Chapter 6
The Adrenal Gland

The adrenal produces three major classes of hormones, each of which aid in dealing with the multitude of small and large stresses faced by people almost daily. At least two of these groups - glucocorticoids and mineralocorticoids - are necessary for life.

6.1. Functional Anatomy of the Adrenal Gland

The two adrenal glands are located immediately anterior to the kidneys, encased in a connective tissue capsule and usually partially buried in an island of fat. Like the kidneys, the adrenal glands lie beneath the peritoneum (i.e. they are retroperitoneal).

- An inner **medulla**, which is a source of the catecholamines **epinephrine** and **norepinephrine**. The chromaffin cell is the principle cell type. The medulla is richly innervated by preganglionic sympathetic fibers and is, in essence, an extension of the sympathetic nervous system.
- An outer **cortex**, which secretes several classes of steroid hormones (glucocorticoids and mineralocorticoids, plus a few others). Histologic examination of the cortex reveals three concentric zones of cells that differ in the major steroid hormones they secrete.

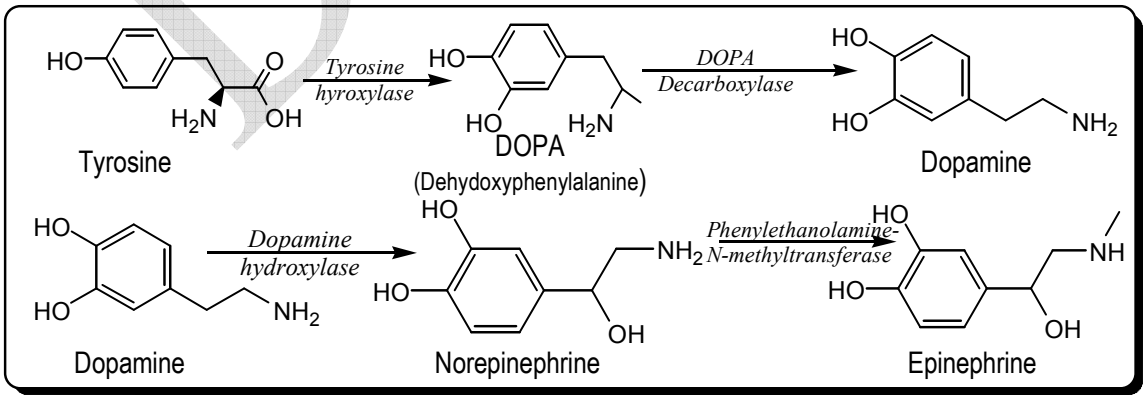
Despite their organization into a single gland, the medulla and cortex are functionally different endocrine organs, and have different embryological origins. The medulla derives from ectoderm (neural crest), while the cortex develops from mesoderm.

6.2. Adrenal Medullary Hormones

Cells in the adrenal medulla synthesize and secrete norepinephrine and epinephrine. The ratio of these two catecholamines differs considerably among species: in humans, roughly 80, 60 and 30% of the catecholamine output is epinephrine. Following release into blood, these hormones bind to adrenergic receptors on target cells, where they induce essentially the same effects as direct sympathetic nervous stimulation.

6.2. 1. Synthesis and Secretion of Catecholamines

Synthesis of catecholamines begins with the amino acid tyrosine, which is taken up by chromaffin cells in the medulla and converted to norepinephrine and epinephrine through the following steps:



Norepinephine and epinephrine are stored in electron-dense granules which also contain ATP and several neuropeptides. Secretion of these hormones is stimulated by acetylcholine release from preganglionic

sympathetic fibers innervating the medulla. Many types of "stresses" stimulate such secretion, including exercise, hypoglycemia and trauma. Following secretion into blood, the catecholamines bind loosely to and are carried in the circulation by albumin and other serum proteins.

6.2. 2. Adrenergic Receptors and Mechanism of Action

The physiologic effects of epinephrine and norepinephrine are initiated by their binding to adrenergic receptors on the surface of target cells. These receptors are prototypical examples of seven-pass transmembrane proteins that are coupled to G proteins which stimulate or inhibit intracellular signalling pathways. Complex physiologic responses result from adrenal medullary stimulation because there are multiple receptor types which are differentially expressed in different tissues and cells.

6.2. 3. Physiologic Effects of Medullary Hormones

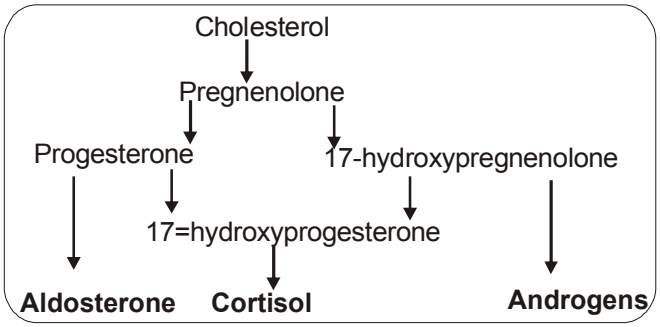
In general, circulating epinephrine and norepinephrine released from the adrenal medulla have the same effects on target organs as direct stimulation by sympathetic nerves, although their effect is longer lasting. Additionally, of course, circulating hormones can cause effects in cells and tissues that are not directly innervated. The physiologic consequences of medullary catecholamine release are justifiably framed as responses which aid in dealing with stress. Some major effects mediated by epinephrine and norepinephrine are:

- **Increased rate and force of contraction of the heart muscle:** this is predominantly an effect of epinephrine acting through beta receptors.
- **Constriction of blood vessels:** norepinephrine, in particular, causes widespread vasoconstriction, resulting in increased resistance and hence arterial blood pressure.
- **Dilation of bronchioles:** assists in pulmonary ventilation.
- **Stimulation of lipolysis in fat cells:** this provides fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose.
- **Increased metabolic rate:** oxygen consumption and heat production increase throughout the body in response to epinephrine. Medullary hormones also promote breakdown of glycogen in skeletal muscle to provide glucose for energy production.
- **Dilation of the pupils:** particularly important in situations where you are surrounded by velociraptors under conditions of low ambient light.
- **Inhibition of certain "non-essential" processes:** an example is inhibition of gastrointestinal secretion and motor activity in case of emergency.

Common stimuli for secretion of adrenomedullary hormones include exercise, hypoglycemia, haemorrhage and emotional distress.

6.3. Adrenal Steroids

Adrenal cortex produces some sex steroids, particularly androgens. **Like all steroids, adrenal "corticosteroids" are synthesized from cholesterol** through a series of enzyme-mediated transformations.



Each of the three major pathways involves sequential processing by a group of enzymes, some of which reside in endoplasmic reticulum and others inside mitochondria. Hence, synthesis involves shuttling of the steroids between these two organelles.

Synthesis of the different steroids is not uniformly distributed through the cortex. For example, the outermost group of cells (*zona glomerulosa*) synthesizes aldosterone, but essentially no cortisol or androgens because those cells do not express the enzyme 17-alpha-hydroxylase which is necessary for synthesis of 17-hydroxypregnenolone and 17-hydroxyprogesterone. That enzyme is however present in cells of the inner zones of the cortex (*zonae fasiculata and reticularis*), which are the major sites of cortisol production.

Like all steroid hormones, cortisol and aldosterone bind to their respective receptors, and the resulting hormone-receptor complexes bind to a hormone response element to modulate transcription of responsive genes. Although the physiologic effects of these two steroid hormones are distinctly different, their receptors are quite similar and, they bind to the same consensus response element in DNA.

6.3.1. Mineralocorticoids

Removal of the adrenal glands leads to death within just a few days. Observation of such a unfortunate patients would reveal several key derangements:

- the concentration of potassium in extracelluar fluid becomes dramatically elevated
- urinary excretion of sodium is high and the concentration of sodium in extracellular fluid decreases significantly
- volume of extracellular fluid and blood decrease
- the heart begins to function poorly, cardiac output declines and shock ensues
- These phenomena are a direct result of loss of mineralocorticoid activity, and can largely be prevented by replacement of salts and mineralocorticoids. Clearly mineralocorticoids are acutely critical for maintenance of life!

(i) Physiologic Effects of Mineralocorticoids

Mineralocorticoids play a critical role in regulating concentrations of minerals - particularly sodium and potassium - in extracellular fluids. As described above, loss of these hormones leads rapidly to life-threatening abnormalities in electrolyte and fluid balance.

The major target of aldosterone is the distal tubule of the kidney, where it stimulates exchange of sodium and potassium. Three primary physiologic effects result:

- Increased resorption of sodium: sodium loss in urine is decreased under aldosterone stimulation.
- Increased resorption of water, with consequent expansion of extracellular fluid volume. This is an osmotic effect directly related to increased resorption of sodium.
- Increased renal excretion of potassium.

Aldosterone stimulates transcription of the gene encoding the sodium-potassium ATPase, leading to increased numbers of "sodium pumps" in the basolateral membranes of tubular epithelial cells. Aldosterone also stimulates expression of a sodium channel which facilitates uptake of sodium from the tubular lumen.

Aldosterone has effects on sweat glands, salivary glands and the colon which are essentially identical to those in the distal tubule of the kidney. The major net effect is again to conserve body sodium by stimulating its resorption or, in the case of the colon, absorption from the intestinal lumen. Conservation of water follows conservation of sodium.

(ii) Control of Aldosterone Secretion

Control over aldosterone secretion is multifactorial and interconnected to other factors which regulate fluid and electrolyte composition and blood pressure. The two most significant regulators of aldosterone secretion are:

- **Concentrations of potassium ion in extracellular fluid:** Small increases in blood levels of potassium strongly stimulate aldosterone secretion.
- **Angiotensin II:** Activation of the renin-angiotensin system as a result of decreased renal blood flow (usually due to decreased vascular volume) results in release of angiotensin II, which stimulates aldosterone secretion.

Other factors which stimulate aldosterone secretion include adrenocorticotropic hormone (short-term stimulation only) and sodium deficiency. Factors which suppress aldosterone secretion include atrial naturetic hormone, high sodium concentration and potassium deficiency.

(iii) Disease States

A deficiency in aldosterone can occur by itself or, more commonly, in conjunction with a glucocorticoid deficiency, and is known as **hypoadrenocorticism or Addison's disease**. Without treatment by mineralocorticoid replacement therapy, aldosterone deficiency is lethal, due to electrolyte imbalances and resulting hypotension and cardiac failure

6.3. 2. Glucocorticoids

In contrast to loss of mineralocorticoids, failure to produce glucocorticoids is not acutely life-threatening. Nevertheless, loss or profound diminishment of glucocorticoid secretion leads to a state of deranged metabolism and an inability to deal with stressors which, if untreated, is fatal. In addition to their physiologic importance, glucocorticoids are also among the most frequently used drugs, and often prescribed for their anti-inflammatory and immunosuppressive properties.

(i) Physiologic Effects of Glucocorticoids

Glucocorticoids affect carbohydrate metabolism and immune function.

(a) Effects on Metabolism

The name *glucocorticoid* derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood. These effects include:

- **Stimulation of gluconeogenesis, particularly in the liver:** This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.
- **Mobilization of amino acids from extrahepatic tissues:** These serve as substrates for gluconeogenesis.
- **Inhibition of glucose uptake in muscle and adipose tissue:** A mechanism to conserve glucose.

- **Stimulation of fat breakdown in adipose tissue:** The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

(b) Effects on Inflammation and Immune Function

Glucocorticoids have potent anti-inflammatory and immunosuppressive properties. This is particularly evident when they administered at pharmacologic doses, but also is important in normal immune responses. As a consequence, glucocorticoids are widely used as drugs to treat inflammatory conditions such as arthritis or dermatitis, and as adjunction therapy for conditions such as autoimmune diseases.

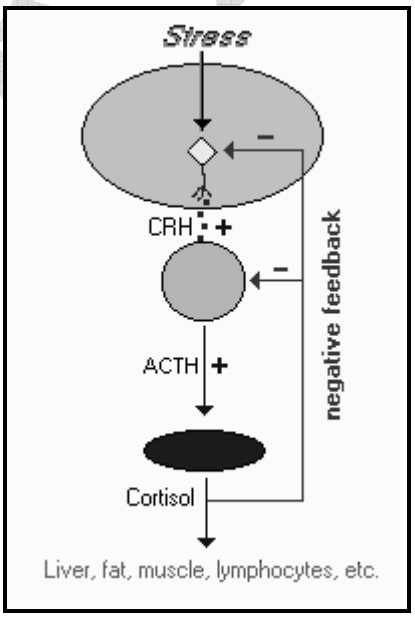
(c) Other Effects of Glucocorticoids

Glucocorticoids have multiple effects on foetal development. An important example is their role in promoting maturation of the lung and production of the surfactant necessary for extrauterine lung function. Excessive glucocorticoid levels resulting from administration as a drug or hyperadrenocorticism have effects on many systems. Some examples include inhibition of bone formation, suppression of calcium absorption and delayed wound healing. These observations suggest a multitide of less dramatic physiologic roles for glucocorticoids.

(ii) Control of Cortisol Secretion

Cortisol and other glucocorticoids are secreted in response to a single stimulator: adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH is itself secreted under control of the hypothalamic peptide **corticotropin-releasing hormone** (CRH). The central nervous system is thus the commander and chief of glucocorticoid responses, providing an excellent example of close integration between the nervous and endocrine systems. Virtually any type of physical or mental stress results in elevation of cortisol concentrations in blood due to enhanced secretion of CRH in the hypothalamus.

Cortisol secretion is suppressed by classical negative feedback loops. When blood concentrations rise above a certain theshold, cortisol inhibits CRH secretion from the hypothalamus, which turns off ACTH secretion, which leads to a turning off of cortisol secretion from the adrenal. The combination of positive and negative control on CRH secretion results in pulsatile secretion of cortisol. Typically, pulse amplitude and frequency are highest in the morning and lowest at night.



ACTH, also known as corticotropin, binds to receptors in the plasma membrane of cells in the zona fasiculata and reticularis of the adrenal. Hormone-receptor engagement activates adenyl cyclase, leading to elevated

intracellular levels of cyclic AMP which leads ultimately to activation of the enzyme systems involved in biosynthesis of cortisol from cholesterol.

(iii) Disease States

The most prevalent disorder involving glucocorticoids in man is **Cushings disease or hyperadrenocorticism**. Excessive levels of glucocorticoids are seen in two situations:

- **Excessive endogenous production of cortisol**, which can result from a primary adrenal defect (ACTH-independent) or from excessive secretion of ACTH (ACTH-dependent).
- **Administration of glucocorticoids** for theraputic purposes. This is a common side-effect of these widely-used drugs.

  Cushing's disease has widespread effects on metabolism and organ function. A diverse set of clinicial manifestations accompany this disorder, including hypertension, apparent obesity, muscle wasting, thin skin, and metabolic aberrations such as diabetes.

  Insufficient production of cortisol, often accompanied by an aldosterone deficiency, is called **Addison's disease or hypoadrenocorticism**. Most commonly, this disease is a result of infectious disease (e.g. tuberculosis in humans) or autoimmune destruction of the adrenal cortex. As with Cushing's disease, numerous diverse clinical signs accompany Addison's disease, including cardiovascular disease, lethargy, diarrhea, and weakness. Aldosterone deficiency can be acutely life threatening due to disorders of electrolyte balance and cardiac function.