ADRENAL GLAND

INTRODUCTION

The adrenal glands are small glands located on top of each kidney. They produce hormones that you can't live without, including sex hormones and cortisol. Cortisol helps you respond to stress and has many other important functions. With adrenal gland disorders, your glands make too much or not enough hormones. In Cushing's syndrome, there's too much cortisol, while with Addison's disease, there is too little. Some people are born unable to make enough cortisol. The **adrenal glands** (also known as **suprarenal glands**) are endocrine glands that produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol. They are found above the kidneys. Each gland has an outer cortex which produces steroid hormones and an inner medulla. The adrenal cortex itself is divided into three zones: the zona glomerulosa, the zona fasciculata and the zona reticularis. The adrenal cortex produces three main types of steroid hormones: mineralocorticoids, glucocorticoids, and androgens.

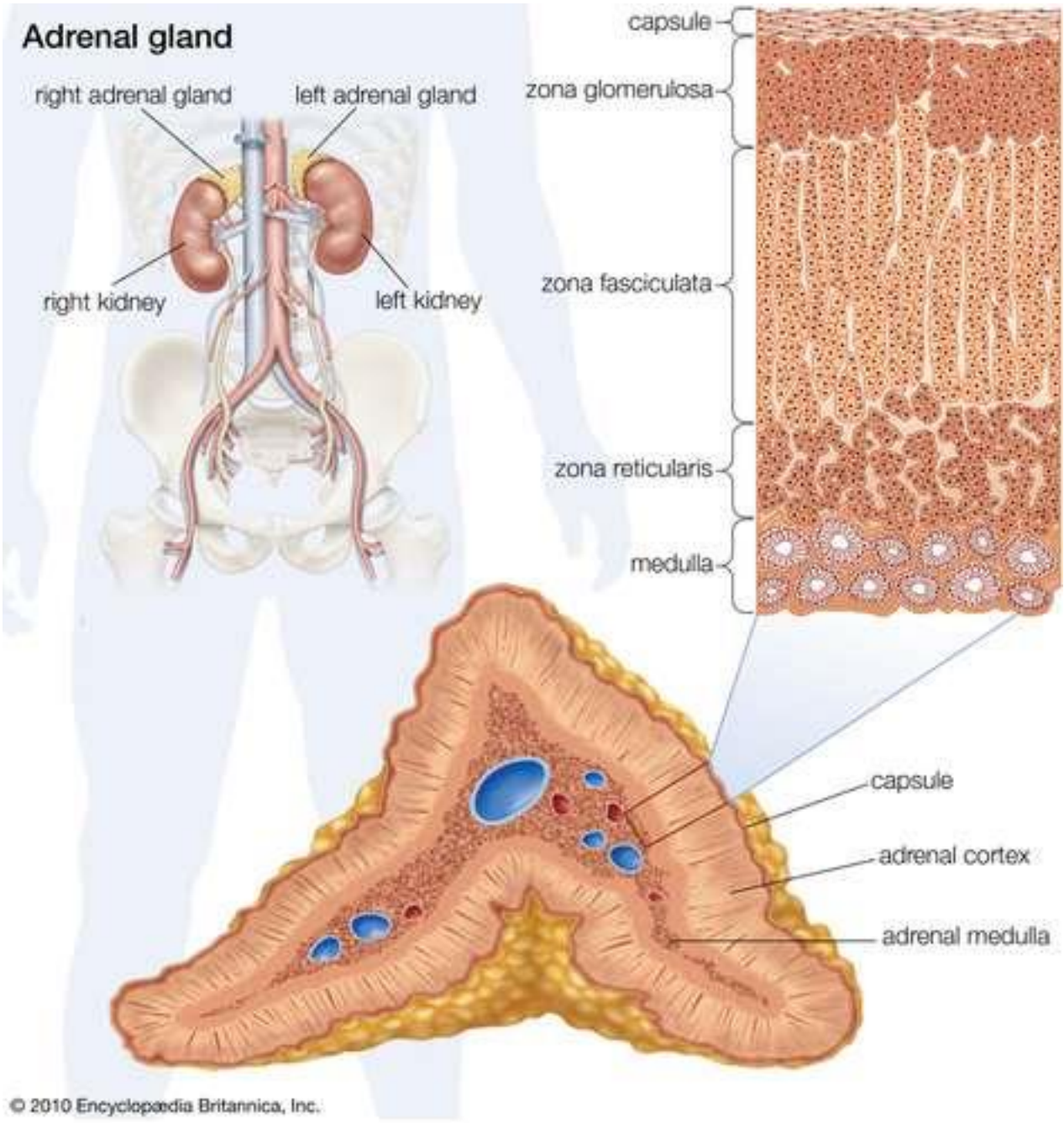
LOCATION OF ADRENAL GLAND

The adrenal glands are located on both sides of the body in the retroperitoneum, above and slightly medial to the kidneys.

STRUCTURE OF ADRENAL GLAND

In humans, the right adrenal gland is pyramidal in shape, whereas the left is semilunar or crescent shaped and somewhat larger. The adrenal glands measure approximately 3 cm in width, 5.0 cm in length, and up to 1.0 cm in thickness. Their combined weight in an adult human ranges from 7 to 10 grams. The glands are yellowish in colour. The adrenal glands are surrounded by a fatty capsule and lie within the renal fascia, which also surrounds the kidneys. A weak septum (wall) of connective tissue separates the glands from the kidneys. The adrenal glands are directly below the diaphragm, and are attached to the crura of the diaphragm by the renal fascia.

Each adrenal gland has two distinct parts, each with a unique function, the outer adrenal cortex and the inner medulla, both of which produce hormones. Each gland consists of two parts: an inner medulla, which produces epinephrine and norepinephrine (adrenaline and noradrenaline), and an outer cortex, which produces steroid hormones. The two parts differ in embryological origin, structure, and function. The adrenal glands vary in size, shape, and nerve supply in other animal species. In some vertebrates the cells of the two parts are interspersed to varying degrees.



ADRENAL CORTEX

The adrenal cortex is the outermost layer of the adrenal gland. Within the cortex are three layers, called "zones". When viewed under a microscope each layer has a distinct appearance, and each has a different function.The adrenal cortex is devoted to production of hormones, namely aldosterone, cortisol, and androgens

Zona glomerulosa

The outermost zone of the adrenal cortex is the zona glomerulosa. It lies immediately under the fibrous capsule of the gland. Cells in this layer form oval groups, separated by thin strands of connective tissue from the fibrous capsule of the gland and carry wide capillaries.

This layer is the main site for production of aldosterone, a mineralocorticoid, by the action of the enzyme aldosterone synthase. Aldosterone plays an important role in the long-term regulation of blood pressure

Zona fasciculata

The zona fasciculata is situated between the zona glomerulosa and zona reticularis. Cells in this layer are responsible for producing glucocorticoids such as cortisol.[19] It is the largest of the three layers, accounting for nearly 80% of the volume of the cortex. In the zona fasciculata, cells are arranged in columns radially oriented towards the medulla. Cells contain numerous lipid droplets, abundant mitochondria and a complex smooth endoplasmic reticulum.

Zona reticularis

The innermost cortical layer, the zona reticularis, lies directly adjacent to the medulla. It produces androgens, mainly dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione (the precursor to testosterone) in humans. Its small cells form irregular cords and clusters, separated by capillaries and connective tissue. The cells contain relatively small quantities of cytoplasm and lipid droplets, and sometimes display brown lipofuscin pigment.

MEDULLA

The adrenal medulla is at the centre of each adrenal gland, and is surrounded by the adrenal cortex. The chromaffin cells of the medulla are the body's main source of the catecholamines adrenaline and noradrenaline, released by the medulla. Approximately 20% noradrenaline (norepinephrine) and 80% adrenaline (epinephrine) are secreted here.

The adrenal medulla is driven by the sympathetic nervous system via preganglionic fibers originating in the thoracic spinal cord, from vertebrae T5–T11. Because it is innervated by preganglionic nerve fibers, the adrenal medulla can be considered as a specialized sympathetic ganglion. Unlike other sympathetic ganglia, however, the adrenal medulla lacks distinct synapses and releases its secretions directly into the blood..

REGULATION OF ADRENAL HORMONE SECRETION

The secretion of cortisol and aldosterone is regulated by different mechanisms. The secretion of cortisol is regulated by the classical hypothalamic-pituitary-adrenal feedback system. The major determinant that controls the secretion of cortisol is corticotropin (adrenocorticotropin; ACTH). In normal subjects there is both pulsatile and diurnal (referred to as a circadian rhythm) secretion of corticotropin, which causes pulsatile and diurnal secretion of cortisol. Variations in the secretion of corticotropin are caused by variations in the secretion of corticotropin-releasing hormone by the hypothalamus and by variations in serum cortisol concentrations. An increase in serum cortisol concentrations inhibits the secretion of both corticotropin-releasing hormone and corticotropin. Conversely, a decrease in serum cortisol concentration results in an increase in the secretion of corticotropin-releasing hormone and corticotropin, thereby restoring the secretion of

cortisol to normal concentrations. However, if the adrenal glands are unable to respond to stimulation by corticotropin, decreased serum cortisol concentrations will persist. Severe physical or emotional stresses stimulate the secretion of corticotropin-releasing hormone and corticotropin, resulting in large increases in serum cortisol concentrations. However, under these circumstances, increased serum cortisol concentrations do not inhibit the secretion of corticotropin-releasing hormone or corticotropin and thereby allow large amounts of cortisol to be secreted until the stress subsides. Corticotropin also stimulates the secretion of adrenal androgens from the adrenal cortex, but the androgens do not inhibit corticotropin secretion.

Aldosterone secretion is regulated primarily by the renin-angiotensin system. Renin is an enzyme secreted into the blood from specialized cells that encircle the arterioles (small arteries) at the entrance to the glomeruli of the kidneys (the renal capillary networks that are the filtration units of the kidney). The renin-secreting cells, which compose the juxtaglomerular apparatus, are sensitive to changes in blood flow and blood pressure, and the primary stimulus for increased renin secretion is decreased blood flow to the kidneys. A decrease in blood flow may be caused by loss of sodium and water (as a result of diarrhea, persistent vomiting, or excessive perspiration) or by narrowing of a renal artery. Renin catalyzes the conversion of a plasma protein called angiotensinogen into a decapeptide (consisting of 10 amino acids) called angiotensin I. An enzyme in the serum called angiotensin-converting enzyme (ACE) then converts angiotensin I into an octapeptide (consisting of eight amino acids) called angiotensin II. Angiotensin II acts via specific receptors in the adrenal glands to stimulate the secretion of aldosterone, which stimulates salt and water reabsorption by the kidneys, and the constriction of arterioles, which causes an increase in blood pressure. Aldosterone secretion is also stimulated by high serum potassium concentrations (hyperkalemia) and to a lesser extent by corticotropin. Excessive aldosterone production or excessive renin secretion, which leads to excessive angiotensin and aldosterone production, can cause high blood pressure (*see* hyperaldosteronism).

DISEASES OF THE ADRENAL GLANDS

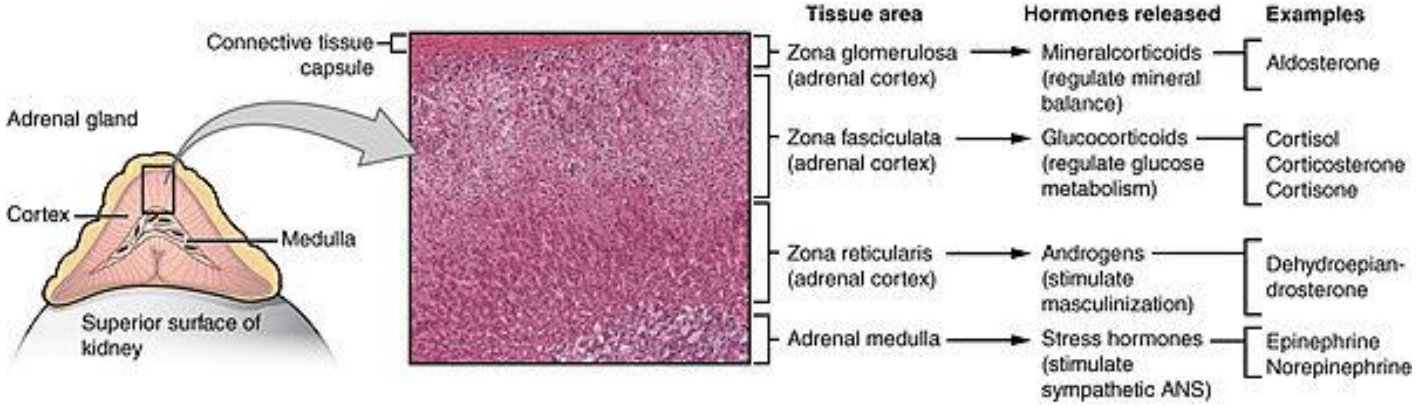
Diseases of the adrenal glands may be divided into those of the medulla and those of the cortex. The only known disease of the adrenal medulla is a tumour known as a pheochromocytoma. Pheochromocytomas secrete excessive quantities of epinephrine and norepinephrine. Many patients with these tumours have periodic episodes of hypertension (high blood pressure), palpitations of the heart, sweating, headaches, and anxiety, whereas other patients have persistently high blood pressure. High blood pressure and other symptoms can be treated with drugs that block the action of epinephrine and norepinephrine; however, the most effective treatment is surgical removal of the tumour. Diseases of the adrenal cortex may be manifested as hyperfunction (excessive secretion of adrenocortical hormones) or hypofunction (insufficient secretion of these hormones), also known as Addison disease.

Adrenocortical hyperfunction may be congenital or acquired. Congenital hyperfunction is always due to hyperplasia (enlargement) of both adrenal glands, whereas acquired hyperfunction may be due to either an adrenal tumour or hyperplasia. Congenital adrenal hyperplasia, also known as adrenogenital syndrome, is a disorder in which there is an inherited defect in one of the enzymes needed for the production of cortisol. Excessive amounts of adrenal androgens must be produced to overcome the block in cortisol production. In female infants this results in

masculinization with pseudohermaphroditism (anomalous development of genital organs), whereas in male infants it results in premature sexual development (sexual precocity).

Acquired adrenocortical hyperfunction is manifested by either cortisol excess (Cushing syndrome), androgen excess, or aldosterone excess (primary aldosteronism). Cushing syndrome is characterized by obesity, rounding and reddening of the face, high blood pressure, diabetes mellitus, osteoporosis, thinning and easy bruising of the skin, muscle weakness, depression, and, in women, cessation of menstrual cycles (amenorrhea). The major causes of Cushing syndrome are a corticotropin-producing tumour of the pituitary gland (known as Cushing disease), production of corticotropin by a nonendocrine tumour, or a benign or malignant adrenal tumour. All these disorders are treated most effectively by surgical removal of the tumour. Androgen excess in women is characterized by excessive hair growth on the face and other regions and amenorrhea; in contrast, androgen excess has few effects in men. The major causes of adrenal androgen excess in adults are late-onset congenital adrenal hyperplasia and adrenal tumours.

Primary aldosteronism is characterized by high blood pressure, caused by increased retention of salt and water by the kidneys, and low serum potassium concentrations (hypokalemia), caused by excess excretion of potassium in the urine. The symptoms and signs of aldosterone excess include not only hypertension but also muscle weakness and cramps and increased thirst and urination. Primary aldosteronism is usually caused by a benign adrenal tumour (adenoma), but some patients have hyperplasia of both adrenal glands. Successful removal of the adrenal tumour usually results in reduction in blood pressure and cessation of potassium loss; patients with bilateral adrenal hyperplasia are treated with antihypertensive drugs.



FUNCTIONS

The adrenal gland secretes a number of different hormones which are metabolised by enzymes either within the gland or in other parts of the body. These hormones are involved in a number of essential biological functions.

Corticosteroids

Corticosteroids are a group of steroid hormones produced from the cortex of the adrenal gland, from which they are named.[24] Corticosteroids are named according to their actions:

- Mineralocorticoids such as aldosterone regulate salt ("mineral") balance and blood volume.
- Glucocorticoids such as cortisol influence metabolism rates of proteins, fats and sugars ("glucose").

Mineralocorticoids

The adrenal gland produces aldosterone, a mineralocorticoid, which is important in the regulation of salt ("mineral") balance and blood volume. In the kidneys, aldosterone acts on the distal convoluted tubules and the collecting ducts by increasing the reabsorption of sodium and the excretion of both potassium and hydrogen ions. Aldosterone is responsible for the reabsorption of about 2% of filtered glomerular filtrate. Sodium retention is also a response of the distal colon and sweat glands to aldosterone receptor stimulation. Angiotensin II and extracellular potassium are the two main regulators of aldosterone production. The amount of sodium present in the body affects the extracellular volume, which in turn influences blood pressure. Therefore, the effects of aldosterone in sodium retention are important for the regulation of blood pressure.

Glucocorticoids

Cortisol is the main glucocorticoid in humans. In species that do not create cortisol, this role is played by corticosterone instead. Glucocorticoids have many effects on metabolism. As their name suggests, they increase the circulating level of glucose. This is the result of an increase in the mobilization of amino acids from protein and the stimulation of synthesis of glucose from these amino acids in the liver. In addition, they increase the levels of free fatty acids, which cells can use as an alternative to glucose to obtain energy. Glucocorticoids also have effects unrelated to the regulation of blood sugar levels, including the suppression of the immune system and a potent anti-inflammatory effect. Cortisol reduces the capacity of osteoblasts to produce new bone tissue and decreases the absorption of calcium in the gastrointestinal tract.

The adrenal gland secretes a basal level of cortisol but can also produce bursts of the hormone in response to adrenocorticotropic hormone (ACTH) from the anterior pituitary. Cortisol is not evenly released during the day – its concentrations in the blood are highest in the early morning and lowest in the evening as a result of the circadian rhythm of ACTH secretion. Cortisone is an inactive product of the action of the enzyme 11β-HSD on cortisol. The reaction catalyzed by 11β-HSD is reversible, which means that it can turn administered cortisone into cortisol, the biologically active hormone.

Formation

All corticosteroid hormones share cholesterol as a common precursor. Therefore, the first step in steroidogenesis is cholesterol uptake or synthesis. Cells that produce steroid hormones can acquire cholesterol through two paths. The main source is through dietary cholesterol transported

via the blood as cholesterol esters within low density lipoproteins (LDL). LDL enters the cells through receptor-mediated endocytosis. The other source of cholesterol is synthesis in the cell's endoplasmic reticulum. Synthesis can compensate when LDL levels are abnormally low. In the lysosome, cholesterol esters are converted to free cholesterol, which is then used for steroidogenesis or stored in the cell.

The initial part of conversion of cholesterol into steroid hormones involves a number of enzymes of the cytochrome P450 family that are located in the inner membrane of mitochondria. Transport of cholesterol from the outer to the inner membrane is facilitated by steroidogenic acute regulatory protein and is the rate-limiting step of steroid synthesis.

The layers of the adrenal gland differ by function, with each layer having distinct enzymes that produce different hormones from a common precursor. The first enzymatic step in the production of all steroid hormones is cleavage of the cholesterol side chain, a reaction that forms pregnenolone as a product and is catalyzed by the enzyme P450scc, also known as *cholesterol desmolase*. After the production of pregnenolone, specific enzymes of each cortical layer further modify it. Enzymes involved in this process include both mitochondrial and microsomal P450s and hydroxysteroid dehydrogenases. Usually a number of intermediate steps in which pregnenolone is modified several times are required to form the functional hormones. Enzymes that catalyze reactions in these metabolic pathways are involved in a number of endocrine diseases. For example, the most common form of congenital adrenal hyperplasia develops as a result of deficiency of 21-hydroxylase, an enzyme involved in an intermediate step of cortisol production.