as a weak mineralocorticoid (Table 43.3), elevated levels of DOC cause hypertension.

Transport and Metabolism of Cortisol

Cortisol is transported in blood predominantly bound to **corticosteroid-binding globulin [CBG]** (also called **transcortin**), which binds about 90% of cortisol, and to albumin, which binds 5% to 7% of cortisol. The liver is the predominant site of steroid inactivation. It both inactivates cortisol and conjugates active and inactive steroids with glucuronide or sulfate so that they can be excreted more readily by the kidney. The circulating half-life of cortisol is about 70 minutes.

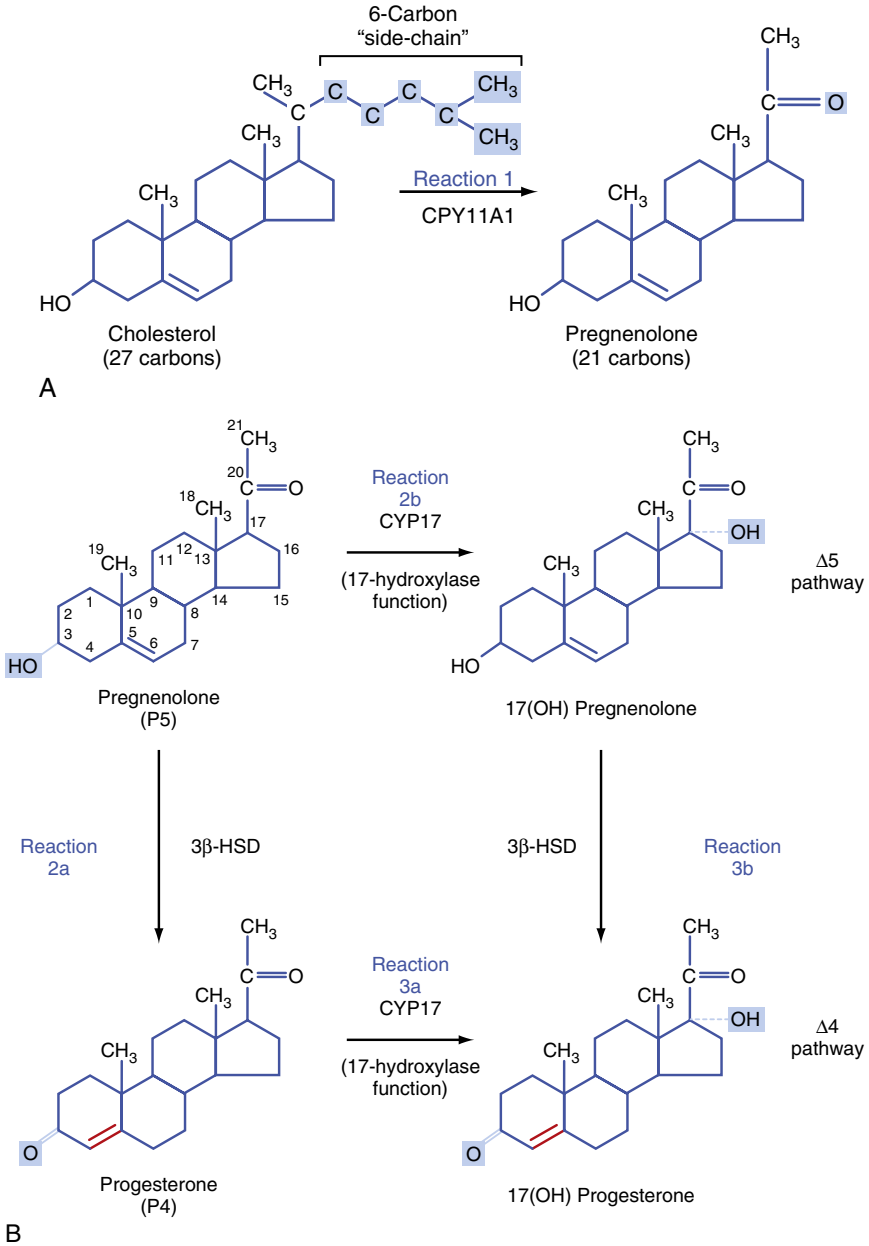


• **Fig. 43.8** Summary of the steroidogenic pathways for each of the three zones of the adrenal cortex. The enzymatic reactions are color coded across zones. *3β HSD*, 3β hydroxysteroid dehydrogenase; *sER*, Smooth endoplasmic reticulum. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

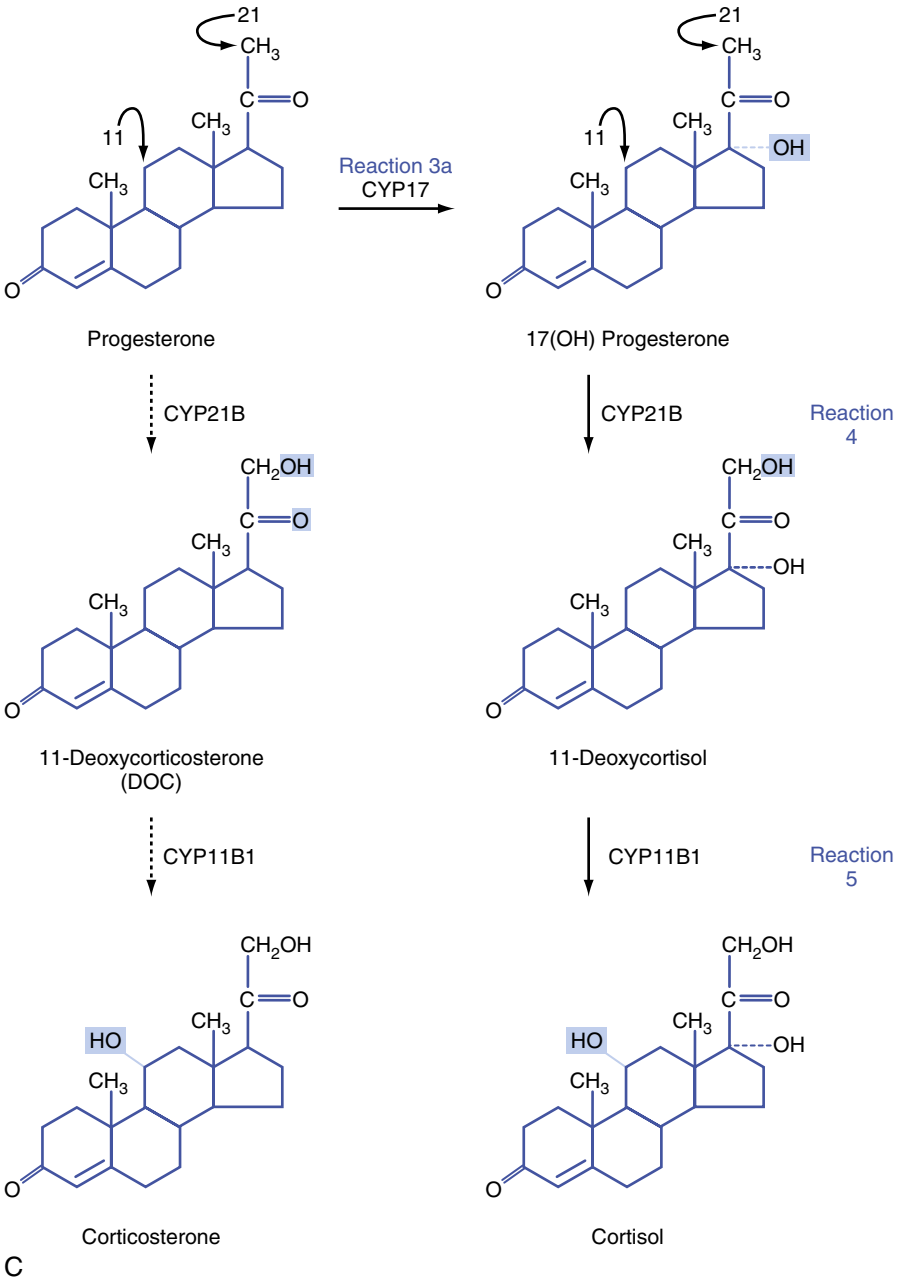
AT THE CELLULAR LEVEL

Steroidogenic enzymes fall into two superfamilies. Most belong to the **cytochrome P-450 mono-oxidase gene family** and are thus referred to as **CYPs.** These enzymes are located either in the inner mitochondrial matrix, where they use molecular oxygen and a flavoprotein electron donor, or in the smooth endoplasmic reticulum, where they use a different flavoprotein for electron transfer. Different CYP enzymes act as hydroxylases, lyases (desmolases), oxidases, or aromatases. Two of these enzymes have multiple functions. CYP17 has both a 17-hydroxylase function and a 17,20-lyase (desmolase) function. CYP11B2, also called *aldosterone synthase,* has three functions: 11-hydroxylase, 18-hydroxylase, and 18-oxidase.

The other enzymes involved in steroidogenesis belong to three **hydroxysteroid dehydrogenase** (HSD) families. **3β-HSDs** have two isoforms that convert the hydroxyl group on carbon 3 of the cholesterol ring to a ketone and shift the double bond from the 5-6 **(Δ5)** position to the 4-5 **(Δ4)** position. All active steroid hormones must be converted to Δ4 structures by 3β-HSD. The **17β-HSDs** have at least five members and can act as either oxidases or reductases. 17β-HSDs primarily act on sex steroids and can be activating or deactivating. Finally, the **11β-HSDs** have two isoforms that catalyze the interchange between cortisol (active) and cortisone (inactive).



• **Fig. 43.9 A,** Reaction 1, catalyzed by CYP11A1, in making cortisol. **B,** Reactions 2a/b and reactions 3a/b, involving *CYP17* (17-hydroxylase function) and 3β-hydroxysteroid dehydrogenase *(3β-HSD)*, in making cortisol. This figure shows the Δ5 versus Δ4 pathway.



• **Fig. 43.9, cont'd C,** Reactions 4 and 5, involving CYP21B and CYP11B1, in which the last two steps in cortisol synthesis are carried out. Also shown is the minor pathway leading to corticosterone synthesis in the zona fasciculata. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

Cortisol is reversibly inactivated by conversion to **cortisone.** This action is catalyzed by the enzyme **11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2).** Inactivation of cortisol by 11β-HSD2 occurs in cells that also express the mineralocorticoid receptor (MR) and are target cells of aldosterone (see later). The conversion of cortisol to cortisone prevents the binding of cortisol to the MR and having inappropriate mineralocorticoid actions on these cells. Inactivation of cortisol by 11β-HSD2 is reversible in that another enzyme, **11β-HSD1,** converts cortisone back to cortisol. This conversion occurs in tissues expressing the glucocorticoid receptor (GR), including liver, adipose tissue, and the CNS, as well as in skin.

Mechanism of Action of Cortisol

Cortisol acts primarily through the **GR,** which regulates gene transcription (see Chapter 3). In the absence of hormone, the GR resides in the cytoplasm in a stable complex with several **molecular chaperones,** including heat shock proteins and cyclophilins. Cortisol-GR binding promotes dissociation of the chaperone proteins, followed by:

TABLE 43.3 Relative Glucocorticoid and Mineralocorticoid Potency of Natural Corticosteroids and Some Synthetic Analogs in Clinical Use[a]

	Glucocorticoid	Mineralocorticoid
Corticosterone	0.5	1.5
Prednisone (1.2 double bond)	4	<0.1
6α-Methylprednisone (Medrol)	5	<0.1
9α-Fluoro-16α-hydroxyprednisolone (triamcinolone)	5	<0.1
9α-Fluoro-16α-methylprednisolone (dexamethasone)	30	<0.1
Aldosterone	0.25	500
Deoxycorticosterone	0.01	30
9α-Fluorocortisol	10	500

[a]All values are relative to the glucocorticoid and mineralocorticoid potencies of cortisol, which have each been arbitrarily set at 1.0. Cortisol actually has only 1/500 the potency of the natural mineralocorticoid aldosterone.

- rapid translocation of the cortisol-GR complex into the nucleus,
- dimerization and binding to **glucocorticoid response elements** (GREs, both "positive" GREs and "negative" GREs) near the basal promoters of cortisol-regulated genes, and
- recruitment of **coactivator proteins** and assembly of general transcription factors leading to increased or decreased transcription of the targeted genes.

In some cases the GR interacts with other transcription factors, such as the proinflammatory nuclear factor (NF)-κB transcription factor and interferes with their ability to activate gene expression.

Physiological Actions of Cortisol

Cortisol has a broad range of actions and is often characterized as a "stress hormone." In general, cortisol maintains blood glucose levels, CNS function, and cardiovascular function during fasting and increases blood glucose during stress at the expense of muscle protein. Cortisol protects the body against the self-injurious effects of unbridled inflammatory and immune responses. Cortisol also partitions energy to cope with stress by inhibiting reproductive function. As stated later, cortisol has several other effects on bone, skin, connective tissue, the GI tract, and the developing fetus that are independent of its stress-related functions.

Metabolic Actions

As the term *glucocorticoid* implies, cortisol is a steroid hormone from the adrenal cortex that regulates **blood glucose.** It increases blood glucose by stimulating **gluconeogenesis** (Fig. 43.10). Cortisol enhances gene expression of the key hepatic gluconeogenic enzyme **phosphoenolpyruvate carboxykinase (PEPCK).** Cortisol also decreases GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue. During the interdigestive period (low insulin-glucagon ratio), cortisol promotes glucose sparing by potentiating the effects of catecholamines on lipolysis, thereby making FFAs available as energy sources. Cortisol inhibits protein synthesis and increases proteolysis, especially in skeletal muscle, thereby providing a rich source of carbon for hepatic gluconeogenesis.

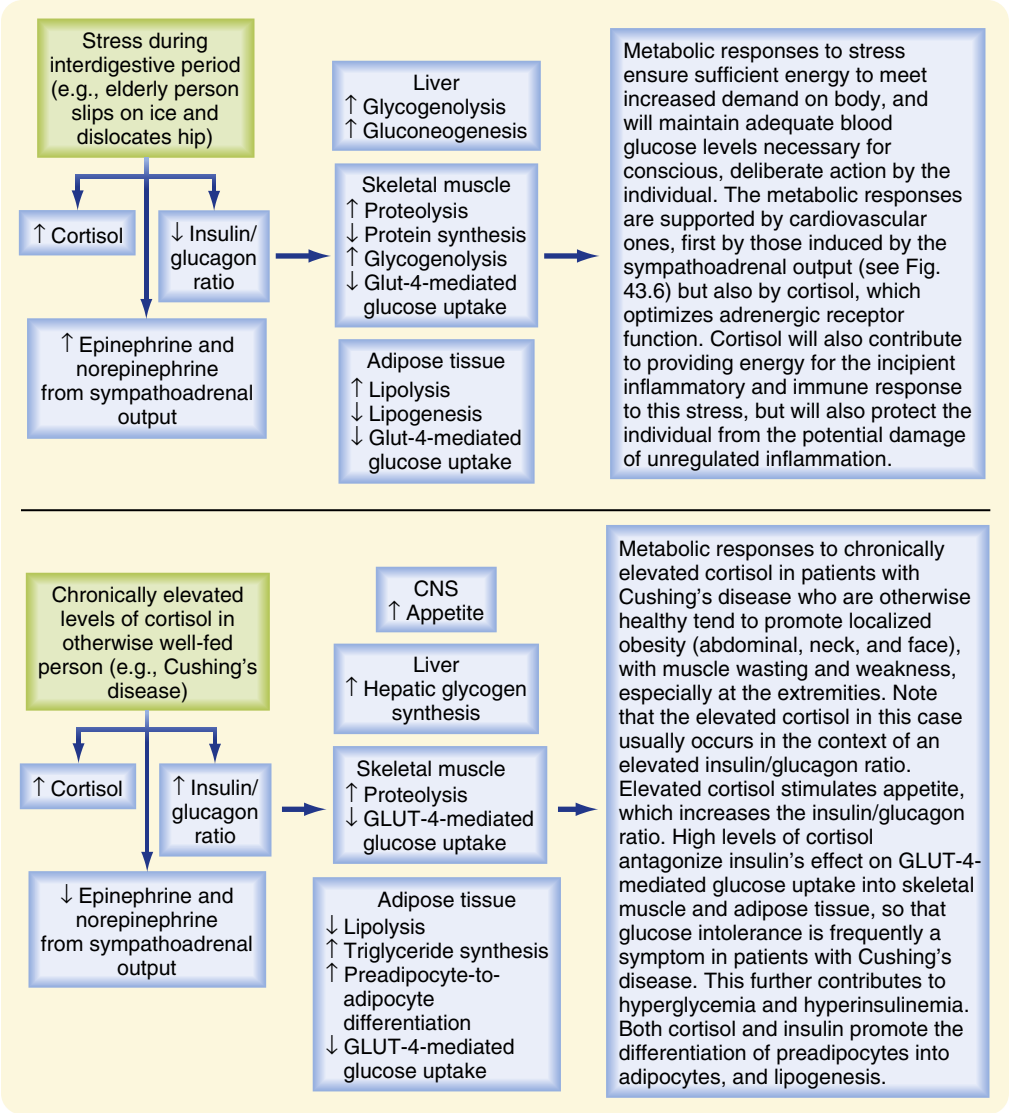
Fig. 43.10 also contrasts the normal role of cortisol in response to stress and the effects of **chronically elevated cortisol** as a result of pathological conditions. As discussed later, there are important differences in the overall metabolic effects of cortisol between these two states, particularly with respect to lipid metabolism. During stress, cortisol synergizes with catecholamines and glucagon to promote a lipolytic, gluconeogenic, ketogenic, and glycogenolytic metabolic response while synergizing with catecholamines to promote an appropriate cardiovascular response. During chronically elevated cortisol secondary to pathological overproduction, cortisol synergizes with insulin in the context of elevated levels of glucose (from increased appetite) and hyperinsulinemia (from elevated glucose and glucose intolerance) to promote lipogenesis and truncal (abdominal/visceral) adiposity.

Cardiovascular Actions

Cortisol reinforces its effects on blood glucose by its positive effects on the cardiovascular system. Cortisol has permissive actions on catecholamines by increasing **adrenergic receptor** expression and thereby contributes to cardiac output and blood pressure. Cortisol stimulates **erythropoietin** synthesis and hence increases red blood cell production. **Anemia** occurs when cortisol is deficient, and **polycythemia** occurs when cortisol levels are excessive.

Anti-inflammatory and Immunosuppressive Actions

Inflammation and immune responses are often part of the response to stress. However, inflammation and immune responses have the potential for significant harm and may cause death if they are not held in homeostatic balance. As a stress hormone, cortisol plays an important role in maintaining immune homeostasis. Cortisol, along with epinephrine and norepinephrine, represses production of proinflammatory cytokines and stimulates production of anti-inflammatory cytokines.



• **Fig. 43.10** Metabolic actions of cortisol (integrated with catecholamines and glucagon) in response to stress *(upper panel)* and contrasted to the actions of chronically elevated cortisol (integrated with insulin) in an otherwise healthy individual *(lower panel).* (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

The inflammatory response to injury consists of local dilation of capillaries and increased capillary permeability, with resultant local edema and accumulation of white blood cells. These steps are mediated by **prostaglandins, thromboxanes, and leukotrienes**. Cortisol inhibits **phospholipase A_2,** a key enzyme in prostaglandin, leukotriene, and thromboxane synthesis. Cortisol also stabilizes lysosomal membranes, thereby decreasing release of the proteolytic enzymes that augment local swelling. In response to injury, leukocytes normally leave the vascular system and migrate to the site of injury. This complex process is generally inhibited by cortisol, as is the phagocytic activity of neutrophils, although release of neutrophils from bone marrow is stimulated. Analogs of glucocorticoid are frequently used pharmacologically because of their anti-inflammatory properties.

Cortisol inhibits the immune response, and for this reason glucocorticoid analogs have been used as **immunosuppressants** in organ transplants. High cortisol levels decrease the number of circulating T lymphocytes (particularly helper T lymphocytes) and reduce their ability to migrate to the site of antigenic stimulation. Glucocorticoids promote atrophy of the thymus and other lymphoid tissue. Although corticosteroids inhibit cellular-mediated immunity, antibody production by B lymphocytes is not impaired.

Effects of Cortisol on the Reproductive Systems

Reproduction exacts a considerable anabolic cost on the organism. In humans, reproductive behavior and function are dampened in response to stress. Cortisol decreases the function of the **reproductive axis** at the hypothalamic, pituitary, and gonadal levels.

Effects of Cortisol on Bone

Glucocorticoids increase **bone resorption.** They have multiple actions that alter bone metabolism. Glucocorticoids decrease **intestinal Ca^{++} absorption** and **renal Ca^{++} reabsorption.** Both mechanisms serve to lower serum [Ca^{++}]. As serum [Ca^{++}] drops, secretion of parathyroid hormone (PTH) increases, and PTH mobilizes Ca^{++} from bone by stimulating resorption of bone. In addition to this action, glucocorticoids directly inhibit **osteoblast bone-forming functions** (see Chapter 40). Although glucocorticoids are useful for treating the inflammation associated with **arthritis,** excessive use will result in bone loss **(osteoporosis).**

Actions of Cortisol on Connective Tissue

Cortisol inhibits **fibroblast proliferation** and **collagen formation.** In the presence of excessive amounts of cortisol, the **skin** thins and is more readily damaged. The connective tissue support of capillaries is impaired, and **capillary injury,** or **bruising,** is increased.

Actions of Cortisol on the Kidney

Cortisol inhibits the secretion and action of **antidiuretic hormone (ADH),** and thus it is an ADH antagonist. In the absence of cortisol, the action of ADH is potentiated, which makes it difficult to increase free water clearance in response to a water load and increases the likelihood of water intoxication. Although cortisol binds to the MR with high affinity, this action is normally blocked by inactivation of cortisol to cortisone by the enzyme 11β-HSD2. However, the mineralocorticoid activity (i.e., renal Na^+ and H_2O retention, K^+ and H^+ excretion) of cortisol depends on the relative amount of cortisol (or synthetic glucocorticoids) and the activity of 11β-HSD2. Certain agents (e.g., compounds in black licorice) inhibit 11β-HSD2 and thereby increase the mineralocorticoid activity of cortisol. Cortisol increases the glomerular filtration rate by both increasing cardiac output and acting directly on the kidney.

Actions of Cortisol on Muscle

When cortisol levels are excessive, **muscle weakness and pain** are common symptoms. The weakness has multiple origins. In part it is a result of the excessive **proteolysis** cortisol produces. High cortisol levels can result in **hypokalemia** (via mineralocorticoid actions), which can produce muscle weakness because it hyperpolarizes and stabilizes the muscle cell membrane and thus makes stimulation more difficult.

Actions of Cortisol on the Gastrointestinal Tract

Cortisol exerts a trophic effect on the **GI mucosa.** In the absence of cortisol, GI motility decreases, GI mucosa degenerates, and GI acid and enzyme production decreases. Because cortisol stimulates **appetite,** hypercortisolism is frequently associated with weight gain. The cortisol-mediated stimulation of gastric acid and pepsin secretion increases the risk for development of **ulcers.**

Psychological Effects of Cortisol

Psychiatric disturbances are associated with either excessive or deficient levels of corticosteroids. Excessive corticosteroids can initially produce a feeling of well-being, but continued excessive exposure eventually leads to emotional lability and depression. Frank psychosis can occur with either excessive or deficient hormone. Cortisol increases the tendency for insomnia and decreases rapid eye movement (REM) sleep. People who are deficient in corticosteroids tend to be depressed, apathetic, and irritable.

Effects of Cortisol During Fetal Development

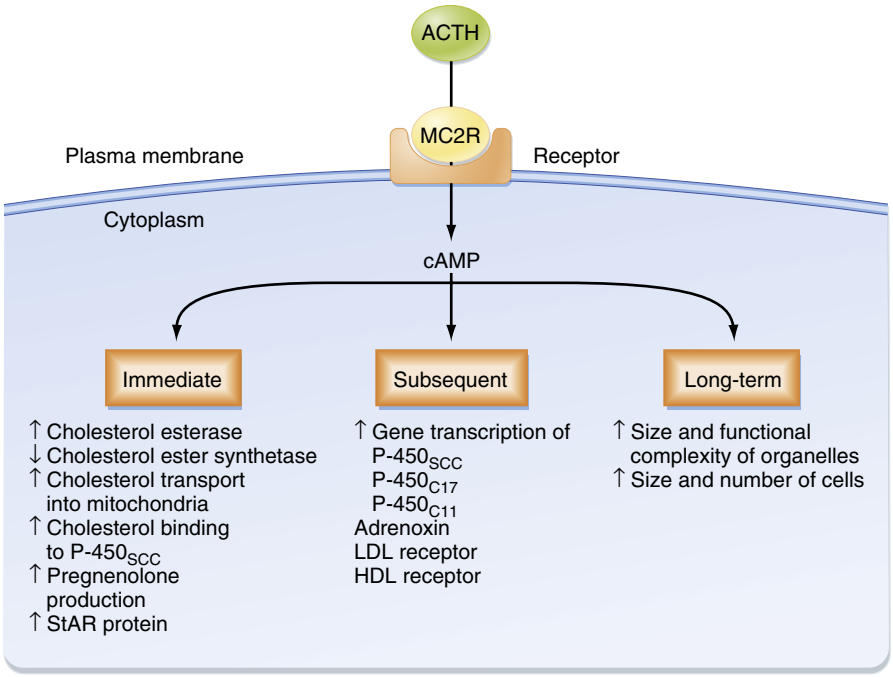
Cortisol is required for normal development of the **CNS, retina, skin, GI tract, and lungs**. The best-studied system is the lungs, in which cortisol induces differentiation and maturation of type II alveolar cells. During late gestation these cells produce **surfactant**, which reduces surface tension in the lungs and thus allows the onset of breathing at birth.

Regulation of Cortisol Production

Cortisol production by the zona fasciculata is regulated by a standard hypothalamic-pituitary-adrenal axis involving **corticotropin-releasing hormone (CRH), ACTH, and cortisol** (see Chapter 41). The hypothalamus and pituitary stimulate cortisol production, and cortisol negatively feeds back on the hypothalamus and pituitary to maintain its set point. Both **neurogenic** (e.g., fear) and **systemic** (e.g., hypoglycemia, hemorrhage, cytokines) **forms of stress** stimulate release of CRH. CRH is also under strong **diurnal rhythmic** regulation emerging from the suprachiasmatic nucleus, such that cortisol levels surge during the early predawn and morning hours and then continually decline throughout the day and evening. CRH acutely stimulates release of ACTH and chronically increases proopiomelanocortin *(POMC)* gene expression and corticotrope hypertrophy and proliferation. Some parvicellular neurons coexpress CRH and ADH, which potentiates the actions of CRH.

ACTH binds to the **melanocortin 2 receptor (MC2R)** located on cells in the zona fasciculata (Fig. 43.11). The effects of ACTH can be subdivided into three phases:

1. The **acute effects** of ACTH occur within minutes. Cholesterol is rapidly mobilized from lipid droplets by post-translational activation of cholesterol ester hydrolase and transported to the outer mitochondrial membrane. ACTH both rapidly increases StAR protein gene expression and activates StAR protein through protein kinase A (PKA)-dependent phosphorylation. Collectively, these acute actions of ACTH increase pregnenolone levels.
2. The **chronic effects** of ACTH occur over a period of several hours. These effects involve increasing transcription of the genes encoding the steroidogenic enzymes and their coenzymes. ACTH also increases expression of the LDL receptor and scavenger receptor BI (SR-BI; the high-density lipoprotein [HDL] receptor).
3. The **trophic actions** of ACTH on the zona fasciculata and zona reticularis occur over a period of weeks and



• **Fig. 43.11** Overview of the actions of ACTH on target adrenocortical cells. Note that the major second messenger, *cAMP*, activates immediate protein mediators and also induces production of later protein mediators. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein.

months. This effect is exemplified by atrophy of the zona fasciculata in patients receiving therapeutic (i.e., supraphysiological) levels of glucocorticoid analogs for at least 3 weeks. Under these conditions the exogenous corticosteroids completely repress CRH and ACTH production, thereby resulting in atrophy of the zona fasciculata and a decline in endogenous cortisol production (Fig. 43.12). At the end of therapy, these patients need to be slowly weaned off exogenous glucocorticoids to allow the hypothalamic-pituitary-adrenal axis to reestablish itself and the zona fasciculata to enlarge and produce adequate amounts of cortisol.

Cortisol inhibits both *POMC* gene expression at the corticotropes and pro-CRH gene expression at the hypothalamus. However, intense stress can override the negative-feedback effects of cortisol at the hypothalamus and reset the "set point" at a higher level.

Zona Reticularis

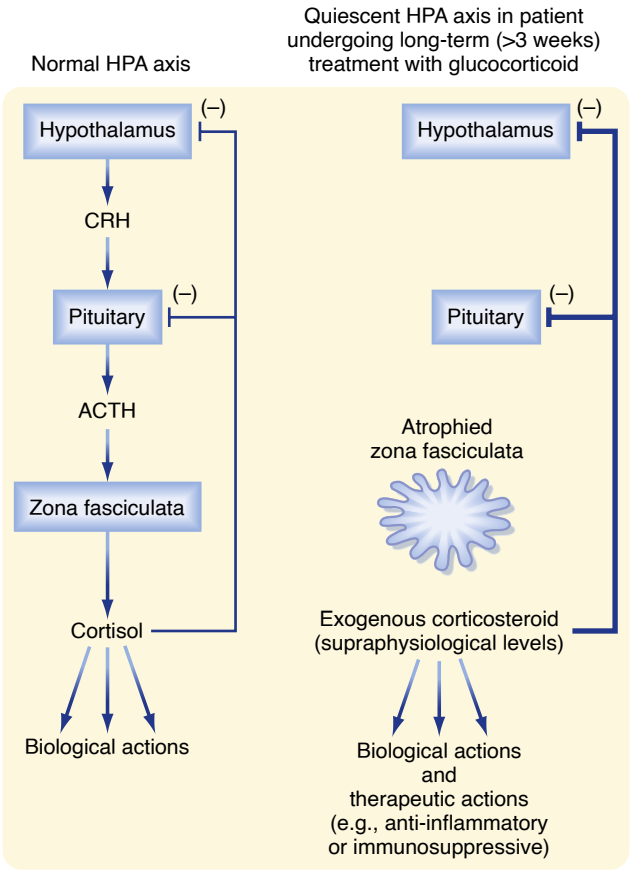
The innermost zone, the zona reticularis, begins to appear after birth at about 5 years of age. Adrenal androgens, especially DHEAS, the main product of the zona reticularis, become detectable in the circulation at about 6 years of age. This onset of adrenal androgen production is called **adrenarche,** and it contributes to the appearance of axillary and pubic hair at about age 8. DHEAS levels continue to increase, peak during the mid-20s, and then progressively decline with age.

Androgen Synthesis by the Zona Reticularis

The zona reticularis differs from the zona fasciculata in several important ways with respect to steroidogenic enzyme activity (see Fig. 43.8). First, 3β-HSD is expressed at very low levels in the zona reticularis; thus the Δ5 pathway predominates in the zona reticularis. Second, the zona reticularis expresses cofactors or conditions that enhance the 17,20-lyase function of CYP17, thereby generating the 19-carbon androgen precursor molecule **dehydroepiandrosterone (DHEA)** from 17-hydroxypregnenolone. Additionally the zona reticularis expresses **DHEA sulfotransferase (*SULT2A1* gene),** which converts DHEA into **DHEAS** (Fig. 43.13). A limited amount of the Δ4 androgen **androstenedione** is also made in the zona reticularis. Although small amounts of potent androgens (e.g., testosterone) or 18-carbon estrogens are normally produced by the human adrenal cortex, most active sex steroids are produced primarily from **peripheral conversion** of DHEAS and androstenedione.

Metabolism and Fate of DHEAS and DHEA

DHEAS can be converted back to DHEA by peripheral **sulfatases,** and DHEA and androstenedione can be converted to active androgens (testosterone, dihydrotestosterone) peripherally in both sexes. DHEA binds to albumin and other globulins in blood with low affinity, so it is excreted efficiently by the kidney. The half-life of DHEA is 15 to 30 minutes. In contrast, DHEAS binds to albumin with very high affinity and has a half-life of 7 to 10 hours.



• **Fig. 43.12** Comparison of a normal hypothalamic-pituitary-adrenal *(HPA)* axis to a quiescent HPA axis in individual receiving exogenous glucocorticoid therapy. The latter causes the zona fasciculata to atrophy after 3 weeks, thus requiring a careful withdrawal regimen to allow rebuilding of the adrenal tissue before total cessation of exogenous corticosteroid administration. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

Physiological Actions of Adrenal Androgens

In men the contribution of adrenal androgens to active androgens is negligible. However, in women the adrenal contributes to about 50% of circulating active androgens, which are required for the growth of axillary and pubic hair and for libido.

Apart from providing androgen precursors, it is not clear what other role or roles if any the zona reticularis plays in adult humans. DHEAS is the most abundant circulating hormone in young adults. It increases steadily until it peaks in the mid-20s and then steadily declines thereafter. Thus there has been considerable interest in the possible role of DHEAS in the aging process. However, the function of this abundant steroid in young adults and the potential impact of its gradual disappearance on aging are still poorly understood. It should be noted that the age-related decline in DHEA and DHEAS has led to the popular use of these steroids as dietary supplements, even though recent studies indicate no beneficial effects.

IN THE CLINIC

During adrenal androgen excess (e.g., adrenal tumor, Cushing's syndrome, congenital adrenal hyperplasia), **masculinization of women** can occur. This involves masculinization of the external genitalia (e.g., enlarged clitoris) in utero and excessive facial and body hair (called **hirsutism**) and acne in adult women. Excessive adrenal androgens also appear to play a role in ovarian dysovulation (i.e., polycystic ovarian syndrome).

IN THE CLINIC

A crucial clinical aspect of regulation of the zona reticularis is that neither adrenal androgens nor their more potent metabolites (e.g., testosterone, dihydrotestosterone, estradiol-17β) negatively feedback on ACTH or CRH (Fig. 43.14). This means that an enzymatic defect associated with the synthesis of cortisol (e.g., CYP21B deficiency) is associated with a dramatic increase in both ACTH (no negative feedback from cortisol) and adrenal androgens (because of the elevated ACTH). It is this "loophole" in the hypothalamic-pituitary-adrenal axis that gives rise to **congenital adrenal hyperplasia (CAH).** This condition leads to excessive androgen levels that cause ambiguous genitalia in female newborns.

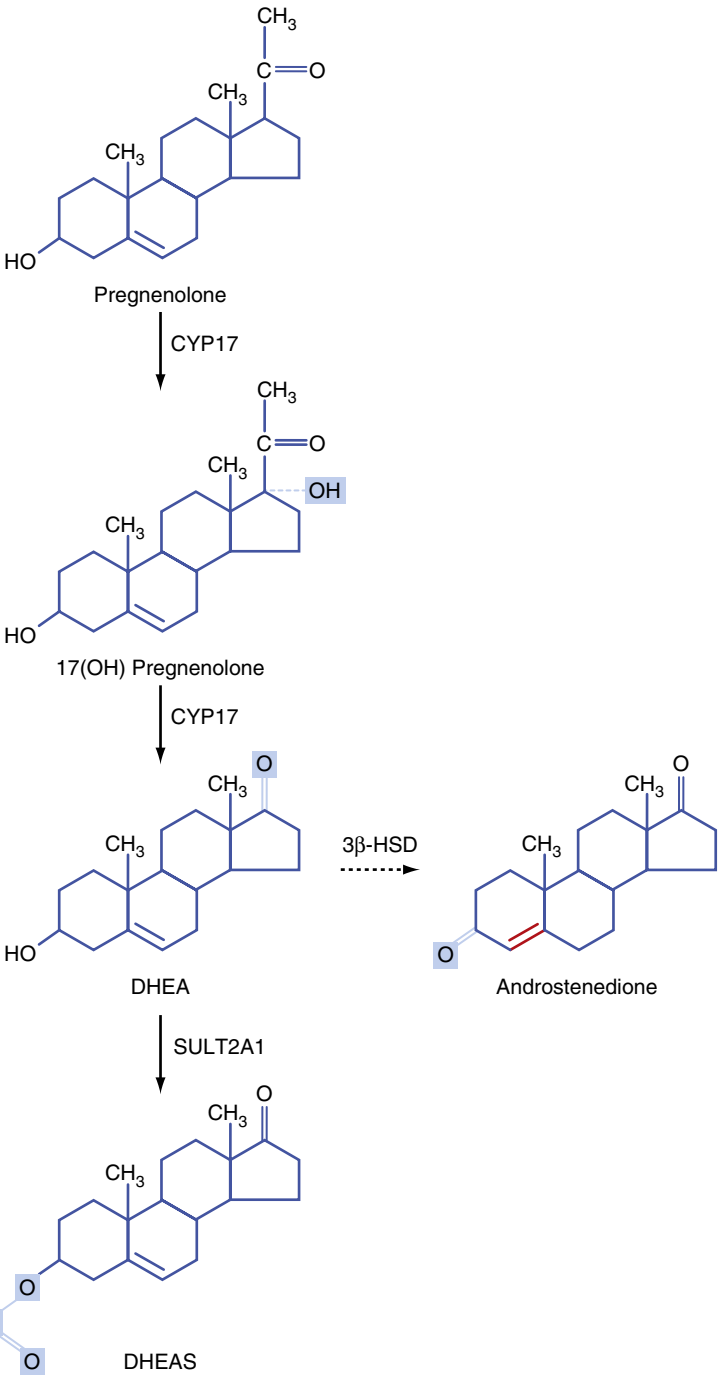
Regulation of Zona Reticularis Function

ACTH is the primary regulator of the zona reticularis. Both DHEA and androstenedione display the same diurnal rhythm as cortisol (DHEAS does not because of its long circulating half-life). Moreover, the zona reticularis shows the same atrophic changes as the zona fasciculata in conditions typified by little or no ACTH. However, other factors must regulate adrenal androgen function. Adrenarche occurs in the face of constant ACTH and cortisol levels, and the rise and decline of DHEAS is not associated with a similar pattern of ACTH or cortisol production. However, the other factors, whether extra-adrenal or intra-adrenal, remain unknown.

Zona Glomerulosa

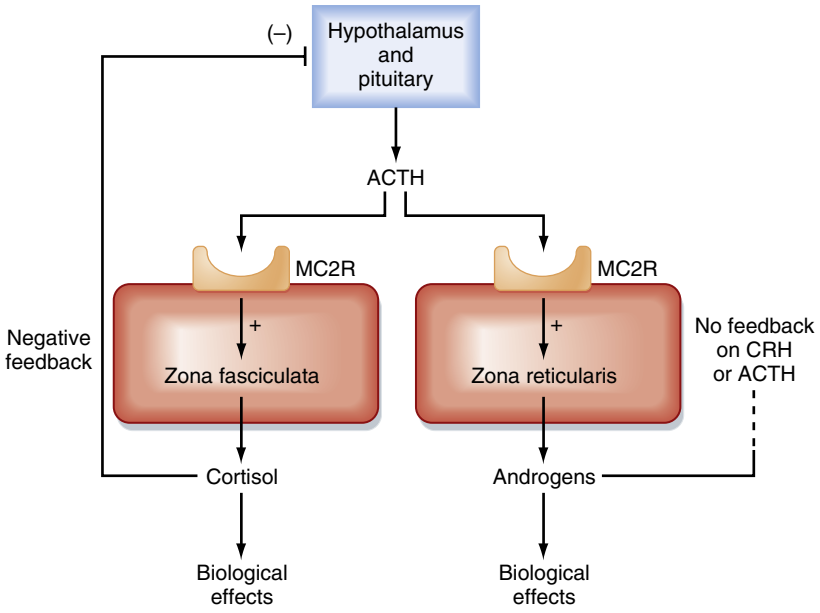
The thin outermost zone of the adrenal, the zona glomerulosa, produces the mineralocorticoid aldosterone, which regulates salt and volume homeostasis (see Chapter 35 and 36). The zona glomerulosa is minimally influenced by ACTH. Rather it is regulated primarily by the renin-angiotensin system, plasma [K^+], and atrial natriuretic peptide (ANP).

An important feature in the steroidogenic capacity of the zona glomerulosa is that it does not express CYP17. Therefore zona glomerulosa cells never make cortisol, nor do they make adrenal androgens in any form. Pregnenolone is converted to progesterone and DOC by 3β-HSD and CYP21,



• **Fig. 43.13** Steroidogenic pathways in the zona reticularis. The first common reaction in the pathway, conversion of cholesterol to pregnenolone by CYP11A1, is not shown. Expression of 3β-hydroxysteroid dehydrogenase *(3β-HSD)* is relatively low in the zona reticularis, so androstenedione is a minor product in comparison to DHEA and DHEAS. The zona reticularis also makes a small amount of testosterone and estrogens (not shown). (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

respectively (Fig. 43.15). A completely unique feature of the zona glomerulosa among the steroidogenic glands is its expression of CYP11B2, which is regulated by different signaling pathways. Furthermore the enzyme coded by CYP11B2, **aldosterone synthase,** catalyzes the last three reactions from DOC to aldosterone within the zona glomerulosa. These reactions are 11-hydroxylation of DOC to form corticosterone, 18-hydroxylation to form 18-hydroxycorticosterone, and 18-oxidation to form aldosterone (see Figs. 43.8 and 43.15).



• **Fig. 43.14** The "loophole" in the hypothalamic-pituitary-adrenal axis. ACTH stimulates production of both cortisol and adrenal androgens, but only cortisol negatively feeds back on ACTH and CRH. Thus if cortisol production is blocked (i.e., CYP11B1 deficiency), ACTH levels increase along with adrenal androgens. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

IN THE CLINIC

CYP11B1 (expressed only in the zona fasciculata) and CYP11B2 (expressed only in the zona glomerulosa) are located on chromosome 8 in humans, display 95% similarity, and are separated from each other by only about 50 kilobases. This increases the possibility of uneven crossing over during gametogenesis, with the formation of hybrid genes. In one case the promoter region and 5′ end of the *CYP11B1* gene is fused to the 3′ end of the *CYP11B2* gene. This arrangement leads to aldosterone synthase being expressed in the zonae fasciculata and reticularis under the control of ACTH. Because aldosterone is no longer under feedback control by the renin-angiotensin system (see Chapter 35), aldosterone levels are high and hypertension ensues. This form of primary aldosteronism is called **glucocorticoid-remediable aldosteronism,** and it is inherited in an autosomal dominant manner. This disease can be confirmed by the polymerase chain reaction technique and by measurement of 18-hydroxycortisol and 18-oxicortisol in a 24-hour urine sample. The disease is treated by the **administration of glucocorticoid,** which suppresses ACTH and thus expression of the hybrid gene.

Transport and Metabolism of Aldosterone

Aldosterone binds to albumin and corticosteroid-binding protein in blood with low affinity and therefore has a biological half-life of about 20 minutes. Almost all aldosterone is inactivated by the liver in one pass, conjugated to a glucuronide group, and excreted by the kidney.

Mechanism of Aldosterone Action

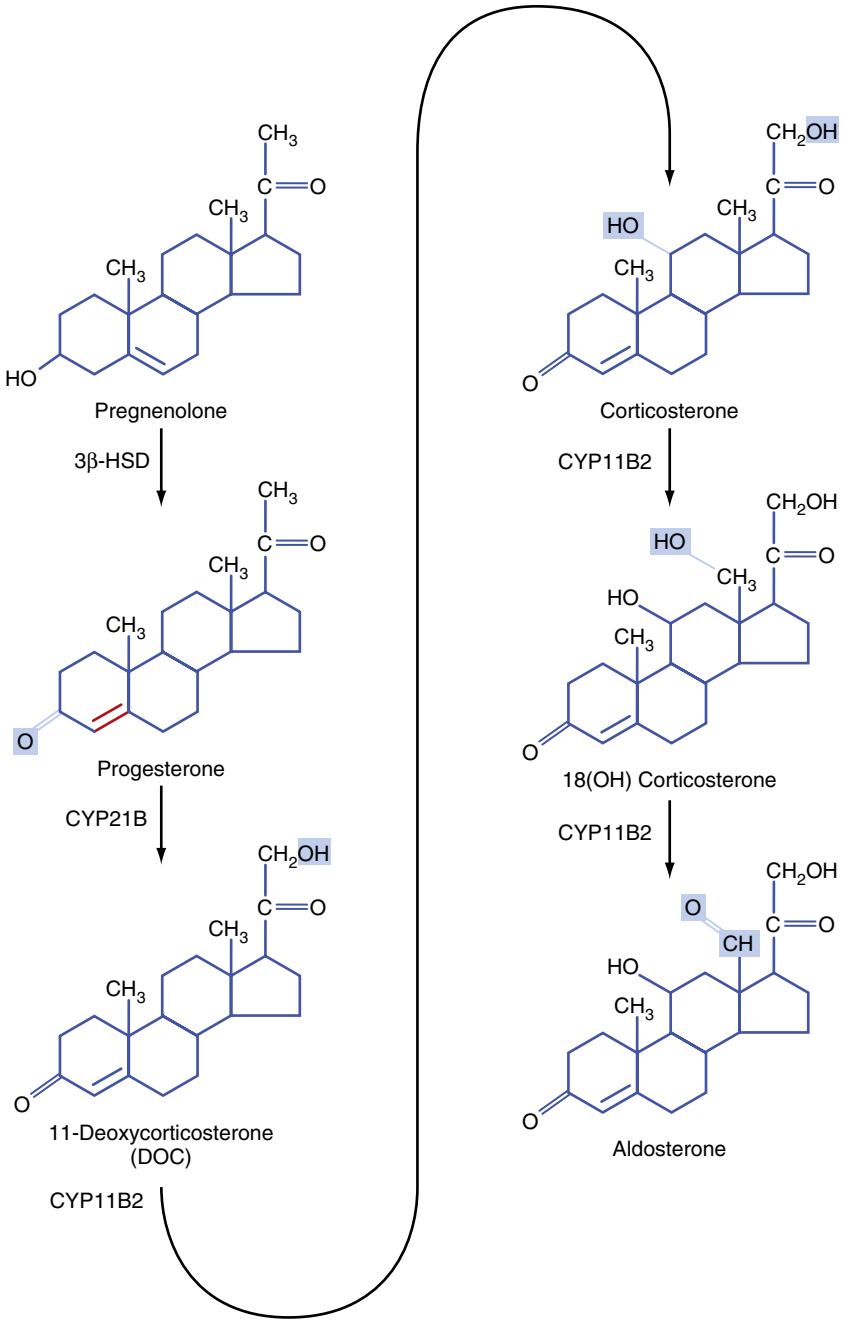
Aldosterone acts much like cortisol (and other steroid hormones) in that its primary mechanism of action is mediated by binding to a specific intracellular receptor (i.e., **mineralocorticoid receptor [MR]**). After dissociation of chaperone proteins, nuclear translocation, dimerization, and binding to the mineralocorticoid response element (MRE), the aldosterone-MR complex regulates expression of specific genes (see Chapter 3). As discussed earlier, cortisol binds to the MR with significant affinity. However, as also discussed, cells that express MR also express 11β-HSD2, which converts cortisol to the inactive steroid cortisone (Fig. 43.16). Cortisone can be converted back to cortisol by 11β-HSD1, which is expressed in several glucocorticoid-responsive tissues, including the liver and skin.

IN THE CLINIC

Clinical studies in humans have revealed a deleterious effect of aldosterone on cardiovascular function independent of its effects on renal sodium and water reabsorption. Aldosterone has a **proinflammatory, profibrotic effect** on the cardiovascular system and causes left ventricular hypertrophy and remodeling. This effect of aldosterone is associated with increased morbidity and mortality in patients with essential hypertension.

Physiological Actions of Aldosterone

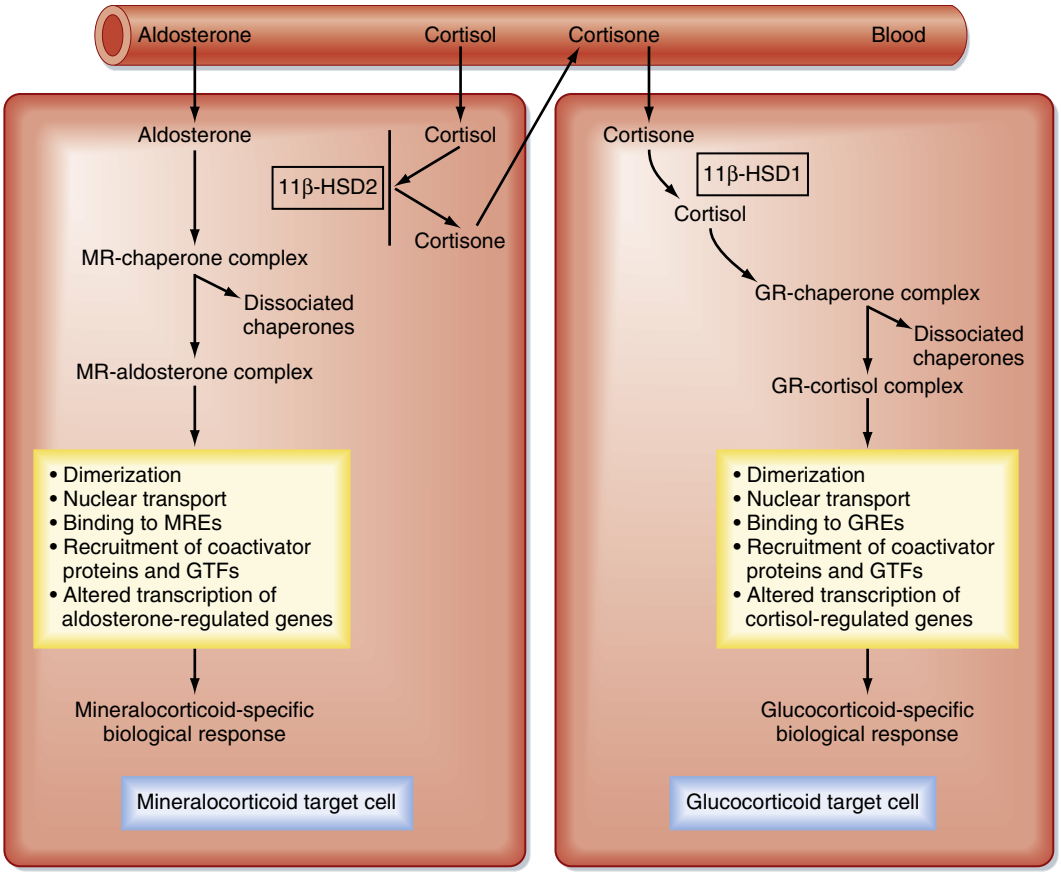
The actions and regulation of aldosterone are discussed in Chapter 35.



• **Fig. 43.15** Steroidogenic pathways in the zona glomerulosa. The first common reaction in the pathway, conversion of cholesterol to pregnenolone by CYP11A1, is not shown. Note that the last three reactions are catalyzed by CYP11B2. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology*. 4th ed. Philadelphia: Mosby; 2013.)

IN THE CLINIC

Addison's disease is defined by **primary adrenal insufficiency,** with both mineralocorticoids and glucocorticoids usually being deficient. In North America and Europe, the most prevalent cause of Addison's disease is **autoimmune destruction of the adrenal cortex.** Because of the cortisol deficiency, ACTH secretion increases. Elevated levels of ACTH can compete for MC1R in melanocytes and cause an increase in skin pigmentation, particularly in skin creases, scars, and gums (see Fig. 43.14). The loss of mineralocorticoids results in contraction of extracellular volume, which produces circulatory hypovolemia and therefore a drop in blood pressure. Because loss of cortisol decreases the vasopressive response to catecholamines, peripheral vascular resistance drops, thereby facilitating the development of hypotension. Individuals with Addison's disease are also prone to hypoglycemia when stressed or fasting, and water intoxication can develop if excess



• **Fig. 43.16** The mineralocorticoid receptor (*MR)* is protected from activation by cortisol by the enzyme 11β-hydroxysteroid dehydrogenase type 2 *(11β-HSD2)*, which converts cortisol to inactive cortisone. Cortisone can be converted back to cortisol in glucocorticoid target cells by the enzyme *11β-HSD type 1*. *GRE*, Glucocorticoid response element; *GTF,* general transcription factors; *MRE*, mineralocorticoid response element. (Modified from White BA, Porterfield SP. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby; 2013.)

water is ingested. Because cortisol is important for muscle function, muscle weakness also occurs in cortisol deficiency. Loss of cortisol results in anemia, decreased GI motility and secretion, and reduced iron and vitamin B_{12} absorption. Appetite decreases with cortisol deficiency, and this decreased appetite coupled with the GI dysfunction predisposes these individuals to weight loss. These patients often have disturbances in mood and behavior and are more susceptible to depression.

Adrenocortical hormone excess is termed **Cushing's syndrome. Pharmacological** use of exogenous corticosteroids is now the most common cause of Cushing's syndrome. The next most prevalent cause is **ACTH-secreting tumors.** The form of Cushing's syndrome caused by a functional pituitary adenoma is called *Cushing's disease.* The fourth most common cause of Cushing's syndrome is **primary hypercortisolism** resulting from a functional adrenal tumor. If the disorder is primary or if it is a result of corticosteroid treatment, secretion of ACTH will be suppressed and increased skin pigmentation will not occur. However, if hypersecretion of the adrenal is the result of an ACTH-secreting nonpituitary tumor, ACTH levels sometimes become high enough to increase skin pigmentation.
Increased cortisol secretion causes weight gain with a characteristic centripetal fat distribution and a "buffalo hump." The face appears rounded (fat deposition), and the cheeks may be reddened, in part because of the polycythemia. The limbs are thin owing to skeletal muscle wasting (from increased proteolysis), and muscle weakness is evident (from muscle proteolysis and hypokalemia). Proximal muscle weakness is apparent, so the patient may have difficulty climbing stairs or rising from a sitting position. The abdominal fat accumulation coupled with atrophy of the abdominal muscles and thinning of the skin produces a large protruding abdomen. Purple abdominal striae are seen as a result of damage to the skin by the prolonged proteolysis, increased intra-abdominal fat, and loss of abdominal muscle tone. Capillary fragility occurs because of damage to the connective tissue supporting the capillaries. Patients are likely to show signs of osteoporosis and poor wound healing. They have metabolic disturbances that include glucose intolerance, hyperglycemia, and insulin resistance (see Fig. 43.10). Prolonged hypercortisolism can lead to manifestations of diabetes mellitus. Because of suppression of the immune system caused by glucocorticoids, patients are more susceptible to infection. The mineralocorticoid activities of glucocorticoids and the possible increase in aldosterone secretion produce salt retention and subsequent water retention that result in hypertension. Excessive androgen secretion in women can produce hirsutism, male pattern baldness, and clitoral enlargement (adrenogenital syndrome).

IN THE CLINIC

Any enzyme blockage that decreases cortisol synthesis will increase ACTH secretion and produce adrenal hyperplasia. The most common form of congenital adrenal hyperplasia is due to deficiency of the enzyme **21-hydroxylase (CYP21).** These individuals cannot produce normal quantities of cortisol, **deoxycortisol,** DOC, corticosterone, or aldosterone (see Figs. 43.8 and 43.10*C*). Because of impaired cortisol production and resultant elevated ACTH levels, steroidogenesis is stimulated, thereby increasing the synthesis products "upstream" of the missing enzyme, as well as products of the zona reticularis. Because the latter include the adrenal androgens, a female fetus will be masculinized. Because they are unable to produce the mineralocorticoids, aldosterone, DOC, and corticosterone, patients with this disorder have difficulty retaining salt and maintaining extracellular volume. Consequently, they are likely to be hypotensive. If the blockage is at the next step, **11β-hydroxylase** (CYP11B1), **DOC** will be formed and levels of DOC will accumulate (see Figs. 43.8 and 43.9*C*). Because DOC has significant **mineralocorticoid activity** and its levels become high, these individuals tend to retain salt and water and become hypertensive.

Key Concepts

1. The adrenal gland is composed of a cortex that is of mesodermal origin and a medulla that is of neuroectodermal origin. The cortex produces steroid hormones, and the medulla produces catecholamines.
2. The rate-limiting enzymes in medullary catecholamine synthesis are tyrosine hydroxylase and dopamine β-hydroxylase, which are induced by sympathetic stimulation, and phenylethanolamine-*N*-methyltransferase, which is induced by cortisol.
3. Catecholamines increase serum glucose and fatty acid levels. They stimulate gluconeogenesis, glycogenolysis, and lipolysis. Catecholamines increase cardiac output but have selective effects on blood flow to different organs.
4. Pheochromocytoma is a tumor of chromaffin tissue that produces excessive quantities of catecholamines. Symptoms of pheochromocytoma are often sporadic and include hypertension, headaches, sweating, anxiety, palpitations, chest pain, and orthostatic hypotension.
5. The adrenal cortex displays clear structural and functional zonation: the zona glomerulosa produces the mineralocorticoid aldosterone, the zona fasciculata produces the glucocorticoid cortisol, and the zona reticularis produces the weak androgens DHEA and DHEAS.
6. Cortisol binds to the glucocorticoid receptor. During stress, cortisol increases blood glucose by increasing gluconeogenesis in the liver and breaking muscle protein down to supply gluconeogenic precursors. Cortisol also decreases glucose uptake by muscle and adipose tissue and has permissive actions on glucagon and catecholamines. Cortisol has multiple effects on other tissue. From a pharmacological point of view, the most important is the immunosuppressive/anti-inflammatory effect.
7. Cortisol is regulated by the CRH-ACTH-cortisol axis. Cortisol negatively feeds back at the hypothalamus on both CRH-producing neurons and pituitary corticotropes. CRH is regulated by several forms of stress, including proinflammatory cytokines, hypoglycemia, neurogenic stress, and hemorrhage, and by diurnal input.
8. The adrenal androgens DHEA, DHEAS, and androstenedione are androgen precursors. They can be converted to active androgens peripherally and provide about 50% of circulating androgens in women. In men the role of adrenal androgens, if any, remains obscure. In women, adrenal androgens promote pubic and axillary hair growth and libido. Excessive adrenal androgens in women can lead to various degrees of virilization and ovarian dysfunction.
9. The zona glomerulosa of the adrenal cortex is the site of aldosterone production. Aldosterone is the strongest naturally occurring mineralocorticoid in humans. It promotes Na^+ and water reabsorption by the distal tubule and collecting duct while promoting renal K^+ and H^+ secretion. Aldosterone promotes Na^+ and water absorption in the colon and salivary glands. It also has a proinflammatory, profibrotic effect on the cardiovascular system and causes left ventricular hypertrophy and remodeling.
10. Major actions of angiotensin II on the adrenal cortex are increased growth and vascularity of the zona glomerulosa, increased StAR and CYP11B2 enzyme activity, and increased aldosterone synthesis.
11. Major stimuli for aldosterone production are a rise in angiotensin II and a rise in serum [K^+]. The major inhibitory signal is ANP.
12. Addison's disease is adrenocortical insufficiency. Common symptoms include hypotension, hyperpigmentation, muscle weakness, anorexia, hypoglycemia, and hyperkalemic acidosis.
13. Cushing's syndrome results from hypercortisolemia. If the basis of the disorder is increased pituitary adrenocorticotropin secretion, the disorder is called *Cushing's disease.* Common symptoms of Cushing's syndrome include centripetal fat distribution, muscle wasting, proximal muscle weakness, thin skin with abdominal striae, capillary fragility, insulin resistance, and polycythemia.
14. Congenital adrenal hyperplasia is caused by a congenital enzyme deficiency that blocks production of cortisol. The enzyme blockage results in elevated ACTH secretion, which stimulates adrenal cortical growth and secretion of precursors produced before the block. 21-Hydroxylase (CYP21B) deficiency is the most common form.