## Adrenocortical Hormones (Mineralocorticoids, Glucocorticoids)

The adrenal gland is composed of two distinct parts:
(1) An inner adrenal medulla, which is functionally related to the sympathetic nervous system and secretes mainly epinephrine but some norepinephrine and
(2) An outer adrenal cortex, which forms the bulk of the gland and secretes corticosteroids.
The primary corticosteroids secreted by the adrenal cortex are as follows:
• Mineralocorticoids. C21 steroids that have important effects on sodium and potassium balance
• Glucocorticoids. C21 steroids that influence carbohydrate, fat, and protein metabolism
• Sex hormones. C19 steroids that are mostly weak androgens and contribute to secondary sex characteristics.
The secretion of mineralocorticoids and glucocorticoids is essential to life. Only small amounts of sex hormones are normally secreted by the adrenal cortex.

**Adrenocortical Hormones Are Synthesized from Cholesterol.**
Most of the cholesterol in adrenocortical cells is taken up from the circulation and then esterified and stored in lipid droplets. The rate-limiting step in the synthesis of adrenocortical hormones is the side-chain cleavage of cholesterol to form pregnenolone. This step includes the delivery of cholesterol to the inner mitochondrial membrane and the enzymatic cleavage (through cholesterol desmolase) of a six-carbon unit from cholesterol to yield pregnenolone. In all three zones of the adrenal cortex, this initial step in steroid biosynthesis is stimulated by the controllers of the major hormone products (aldosterone and cortisol). The conversion of cholesterol to pregnenolone and all the subsequent steps in the synthesis of adrenocortical hormones occur either in the endoplasmic reticulum or mitochondria.
**Adrenocortical Hormones Are Metabolized in the Liver.**
Cortisol and aldosterone are metabolized to various compounds in the liver and then conjugated to glucuronic acid. These inactive conjugates are freely soluble in plasma and are not bound to plasma proteins. Once released into the circulation,

they are readily excreted in urine. The rate of inactivation of adrenocortical hormones is depressed in liver disease.

## Functions of the Glucocorticoids

**Cortisol** Is the Primary Glucocorticoid Secreted by the Adrenal Cortex. More than 95% of glucocorticoid activity exerted by the adrenocortical hormones can be attributed to cortisol; most of the remaining glucocorticoid activity is due to corticosterone.

Cortisol mediates most of its effects by binding with intracellular receptors in target tissues and inducing or repressing gene transcription; this results in alterations in the synthesis of enzymes that alter cell function. Cortisol Has Widespread Effects on Metabolism. There are pronounced disturbances in carbohydrate, fat, and protein metabolism in adrenal insufficiency. Some of the metabolic effects of cortisol are permissive in that cortisol does not initiate the changes, but its presence at normal plasma levels permits certain metabolic processes.

**Cortisol exerts the following effects on metabolism:**

• Decreases protein stores in extra hepatic tissues. In muscle and other extra hepatic tissues, cortisol decreases amino acid uptake and inhibits protein synthesis; at the same time, it increases the degradation of proteins. As a result of these catabolic and antianabolic effects of cortisol, amino acids tend to increase in the blood and are taken up by the liver, where they are converted to glucose and proteins, including gluconeogenic enzymes.

• Tends to increase the blood glucose concentration in two ways. First, cortisol increases hepatic production of glucose by increasing gluconeogenesis. The proteins mobilized from peripheral tissues are converted to glucose and glycogen in the liver. By maintaining glycogen reserves, cortisol allows other glycolytic hormones, such as epinephrine and glucagon, to mobilize glucose in times of need, such as between meals. A second way in which cortisol tends to increase the blood glucose concentration is by impairing the utilization of glucose in peripheral tissues; cortisol has an anti-insulin effect in tissues such as muscle and adipose tissue and impairs the uptake and utilization of glucose for energy. Like growth hormone, cortisol is diabetogenic because it tends to increase the blood glucose concentration.

• Plays an important role in the mobilization of fatty acids from adipose tissue. Although weakly lipolytic itself, normal levels of cortisol exert a permissive effect on the mobilization of fatty acids during fasting. During fasting, cortisol allows other lipolytic hormones, such as epinephrine and growth hormone, to mobilize fatty acids from lipid stores. Increased Cortisol Secretion Is Important for Resistance to Stress. Physical or mental stress increases ACTH secretion, which in turn stimulates the adrenal cortex to secrete cortisol. Although it is not clear how hypercortisolism mediates this response, the large rise in cortisol secretion in response to many stressors is essential to survival. Patients with adrenal dysfunction who are administered maintenance doses of steroids require extra glucocorticoid under stressful conditions.

**Pharmacological Doses of Glucocorticoids Have Anti-Inflammatory and Antiallergic Effects and Suppress Immune Responses**

Large doses of glucocorticoids decrease the inflammatory response to tissue trauma, foreign proteins, or infections through several effects, including the following:

• Inhibition of phospholipase. This decreases the synthesis of arachidonic acid, which is the precursor of leukotrienes, prostaglandins, and thromboxanes, mediators of the local inflammatory response that includes dilation of capillaries, increased capillary permeability, and migration of leukocytes into the area of tissue injury.

• Stabilization of lysosomal membranes. This decreases the release of proteolytic enzymes by damaged cells.

• Suppression of the immune system. Suppression is a result of decreased production of T cells and antibodies that contribute to the inflammatory process.

• Inhibition of fibroblastic activity.

**Controller of Cortisol Secretion—ACTH**

ACTH Stimulates Cortisol Secretion. The secretion of cortisol is under the control of the hypothalamicpituitary, corticotropin-releasing hormone (CRH)-ACTH axis. The release of ACTH (corticotropin) from the pituitary is dependent on the hypophysiotropic hormone CRH. Once ACTH is secreted into the blood, it has a rapid effect on the inner two zones of the adrenal cortex, especially the zona fasciculata, to increase the secretion of cortisol. This effect of ACTH is achieved by increasing the conversion of cholesterol to pregnenolone and is mediated via the second messenger cyclic AMP. Chronic stimulation of the adrenal cortex by

ACTH causes hypertrophy and hyperplasia of the zona fasciculata and zona reticularis and increased synthesis of several enzymes that convert cholesterol into the final product cortisol. Under conditions of chronic ACTH excess, such as with Cushing's syndrome, there are sustained increases in the secretion of cortisol and adrenal androgens. Blood levels of free (unbound) cortisol are controlled in a negative feedback fashion. Increased plasma levels of cortisol decrease ACTH secretion through a direct effect on the pituitary as well as indirect inhibition of CRH release from the hypothalamus. The secretion of cortisol is highest in the early morning and reaches its lowest in the late evening because there is a diurnal or circadian rhythm in ACTH secretion as a result of changes in the frequency and duration of CRH bursts from the hypothalamus. Because of the cyclic changes in cortisol secretion, plasma levels of cortisol are meaningful only when expressed in terms of the time of day when blood sampling occurred.

## Functions of the Mineralocorticoids—Aldosterone

**Aldosterone** Is the Primary Mineralocorticoid Secreted by the Adrenal Cortex. Aldosterone accounts for approximately 90% of the mineralocorticoid activity of adrenocortical hormones. Most of the remainder of themineralocorticoid activity can be attributed to (1) deoxycorticosterone, which has approximately 3% of the mineralocorticoid activity of aldosterone and is secreted at a comparable rate, and (2) cortisol, a glucocorticoid with weak mineralocorticoid activity that is normally present at plasma concentrations of more than 1000 times that of aldosterone. In vitro studies have shown that cortisol binds with high affinity to mineralocorticoid receptors. Because the kidneys have the enzyme 11b-hydroxysteroid dehydrogenase type 2, cortisol is converted to cortisone, which does not avidly bind mineralocorticoid receptors. Consequently, cortisol does not normally exert significant mineralocorticoid effects in vivo. Under conditions in which 11b hydroxysteroid dehydrogenase is either congenitally absent or inhibited (e.g., during excessive licorice ingestion), cortisol may have substantial mineralocorticoid effects.

**Aldosterone Increases Sodium Reabsorption and Potassium Secretion.**

Aldosterone and other mineralocorticoids act on the distal nephron, especially the principal cells of the collecting duct, to increase sodium reabsorption and

potassium secretion. These effects occur after the binding of aldosterone to intracellular receptors and the subsequent synthesis of proteins, including Na,K-ATPase in the basolateral membrane and sodium and potassium channel proteins in the apical membrane. As a result of increased Na,K-ATPase activity, sodium is pumped out of the tubular cells into the blood and exchanged for potassium. Potassium then diffuses into the tubular urine. As sodium is reabsorbed under the influence of aldosterone, there is enhanced tubular secretion of potassium ions. Aldosterone also causes secretion of hydrogen ions in exchange for sodium in the intercalated cells of the cortical collecting tubules. Because protein synthesis is required to mediate the tubular actions of aldosterone, a lag time of about 60 minutes occurs between exposure to aldosterone and its onset of action.

**Aldosterone Affects Electrolyte Transport in Organs Other Than the Kidneys**.
Aldosterone binds to mineralocorticoid receptors in epithelial cells other than those of the kidney. Aldosterone increases sodium reabsorption from the colon and promotes potassium excretion in the feces. Similarly, aldosterone has an effect on sweat and salivary glands, decreasing the sodium/potassium ratio in their respective secretions.

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**Controllers of Aldosterone Secretion—Angiotensin II and Potassium**

Angiotensin II Stimulates Aldosterone Secretion.

Angiotensin II directly stimulates the cells of the zona glomerulosa to secrete aldosterone. This effect of angiotensin II is mediated via increments in intracellular levels of calcium and the phosphatidylinositol products, diacylglycerol and inosital triphosphate. These second messengers activate protein kinase C, which in turn stimulates both early (cholesterol desmolase) and late (aldosterone synthase) steps in the biosynthesis of aldosterone. The control of aldosterone secretion by angiotensin II is closely linked to the regulation of extracellular fluid volume and arterial pressure.

The renin-angiotensin system is activated in the presence of hypovolemia and hypotension; and high plasma levels of angiotensin II stimulate aldosterone secretion. In turn, aldosterone increases sodium reabsorption in the distal nephron; as fluid retention returns body fluid volumes and arterial pressure to normal levels, the stimulus for activation of the reninangiotensin system wanes, and aldosterone secretion falls to basal levels. Accordingly, the activity of the renin-angiotensin system is inversely related to dietary sodium intake. Potassium Stimulates Aldosterone Secretion. The cells of the zona glomerulosa are sensitive to small changes in the plasma potassium concentration. Increments in plasma potassium concentration increase aldosterone secretion by depolarizing the cell membrane, opening calcium channels, thereby increasing the intracellular calcium concentration. In response to these events, aldosterone secretion increases as a result of stimulation of the same early and late biosynthetic steps affected by angiotensin II (see previous discussion). Aldosterone plays a critical role in eliminating ingested potassium and in feedback regulation of the plasma potassium concentration. Increments in plasma potassium concentration increase aldosterone secretion, which in turn stimulates tubular secretion of potassium. As plasma potassium concentrations fall to normal levels, the stimulus for aldosterone secretion is removed. The opposite sequence of events occurs when plasma potassium concentration decreases. Increases in plasma potassium concentration depolarize the cell membrane, activating voltage-dependent calcium channels. The rise in cytoplasmic calcium stimulates aldosterone secretion by the mechanism described above for angiotensin II.

**ACTH Plays a Permissive Role in the Regulation of Aldosterone Secretion.**

So long as normal plasma levels of ACTH are present, the responsiveness of the zona glomerulosa to its major controllers, angiotensin II and potassium, is maintained. In contrast, if ACTH is chronically deficient, the aldosterone response to angiotensin II and potassium is diminished. High plasma levels of ACTH, which occur acutely during stress, stimulate aldosterone secretion; but in states of chronic ACTH excess (e.g., with Cushing’s disease), hyperaldosteronism is not sustained.