9.5 The Adrenal Cortex

Learning Objectives

- Describe the anatomical location of the adrenal glands
- List the three major histological divisions of the adrenal cortex and the major hormones secreted by each part
- Draw the steroid nucleus
- Distinguish between the structures of DHEA, cortisol, and cortisone
- Identify ACTH by name and indicate the location of cells that secrete it
- Define CRH and indicate the location of cells that secrete it
- Define POMC and name the peptide hormones that derive from it
- Describe the mechanism by which ACTH increases cortical steroid secretion
- Describe the mechanism of the anti-inflammatory effect of cortisol
- List the major secretagogues for aldosterone
- Describe the negative feedback loops involved in the renin–angiotensin–aldosterone system
- Describe the major features of aldosterone action on the distal nephron

THE ADRENAL GLANDS LIE ATOP THE KIDNEYS, ARE RICHLY VASCULARIZED, AND SECRETE MANY HORMONES

In 1856, Brown-Sequard performed adrenalectomies in dogs, cats, and guinea pigs and showed that the procedure was uniformly fatal. He declared that the adrenals were "organs essential for life." Each of two adrenal glands sits on top of the kidneys along their posteromedial aspect. The glands are roughly pyramidal, weighing about 4 g apiece and having a rich blood supply. Each gland consists of two main divisions, the **cortex** and the **medulla**, which together secrete four main classes of hormones. The cortex produces:

- glucocorticoids (cortisol, corticosterone);
- mineralocorticoids (aldosterone, deoxycorticosterone);
- sex hormones (androgrens);

whereas the medulla produces

- catecholamines (epinephrine and norepinephrine).

These hormones are essential for the regulation of metabolism including blood glucose, protein turnover and fat metabolism, regulation of blood volume and pressure through Na^+ balance, tissue response to infection or injury, and the whole body response to stress.

The whole gland is covered by a connective tissue **capsule**. The outer zone, the **cortex**, comprises 80–90% of the weight of the gland. The innermost zone, the **medulla**, makes up the remainder. The cortex consists of an outermost area, the **zona glomerulosa**, so named because the cells form into tiny balls. This layer is only a few cells thick. The **zona fasciculata** lies below the zona glomerulosa; it consists of long cords of polyhedral cells running radially out toward the zona glomerulosa. The innermost layer of the cortex is the **zona reticularis**. The zona reticularis forms a more branching network so that the radial arrangement of the cords is less obvious (see Figure 9.5.1).

The zona glomerulosa produces the **mineralocorticoids** because only this part of the adrenal gland expresses the enzymes required for their synthesis. It secretes some 100–150 μg/day. Similarly, the zona fasciculata produces some 10–20 mg of glucocorticoids each day. The androgen steroid **dehydroepiandrosterone (DHEA)** is sulfated to form DHEAs only in the zona reticularis. The adult adrenal secretes more than 20 mg/day of DHEA and DHEAs (dehydroepiandrosterone sulfate).

STEROID HORMONES DERIVE FROM CHOLESTEROL

All adrenal steroidogenesis begins with cholesterol. The cholesterol has two origins: (1) uptake from low-density lipoproteins (LDL) by specific LDL receptors on the surfaces of adrenal gland cells and (2) *de novo* synthesis of cholesterol within the adrenal cortex from acetyl CoA. The structure of cholesterol is shown in Figure 9.5.2. Cholesterol has a four ring structure called the **steroid nucleus** that is common to all steroid hormones. These steroid hormones possess a wide variety of activities that are due to surprisingly small variations in their structure. The classification of the steroid hormones is based not only on their activities but also on their structure, as shown in Figure 9.5.2.

The synthesis of the adrenal cortex steroid hormones begins with the import of cholesterol into the mitochondria. This transport is mediated by StAR, for

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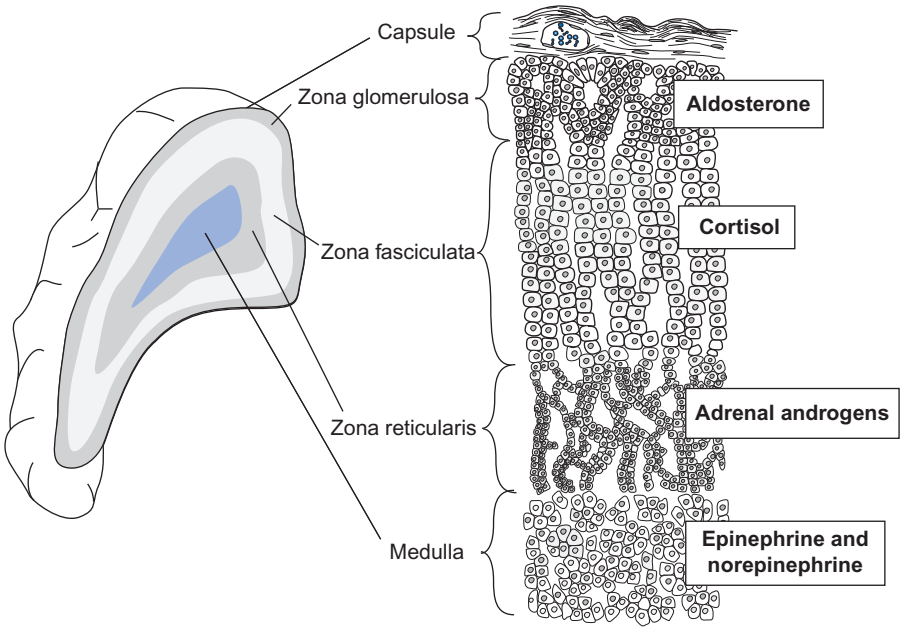

FIGURE 9.5.1 Appearance of the adrenal gland. A cross section of the adrenal gland reveals several macroscopically distinct regions: the capsule, cortex, and medulla. The cortex is further differentiated into three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis, from outer to inner cortex. The zona glomerulosa secretes predominantly aldosterone, a mineralocorticoid. The zonae fasciculata and reticularis secrete glucocorticoids and androgens. The medulla secretes epinephrine.

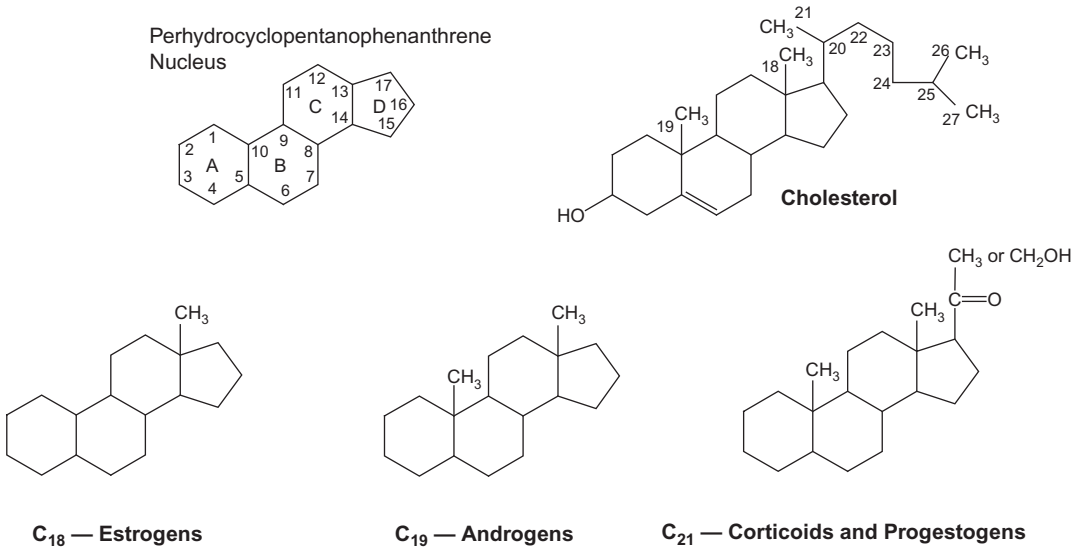

FIGURE 9.5.2 Chemical structures of cholesterol and the three major structural groups of steroid hormones. All of these have the classic steroid nucleus consisting of three six-carbon rings (perhydrophenanthrene) and another five-carbon ring (cyclopentano).

steroidogenic **a**cute **r**egulatory protein, a 30 kDa protein. The activity of StAR is regulated by cAMP levels that are controlled in these cells by **ACTH**, **adrenocorticotrophic hormone**. Steroidogenesis begins in the mitochondria, but some crucial enzymes lie in the endoplasmic reticulum. The relevant biochemical pathways are shown in Figure 9.5.3.

THE PITUITARY–HYPOTHALAMUS AXIS CONTROLS ADRENAL FUNCTION THROUGH ACTH

As described in Chapter 9.2, corticotrophs in the anterior pituitary secrete ACTH in response to corticotropin-releasing hormone (CRH) secreted by cells in the paraventricular nucleus of the hypothalamus (see Figure 9.5.4). CRH is a 41-amino-acid peptide that is secreted into the hypophyseal portal circulation in response to a variety of stimulati and inputs including: circadian rhythms, hypoglycemia, surgery, fever, and injury. CRH stimulates the release of ACTH from corticotrophs through a G_s-coupled mechanism.

Corticotrophs make proopiomelanocortin, POMC, as their principal secretory protein. This protein has 241 amino acids and contains within it several other smaller peptide hormones. Tissue-specific proteolytic cleavage releases these other peptides. POMC is cleaved within secretory granules and therefore stimulation of secretion releases ACTH and POMC's other cleaved product, β **lipotropin** (βLPH). βLPH has effects on lipid metabolism,

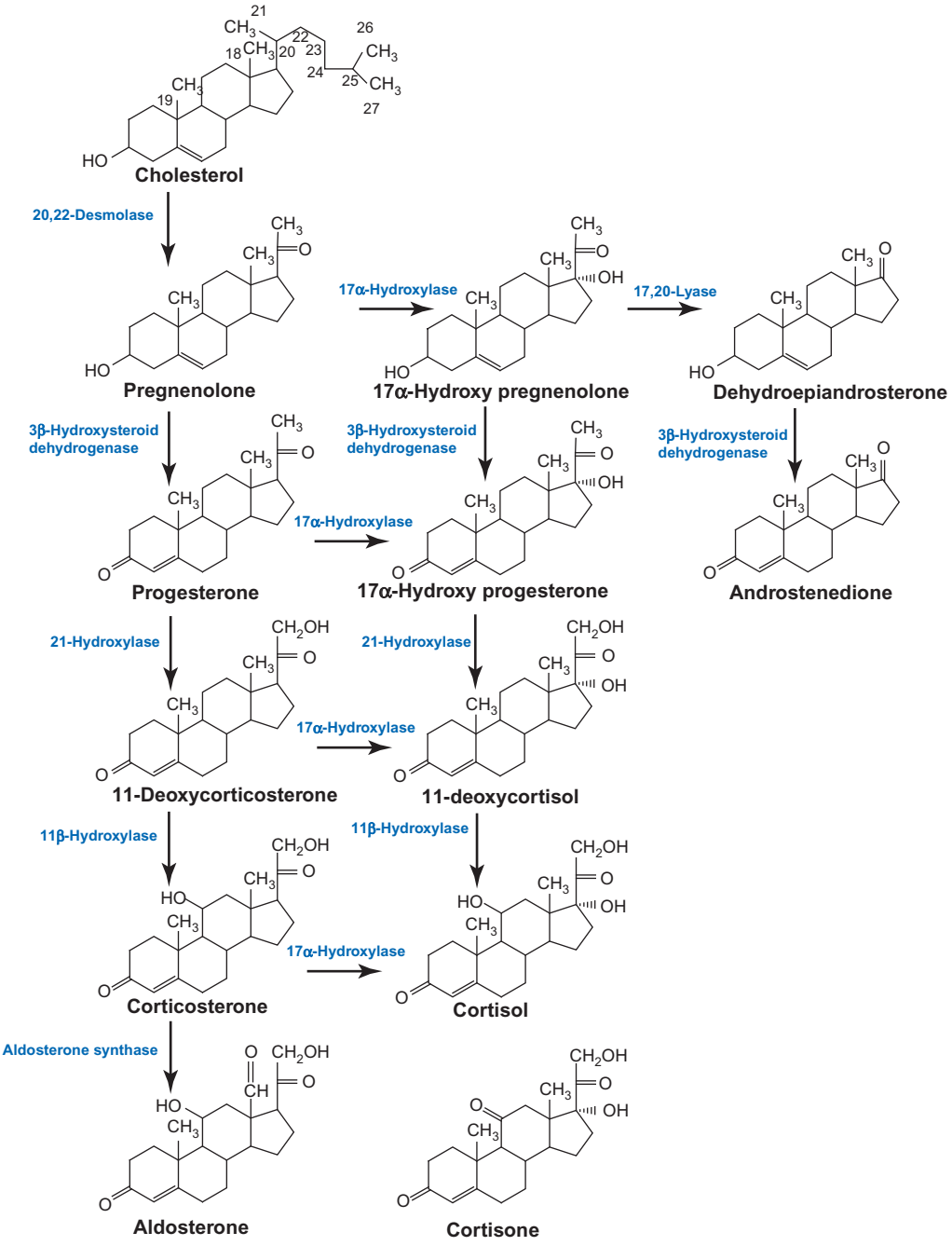

FIGURE 9.5.3 Biochemical pathways for the synthesis of adrenal cortical steroid hormones. Aldosterone, cortisol, and adrenal androgens are synthesized in specific zones of the cortex in a coordinated series of reactions. Each zone of the cortex contains its own set of steroidogenic enzymes.

but its effects in humans are not established. Figure 9.5.5 shows the origin of POMC and the peptide hormones it generates after proteolytic cleavage.

Human skin contains melanocytes that produce melanin, which determines the color of the skin. These cells respond to melanophore stimulating hormone, MSH. In lower animals, the pars intermedia or the pituitary gland secretes MSH. The pars intermedia is the intermediate lobe of the pituitary gland, between the anterior and posterior pituitary. In humans, the pars intermedia is vestigial and produces insignificant amounts of MSH. Persons with Addison's disease (primary adrenal insufficiency) have high levels of ACTH and they develop increased skin pigmentation that is thought to arise from ACTH stimulation of the melanocortin receptor on melanocytes. Peptide sequences homologous to MSH can be found in ACTH and βLPH.

ACTH INCREASES ADRENAL CORTICAL STEROID SECRETION

ACTH binds to a G_s-coupled melanocortin-2 receptor on adrenocortical cells. Binding is followed principally by increases in cytoplasmic [cAMP], although intracellular [Ca^{2+}] also plays a role. ACTH stimulation results in short-

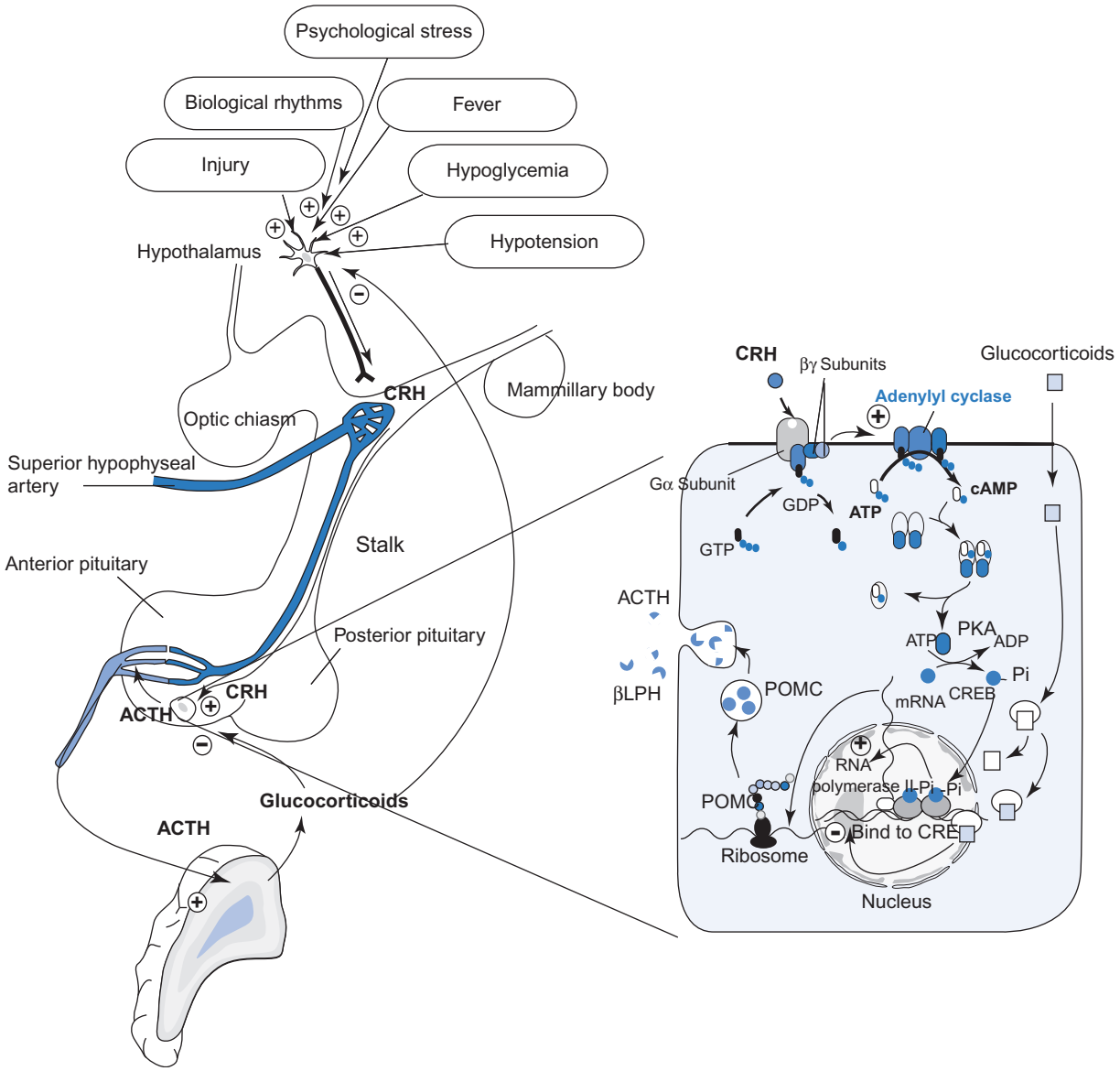

FIGURE 9.5.4 Control of adrenal cortical hormone secretion. Neurons in the paraventricular nucleus of the hypothalamus release CRH into the hypophyseal portal circulation in response to a variety of stimuli. CRH activates G_s-coupled receptors on corticotrophs in the anterior pituitary. The increased [cAMP] stimulates synthesis of POMC (proopiomelanocortin, a precursor of ACTH) probably through a CREB (cyclic AMP response element binding protein) mechanism. POMC is cleaved within granules and both ACTH and βLPH (lipotropin) are released. Glucocorticoids provide negative feedback by inhibition of CRH secretion in the hypothalamus and by inhibition of ACTH secretion.

term and long-term effects. Acutely, **StAR (steroidogenesis acute regulatory protein)** increases cholesterol delivery to the cholesterol side chain cleavage enzyme located in the inner mitochondria. Increasing this rate-limiting step increases steroid hormone synthesis. Prolonged exposure to ACTH increases the transcription of genes that produce all of the enzymes for steroid hormone synthesis: cholesterol side chain cleavage enzyme (also known as CYP11A1), 17α-hydroxylase (CYP17), 21-hydroxylase (CYP21A2), and 11β-hydroxylase (CYP11B1). ACTH also increases the number of surface receptors for LDL. In addition to these effects, ACTH also exerts a general trophic effect on the adrenal gland, increasing its weight due to both **hyperplasia** and **hypertrophy**. These effects are shown diagrammatically in Figure 9.5.6.

CORTISOL BINDING PROTEIN CARRIES GLUCOCORTICOIDS IN BLOOD

An α_2 globulin called **cortisol binding globulin** (**CBG**) binds about 90% of the total circulating cortisol. CBG is synthesized and secreted by the liver and binds cortisol with high affinity. Levels of CBG are increased by estrogen and reduced by glucocorticoids. Because of this, pregnant women may have elevated total cortisol levels even though the free cortisol concentration remains unchanged. Only the free hormone can diffuse into the tissues to bind to target cells and alter their behavior. As free hormone is taken up by peripheral tissues, the bound hormone dissociates from its carrier to take the place of the hormone that has left.

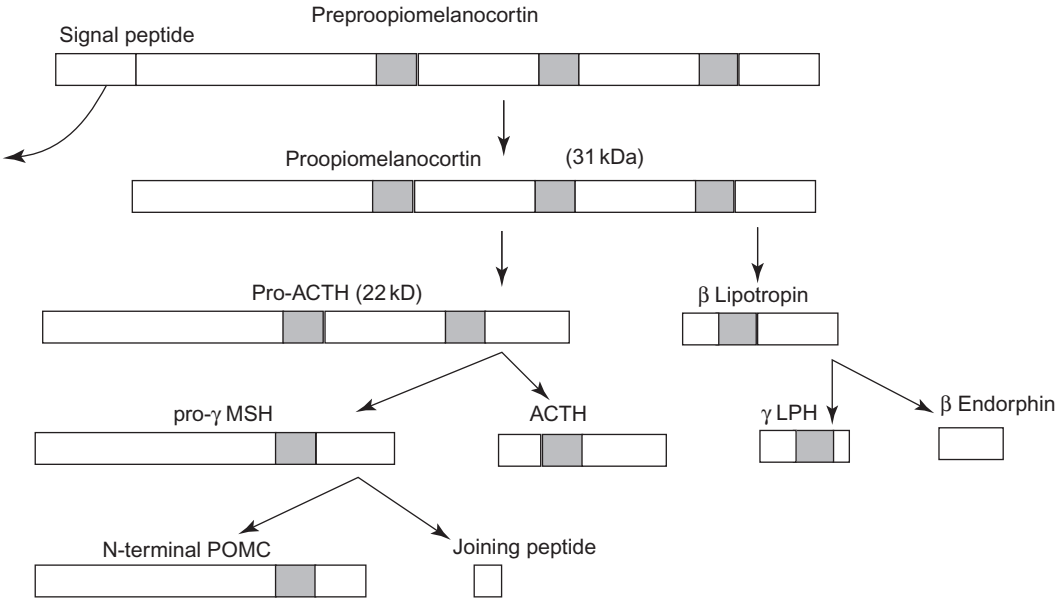

FIGURE 9.5.5 Relationship between POMC and its various cleavage products. Corticotrophs in the anterior pituitary synthesize prePOMC. This contains a signal sequence to get the protein into the secretory granules. Cleavage of the signal sequence produces POMC, proopiomelanocortin. Further cleavage results in the formation of ACTH and β lipotropin, which are the principal secretory products of the corticotrophs. Further cleavage can produce γMSH and β endorphin. β Endorphins are endogenous ligands for opioid receptors, from which POMC partly derives its name. Shaded area represents regions of MSH structural units.

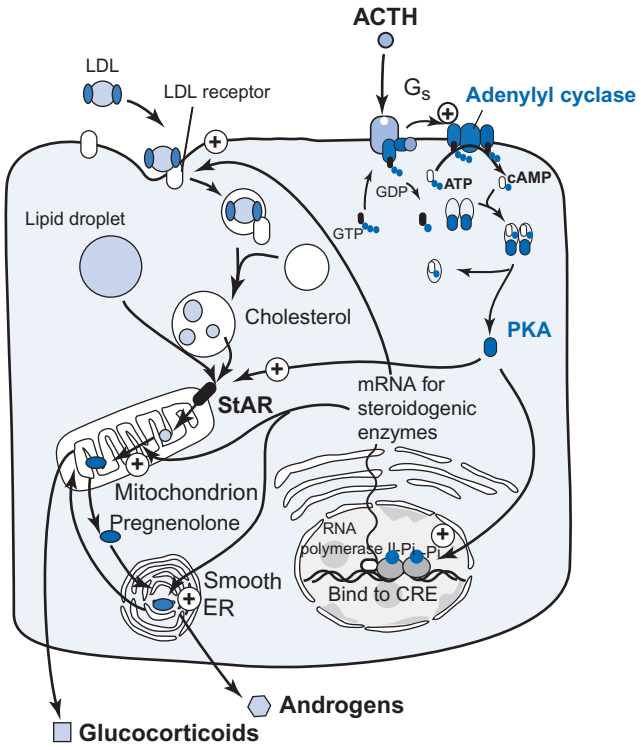

FIGURE 9.5.6 Stimulation of steroidogenesis by ACTH in adrenocortical cells. ACTH acutely increases the activity of StAR, a 30-kDa protein that imports cholesterol into mitochondria. The cholesterol originates from uptake of cholesteryl esters from low-density lipoproteins (LDL) from the blood, or from cholesterol in lipid stores, or from cholesterol newly synthesized on the smooth endoplasmic reticulum. Cholesterol is converted to pregnenolone within the mitochondria by cholesterol side chain cleavage enzyme (CYP11A1). Steroid conversions continue in the smooth endoplasmic reticulum to generate glucocorticoids and androgens. ACTH stimulates steroidogenesis by increasing the number of LDL receptors on the surface of the cell, by increasing cholesterol transport into the inner mitochondria, and by increasing the amounts of several enzymes in the steroid synthesis pathway, including CYP11A1, CYP17, CYP21A2, and CYP11B1. ACTH also stimulates the growth and division of adrenocortical cells.

The circulating half-life of cortisol is about 70–120 min. Corticoid hormones are excreted by the kidney after structural modification destroys their hormone activity and increases their water solubility.

CORTISOL AFFECTS TARGET CELLS THROUGH REGULATION OF TRANSCRIPTION

Glucocorticoids exert their effects on target cells by binding to receptors in the cytosol, called glucocorticoid receptors, or GR. In the unstimulated state, the GR associate with **heat shock proteins**, **HSP70** or **HSP90**. Upon binding of steroid hormone to GR, HSP70 or HSP90 dissociates from the complex, and the GR–steroid complex migrates to the nucleus. The GR–steroid complex dimerizes and then binds to specific sequences of nucleotides in the promoter regions of target genes. These specific nucleotide sequences that bind the GR–steroid complex are **glucocorticoid-response elements** (GREs). The complex begins transactivation by recruiting proteins with histone acetyl transferase (HAT) activity. Acetylation of the histones facilitates their unwinding and exposure of regions of the DNA for transcription. The complex stabilizes RNA polymerase II, and transcription is initiated. The target genes differ among the many cell types that are affected by the glucocorticoids. For example, glucocorticoids reduce the expression of TNF-α in macrophages but decrease the expression of osteocalcin in bone cells.

In some cells, glucocorticoids exert a negative effect. For example, cortisol possesses potent anti-inflammatory activity. The likely mechanism for this effect in macrophages is described in Figure 9.5.7. Glucocorticoids also exhibit anti-inflammatory effects in other cell types. For example, glucocorticoids inhibit

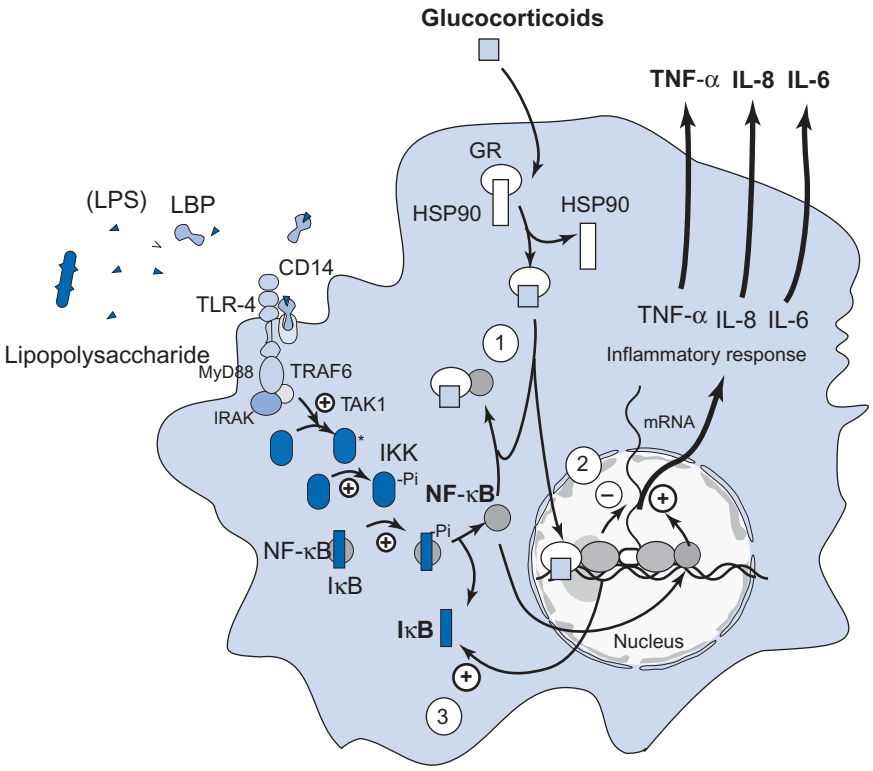

FIGURE 9.5.7 Mechanism of the anti-inflammatory action of the glucocorticoids. Inflammation in this macrophage is brought about by the binding of a bacterial product, lipopolysaccharide or LPS, to plasma LPS binding protein (LBP). The complex of LPS—LBP then binds to a membrane receptor on the surface of the macrophage, CD14, which is linked to another protein called TLR-4, for toll-like receptor 4. This is linked by another complex of proteins to a MAP kinase kinase kinase called TAK1 that phosphorylates and activates an IκB kinase (IKK) that phosphorylates IκB. IκB in its unphosphorylated state inactivates nuclear factor κB (NF-κB), and the phosphorylation removes this inactivation. NF-κB travels to the nucleus where it activates the genes that cause the release of inflammatory cytokines and chemokines, TNF-α, IL-8, IL-6. Glucocorticoids enter the cell passively by diffusion (they are lipid soluble and sparingly water soluble) and bind to a cytoplasmic receptor (glucocorticoid receptor, GR) that is complexed with heat shock protein 90 (HSP90). Binding of glucocorticoid displaces HSP90. The GR—glucocorticoid complex then interferes with inflammation in three separate ways. First, the GR—glucocorticoid complex binds NF-κB so that it cannot exert its stimulatory effect in the nucleus (1). Second, the GR—glucocorticoid complex binds to its own DNA sequences and competes with NF-κB for available coactivators (2). Third, GR—glucocorticoids induce the synthesis of IκB that binds and inactivates NF-κB (3).

transmigration of leukocytes. Glucocorticoids induce the expression of **annexin 1** (formerly called lipocortin), a protein that binds Ca^{2+} and phospholipids and translocates from cytoplasm to cell surface in neutrophils when they adhere to the endothelial cell wall. Annexin 1 causes detachment of the neutrophils, and thereby it inhibits neutrophil transmigration.

CORTISOL AFFECTS MANY BODY FUNCTIONS

The glucocorticoids have many effects on multiple organ systems, and the multitude of these effects is summarized briefly in Table 9.5.1. Cortisol affects carbohydrate, protein, and lipid metabolism and also muscle, skeleton, kidney, and the immune system.

THE ZONA GLOMERULOSA MAKES ALDOSTERONE IN RESPONSE TO ANGIOTENSIN II, ACTH AND K^+

Aldosterone is a mineralocorticoid synthesized and secreted by cells in the zona glomerulosa. Its structure is shown in Figures 9.5.3 and 7.6.9. It is called a mineralocorticoid because its principal actions are on the excretion of minerals, particularly Na^+ and K^+, by various epithelial cells, including the **distal nephron**, **colon, salivary glands**, and **sweat glands**. Its synthesis and secretion are controlled mainly by angiotensin II, but plasma $[K^+]$ and ACTH also directly stimulate aldosterone levels.

Granule cells that line the afferent arteriole in the juxtaglomerular apparatus of the kidney secrete **renin** into the blood in response to:

- decreased afferent arteriolar pressure;
- renal sympathetic nerve stimulation;
- decreased distal tubule load of NaCl.

Renin is an enzyme that cleaves circulating **angiotensinogen** to form **angiotensin I**, a 10-amino-acid-long peptide. The liver makes angiotensinogen. Another enzyme, **angiotensin converting enzyme**, or **ACE**, converts angiotensin I to **angiotensin II**, an eight-amino-acid peptide. The lungs contain most ACE activity, but it is also found in the kidney.

ANGIOTENSIN II EXERTS MULTIPLE EFFECTS

Angiotensin II formed by renin action on angiotensinogen and ACE conversion, acts on several tissues. It causes the following:

- Vasoconstriction
- The sensation of thirst
- Release of antidiuretic hormone (ADH)
- Release of aldosterone
- Increased reabsorption of Na^+ and HCO_3^- in the proximal tubule.

All of these effects of angiotensin II work to increase the circulatory volume and maintain circulatory pressure. It motivates us to drink more water while it simultaneously increases the retention of extracellular ions, mainly Na^+.

TABLE 9.5.1 Overview of the Physiological Actions of the Glucocorticoids

1	**Effects on carbohydrate metabolism**
1.1	Glucocorticoids increase liver gluconeogenesis
1.2	Glucocorticoids promote protein and fat catabolism, providing amino acids and glycerol for gluconeogenesis
1.3	Glucocorticoids inhibit glucose utilization by muscle and adipose tissue
1.4	Glucocorticoids enhance glycogen stores in liver
1.5	Glucocorticoids raise blood glucose levels
2	**Effects on protein metabolism**
2.1	Glucocorticoids accelerate protein catabolism
2.2	Glucocorticoids increase amino acid uptake and protein synthesis in the liver
2.3	Long-term effects of glucocorticoids are "protein wasting"
3	**Effects on fat metabolism**
3.1	Glucocorticoids increase lipolysis
3.2	Glucocorticoids increase plasma levels of free fatty acids
4	**Effects on muscle tissue**
4.1	Basal levels of glucocorticoids are essential for normal muscle contractility and performance
4.2	Excessive glucocorticoids cause muscle wasting and atrophy
5	**Effects on the skeleton**
5.1	Glucocorticoids decrease Ca^{2+} absorption from the intestines
5.2	Glucocorticoids decrease bone formation
5.3	Glucocorticoids increase bone resorption
6	**Effects on the kidneys**
6.1	Glucocorticoids increase the GFR
6.2	Glucocorticoids increase the free water clearance
6.3	Glucocorticoids inhibit ADH secretion and action
7	**Effects on the immune system**
7.1	Glucocorticoids induce annexin I that inhibits neutrophill transmigration
7.2	Glucocorticoids inhibit NF-κB
7.3	Glucocorticoids decrease production of cytokines (IL-1, IL-6, and TNF-α)

The overall negative feedback loops are shown diagrammatically in Figure 9.5.8.

Angiotensin II binds to AT_1 or AT_2 receptors on the surface of its target cells. Most of its effects are mediated by AT_{1A} receptors except in the adrenal gland where increase of aldosterone secretion appears to be mediated by AT_{1B} receptors. The AT_{1B} receptors couple to G_q-coupled receptors. Activation of CAM kinase (through increased cytosolic $[Ca^{2+}]$ through IP3-induced release of ER stores) appears to be responsible for the early increase in aldosterone secretion in response to AII. DAG released by phospholipase C activates protein kinase C and appears to be responsible for more sustained secretion of aldosterone.

ALDOSTERONE INCREASES Na^+ REABSORPTION AND K^+ SECRETION BY GENOMIC AND NONGENOMIC MECHANISMS

The primary renal target of aldosterone is the **principal cells in the cortical collecting duct**. The mechanism of Na^+ reabsorption and K^+ in these cells is shown diagrammatically in Figure 9.5.9. Aldosterone increases Na^+ reabsorption by increasing the activity of apical membrane **epithelial Na channel (ENaC)**, and an **apical K^+ channel**, which increases Na^+ reabsorption and K^+ secretion. The effects of aldosterone on these activities are indirect. Aldosterone exerts these effects by altering genomic expression of another set of proteins that include **SGK1** (for serum and glucocorticoid-inducible kinase) and **K-RasA**. The increased expression of these proteins is accomplished by classical genomic mechanisms for the steroid hormones.

Aldosterone first binds to its cytosolic mineralocorticoid receptor, MR. This receptor has similar affinities for aldosterone and cortisol, but the circulating levels of cortisol are 100−1000 times those of aldosterone. Why are not the mineralocorticoid receptors continuously activated by cortisol? Those tissues that express MR also express 11β-hydroxysteroid dehydrogenase, which has been proposed to protect the MR from being occupied by glucocorticoids by metabolizing the glucocorticoids to products with much lower affinity for the MR.

SGK1 increases ENaC activity by reducing its interaction with another protein, **Nedd4-2**, which appears to tag ENaC with ubiquitin, a 76-amino-acid protein that is used to tag proteins for degradation. SGK1 phosphorylates Nedd4-2, blocking its ubiquitination of ENaC. By decreasing its degradation, SGK1 increases the membrane density of this channel. In addition to increasing the density of epithelial Na^+ channels, aldosterone may alter the activity of these channels indirectly through increasing expression of K-RasA. Aldosterone-induced methylation activates ENaC activity, but the effect may be mediated by other proteins in a cascade of activation. This complicated pathway is under active investigation.

SUMMARY

An adrenal gland sits atop each kidney. These small glands are encapsulated and contain a cortex and a medulla. The cortex secretes steroid hormones, and the medulla secretes primarily epinephrine. The cortex consists of three regions: the zona glomerulosa is the outermost and it secretes primarily aldosterone; the next layer is the zona fasciculata and it secretes glucocorticoids; the innermost layer of the cortex, the zona reticularis, secretes adrenal androgens.

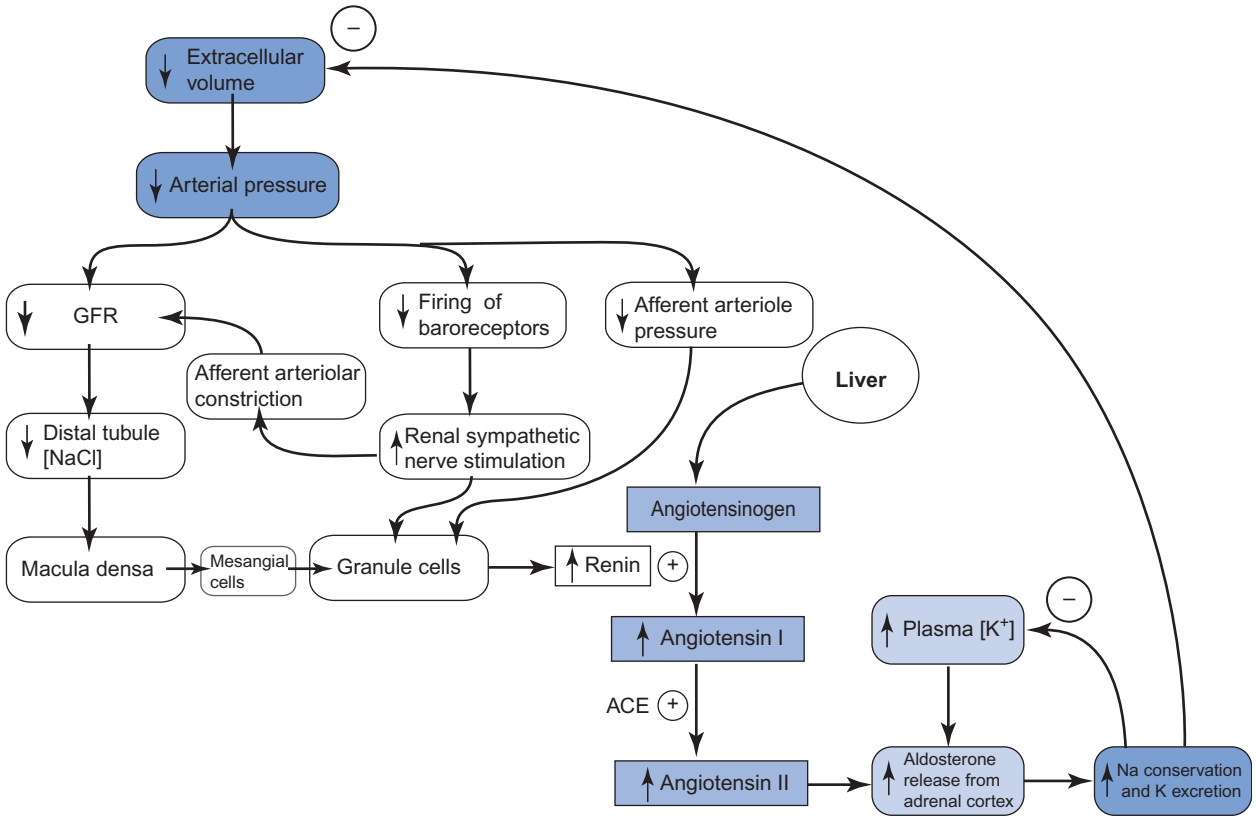

FIGURE 9.5.8 Overall control of aldosterone secretion and its effects on mineral balance. Aldosterone secretion is primarily controlled by angiotensin II levels and plasma [K^+]. Aldosterone's primary effect is retention of Na^+ and excretion of K^+ by the kidney. Since aldosterone secretion is stimulated by increased plasma [K^+], its effect completes a simple negative feedback loop. Similarly, aldosterone secretion is increased by angiotensin II, whose circulating levels are controlled indirectly by the rate of secretion of renin from granule cells in the juxtaglomerular apparatus. The stimuli for renin release include decreased afferent arteriolar pressure, increased renal sympathetic stimulation, and decreased distal tubule [NaCl]. The aldosterone increases Na^+ reabsorption and K^+ secretion. The result is a tendency to retain the extracellular fluid volume. This tends to raise arteriolar pressure toward normal, decrease renal sympathetic nervous stimulation, and return distal tubule NaCl loads back toward normal, completing another set of negative feedback loops.

Clinical Applications: Cushing's Disease and Cushing's Syndrome

Cushing's *syndrome* is caused by an excess of glucocorticoids, regardless of source or cause. Cushing's *disease* refers to those cases that are caused by inappropriately increased pituitary production of ACTH. Both originate in clinical observations of Harvey Cushing, who in 1912 first described a woman with obesity, hirsuitism and amenorrhea, and who in 1932 recognized the syndrome as a primary pituitary abnormality causing adrenal hyperplasia. Causes include exogenous corticosteroid therapy, adrenal tumors, ectopic ACTH or CRH production, and pituitary tumors.

The clinical symptoms of Cushing's syndrome involve multiple organ systems because glucocorticoids regulate metabolism all over. Afflicted persons often have a distinct pattern of centripetal obesity while legs and arms may be normal. Patients develop adipose deposits over the thoracocervical spine, the so-called buffalo hump. Fat buildup over the cheeks and temporal regions of the face produce the rounded, "moon" face. The skin is fragile and thin, and easily bruised. The thin skin is stretched by the underlying fat and produces "purple striae," or stripes of livid red-purple usually found on the abdomen but also occurring on the arms and thighs. Stretch marks caused by birth or rapid weight loss are less pigmented. Skin pigmentation is rare in Cushing's disease but is common in ectopic ACTH syndrome. Cushing's syndrome also impairs glucose intolerance. Overt diabetes mellitus presents in a third of cases. Persons with Cushing's syndrome have high blood pressure.

Cushing's syndrome is also associated with muscle wasting and weakness, osteoporosis, hirsuitism, and reproductive dysfunction. The organic matrix of bone is depleted with particular susceptibility of the vertebral column. Patients may lose height due to vertebral collapse. Hirsuitism is due to overproduction of adrenal androgens. The high circulating glucocorticoids inhibit gonadotropin-releasing hormone pulsatility and subsequent LH and FSH secretion, causing hypogonadism. These effects are reversed upon correction of the hypercortisolism.

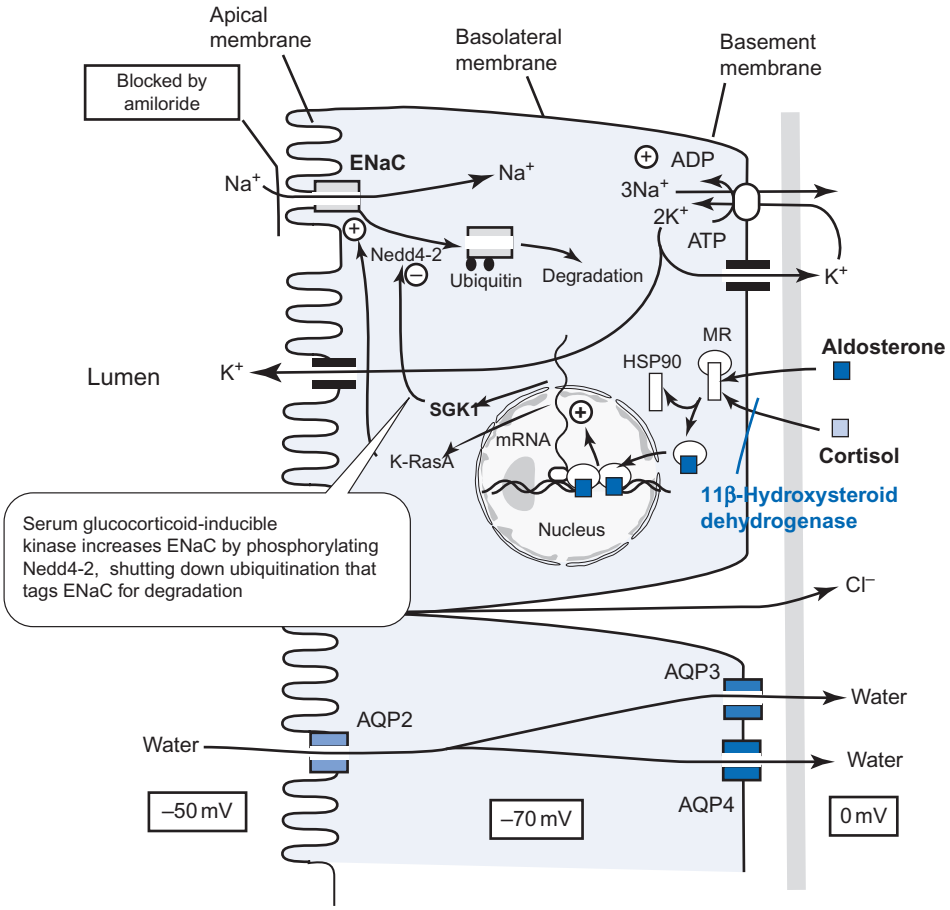

FIGURE 9.5.9 Mechanism of action of mineralocorticoids on principal cells of the cortical collecting duct. Aldosterone binds to mineralocorticoid receptors in the cytosol of the cells. The overall effect of aldosterone is to increase the activity of the epithelial Na channel, ENaC, as well as the apical K channel and basolateral Na,K-ATPase. The signal pathways by which these actions occur are still being actively investigated. The current hypothesis is that ENaC levels are increased by inhibition of degradation by phosphorylation of Nedd4-2, which inhibits its ubiquitination of ENaC, a process that "tags" the protein for degradation by the cell. Synthesis of K-RasA appears to regulate the function of ENaC by activating it by as yet unknown mechanisms. Activity of K-RasA requires methylation.

Clinical Applications: Addison's Disease

Thomas Addison first described **primary hypoadrenalism** in a classical monograph published in 1855. It is a rare condition with a prevalence of some 4—11 affected persons per 100,000. The majority of these cases (about 70%) are caused by autoimmune adrenalitis. The adrenal glands atrophy, with complete loss of the cortex while the medulla remains intact. In primary adrenal failure, the patient usually has glucocorticoid and mineralocorticoid deficiency. Secondary hypoadrenalism is caused by a lack of ACTH, and afflicted persons have glucocorticoid deficiency but generally have an intact renin—angiotensin—aldosterone system. This presence of adequate aldosterone in secondary hypoadrenalism accounts for the difference in clinical presentation between primary and secondary hypoadrenalism.

The most visible distinction between primary and secondary hypoadrenalism is the presence of excess skin pigmentation in primary hypoadrenalism due to high ACTH secretion because there is little negative feedback from blood levels of glucocorticoids. Increased stimulation of melanocortin-2 receptors by the high circulating ACTH levels causes the pigmentation. In persons with secondary hypoadrenalism, low ACTH causes their adrenal insufficiency.

The clinical features of adrenal insufficiency usually develop slowly and diagnosis is made when the patient is stressed with some other illness. Patients may present themselves with an acute adrenal crisis, with dehydration, hypotension, and imminent circulatory collapse. They have unexplained hypoglycemia, hyponatremia, hyperkalemia, nausea, vomiting, diarrhea, and sometimes abdominal pain. This adrenal crisis needs prompt attention. Patients that do not present with an adrenal crisis show postural hypotension. In normal individuals, blood levels of aldosterone respond rapidly to shifts in posture, which suggests that some actions of aldosterone must be nongenomic: a fast-responding hormone would, from a teleologically perspective, require a fast-acting mechanism of response.

All of the steroid hormones derive from cholesterol. They are not stored in secretory granules like the peptide hormones but are synthesized as needed from cholesterol that is imported from the blood or from cholesterol within the adrenal cells either in lipid droplets or freshly synthesized. The cholesterol is first imported into the mitochondria where its side chain is cleaved. Cholesterol is carried into the mitochondria by StAR, or steroidogenesis acute regulatory protein. Its activity is controlled by ACTH, which is secreted by the corticotrophs in the anterior pituitary in response to CRH release from neurons in the paraventricular nucleus of the hypothalamus. CRH

release, in turn, is stimulated by a variety of stresses sensed by the central nervous system, including circadian rhythms, hypoglycemia, fever, and injury. Secreted glucocorticoids provide negative feedback to both CRH and ACTH release.

ACTH is synthesized by corticotrophs as prePOMC—pre proopiomelanocortin. Its cleavage produces POMC, and further cleavage makes ACTH and lipotropin. Further cleavage can produce γMSH and β endorphin. Some of these parts of POMC stimulate melanocortin receptors that cause increased pigmentation of the skin. For this reason, excess POMC changes skin pigmentation. ACTH binding to the melanocortin-2 receptor is coupled to a G_s mechanism in the adrenal secretory cells.

Glucocorticoids have metabolic effects on all organ systems. They promote gluconeogenesis in liver and raise blood glucose levels. They cause muscle wasting and thinning of the skin and promote adipose deposition around the viscera. They decrease osteoblast activity and therefore ultimately contribute to bone loss and osteoporosis. They are anti-inflammatory and suppress the immune system. These effects seem counterproductive, but the glucocorticoids help the body respond to stress by mobilizing fuel resources.

The glucocorticoids classically act by binding to a cytosolic receptor which is bound with heat shock protein. Binding of glucocorticoids sheds the heat shock protein and allows the receptor to migrate to the nucleus where it binds to GREs on the DNA. The result is either a stimulation or an inhibition of transcription of DNA into mRNA.

Aldosterone is a mineralocorticoid and is involved in regulating the extracellular volume. Its synthesis and secretion is controlled mainly by angiotensin II and plasma [K]. Angiotensin II in turn is produced by a cascade of proteolytic cleavage of angiotensinogen, a precursor molecule made in the liver and circulating in the blood. When renal arteriolar blood pressure falls, renal sympathetic stimulation increases, or the distal tubule [Na] falls, granule cells in the afferent arteriole are stimulated to secrete renin. This enzyme cleaves angiotensinogen to angiotensin I, containing 10 amino acids. Angiotensin converting enzyme, or ACE, cleaves angiotensin I to angiotensin II, containing eight amino acids. Angiotensin II then exerts multiple effects, including vasoconstriction (to increase blood pressure) and stimulating secretion of aldosterone and ADH. Aldosterone increases Na reabsorption and K excretion by altering the activity of ENaC on the apical membrane of distal tubule cells.

REVIEW QUESTIONS

1. What part of the adrenal gland makes glucocorticoids? What stimulates it?
2. What controls ACTH secretion? Where is CRH produced? What is CRH?
3. Why does excess ACTH production increase skin pigmentation? What is POMC?
4. What effects does cortisol have on blood glucose, liver, muscle, bone, and fat?
5. What effects does cortisol have on the immune system?
6. How does cortisol exert its effects?
7. What is aldosterone and where is it made? What causes its secretion?
8. What are aldosterone's main effects?
9. What is aldosterone's mechanism of action?