Lec.8 Hormones of the adrenal gland

The structure of the adrenal gland:

The two adrenal glands (also called the suprarenal glands) are situated in the abdomen, on either side of the vertebral column, above the kidneys and below the diaphragm. When cut in half each gland consists of

1. An outer cortex, yellow in color and
2. An inner medulla, which is dark red, or grey.

▲ The cortex consists of three distinct zones

1. Zona glomerulosa
2. Zona fasciculata
3. Zona reticularis

Each zone has a characteristic histology and secretes different types of hormone

- **Most superficial cortical layer Zona glomerulosa** mineralocorticoid (aldosterone) which is responsible for the regulation of salt and water balance in the body
- **Middle cortical layer Zona fasciculata** glucocorticoid (cortisol) which regulates the level of carbohydrate in the body
- **Deepest cortical layer Zona reticularis** sex hormones (progesterone, oestrogen precursors and androgens) which have a role in the development of sexual Characteristics.

▲ The medulla consists of many large columnar cells called "chromaffin cells". These synthesize and secrete catecholamines when stimulated by the sympathetic nervous system.

Hormone synthesis:

All adrenocortical hormones are synthesized from cholesterol. Cholesterol is transported into the adrenal gland. Subsequent steps to generate aldosterone and cortisol, primarily occur in the adrenal cortex:

- Progesterone → (hydroxylation at C21) → 11-Deoxycorticosterone → (two further hydroxylations at C11 and C18) → Aldosterone

- Progesterone → (hydroxylation at C17) → 17-alpha-hydroxyprogesterone → (hydroxylation at C21) → 11-Deoxycortisol → (hydroxylation at C11) → Cortisol

Cholesterol is converted to pregnenolone (P5) by cytochrome P450 cholesterol side chain cleavage.

P5 is the precursor of all the other steroids and stands at the first branch point in the adrenal steroidogenic network. Steroidogenic defects can cause congenital adrenal hyperplasia (CAH). This condition may cause symptoms ranging from mild acne to salt wasting, depending on the nature of the genetic mutation.

In hypoandrenocorticism (Addison’s disease) and CAH the error involves the two enzymes cytochrome P450 17a-hydroxylase/17-20 lyase and cytochrome P450 21- hydroxylase respectively. Because of a lack of the glucocorticoids and mineralocorticoids the brain signals the adrenal gland with adrenocorticotropic hormone (ACTH) to produce more of the deficient steroids. Consequently, there is an over production of P5 that in turn leads to an over production of DHEA, which is converted to androgens and estrogens outside of the adrenal gland due to the DHEA in circulation diffusing into other steroidogenic tissues with the appropriate activities.
Hormones secreted by the Adrenal Cortex:

1. Mineralocorticoids

The primary mineralocorticoids aldosterone is aldosterone. Its secretion is regulated by the oligopeptide angiotensin II (angiotensin II is regulated by angiotensin I, which in turn is regulated by renin). Aldosterone is secreted in response to high extracellular potassium levels, low extracellular sodium levels, and low fluid levels and blood volume. Aldosterone affects metabolism in different ways:

a. It increases urinary excretion of potassium ions
b. It increases interstitial levels of sodium ions
c. It increases water retention and blood volume

Removal of the adrenal glands leads to death within just a few days. Due to:

1. the concentration of potassium in extracellular fluid becomes dramatically elevated.
2. urinary excretion of sodium is high and the concentration of sodium in extracellular fluid decreases significantly.
3. volume of extracellular fluid and blood decrease
4. the heart begins to function poorly, cardiac output declines and shock ensues clearly mineralocorticoids are acutely critical for maintenance of life!

Aldosterone and Mineralocorticoid Receptors:

Cortisol, have "weak mineralocorticoid activity", which is of some importance because cortisol is secreted very much more abundantly than aldosterone. i.e. a small fraction of the mineralocorticoid response in the body is due to cortisol rather than aldosterone. The mineralocorticoid receptor binds both aldosterone and cortisol with equal affinity. Moreover, the same DNA sequence serves as a hormone response element for the activated (steroid-bound) forms of both mineralocorticoid and glucocorticoid receptors.

Q: How can aldosterone stimulate specific biological effects in this kind of system, particularly when blood concentrations of cortisol are something like 2000-fold higher than aldosterone?

A: In aldosterone-responsive cells, cortisol is effectively destroyed, allowing aldosterone to bind its receptor without competition. Target cells for aldosterone express the enzyme 11-beta-hydroxysteroid dehydrogenase, which has no effect on aldosterone, but converts cortisol to cortisone, which has only a very weak affinity for the mineralocorticoid receptor. In essence, this enzyme "protects" the cell from cortisol and allows aldosterone to act appropriately.

Control of Aldosterone Secretion:

The two most significant regulators of aldosterone secretion are:

- Concentration of potassium ions 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.

Factors which suppress aldosterone secretion include atrial naturetic hormone, high sodium concentration and potassium deficiency.
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.

2. Glucocorticoids Cortisol and Glucocorticoid Receptors:
Cortisol binds to the glucocorticoid receptor in the cytoplasm and the hormone-receptor complex is then translocated into the nucleus, where it binds to its DNA response element and modulates transcription from a battery of genes, leading to changes in the cell's phenotype. Only about 10% of circulating cortisol is free. The remaining majority circulates bound to plasma proteins, particularly corticosteroid-binding globulin ( transcortin).

Metabolic Effects of Glucocorticoids:
There seem to be no cells that lack glucocorticoid receptors and as a consequence, these steroid hormones have a huge number of effects on physiologic systems. The name glucocorticoid derives from early observations that these hormones were involved in glucose metabolism.

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. 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.

Cortisol Secretion Control:
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). 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. This fact sometimes makes it very difficult to assess glucocorticoid levels, especially being restrained for blood sampling, is enough stress to artificially elevate cortisol levels several fold!

Cortisol secretion is suppressed by classical negative feedback loops.
When blood concentrations rise above a certain threshold, 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 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.

**Disease States:**
1. Cushings disease or hyperadrenocorticism.
2. Insufficient production of cortisol, often accompanied by an aldosterone deficiency, is called Addison's disease or hypoadrenocorticism.

3. **Androgens:**
   The most important androgens include:
   1. **Testosterone:** a hormone with a wide variety of effects, ranging from enhancing muscle mass and stimulation of cell growth to the development of the secondary sex characteristics.
   2. **Dihydrotestosterone (DHT):** a metabolite of testosterone, and a more potent androgen than testosterone in that it binds more strongly to androgen receptors.
   3. **Androstenedione (Andro):** an androgenic steroid produced by the testes, adrenal cortex, and ovaries. While androstenediones are converted metabolically to testosterone and other androgens, they are also the parent structure of estrone.
   4. **Dehydroepiandrosterone (DHEA):** It is the primary precursor of natural estrogens. DHEA is also called dehydroisoandrosterone or dehydroandrosterone.