Hormones of the adrenal gland

[Prof. Dr. H.D.El-Yassin 2013]
Hormones of the adrenal gland

Objectives:
1. Describe the structure and function of the adrenal cortex
2. List the hormones synthesized by each specific zone of the adrenal cortex and state their functions
3. Describe the following adrenal disorders:
   a. Addison's disease
   b. Conn's syndrome
   c. Cushing syndrome
   d. Congenital adrenal hyperplasia

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 hormones.

<table>
<thead>
<tr>
<th>Layer</th>
<th>Name</th>
<th>Primary product</th>
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</thead>
<tbody>
<tr>
<td>Most superficial</td>
<td>Zona glomerulosa</td>
<td>mineralocorticoid (aldosterone) which is responsible for the regulation of salt and water balance in the body</td>
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<td>cortical layer</td>
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<tr>
<td>Middle cortical</td>
<td>Zona fasciculata</td>
<td>glucocorticoid (cortisol) which regulates the level of carbohydrate in the body</td>
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<td>layer</td>
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<tr>
<td>Deepest cortical</td>
<td>Zona reticularis</td>
<td>sex hormones (progesterone, oestrogen precursors and androgens) which have a role in the development of sexual characteristics</td>
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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:

Cholesterol is converted to pregnenolone, which 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.

**Quick quiz:** Which of the following is responsible for the biosynthesis of steroid hormones?

1. 7-dehydrocholesterol
2. 7-hydroxycholesterol
3. cholesterol
4. calciferol
CAH Due to 21-Hydroxylase Deficiency

Greater than 90% of the cases of CAH are the result of deficiency in the enzyme steroid 21-hydroxylase. Absolute or partial deficiency in this enzyme leads to two problems:

1. *Deficiency in production of cortisol and aldosterone*: Aldosterone is necessary for normal retention of sodium by the kidney, and in its absence, a "salt wasting" disorder occurs.

2. *Shunting of steroid precursors to form androgens*: In the absence of 21-hydroxylase, concentrations of 17-hydroxyprogesterone increase substantially and is converted to androgens including testosterone and dihydrotestosterone. The resulting secretion of relative large quantities of androgens early in life leads to virilization of female fetuses and abnormal development in male children.

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**Diagram:**

**Normal pathway of adrenal steroid synthesis**

- Progesterone → 17-hydroxyprogesterone → Adrenal androgens
- Deoxycorticosterone → Cortisol
- Cortisosterone
- 18-hydroxyprogesterone → Aldosterone

**21-hydroxylase deficiency (absolute)**

- Progesterone → 17-hydroxyprogesterone → Adrenal androgens
Hypoadrenocorticism (Addison's disease) results from idiopathic atrophy of the adrenal cortex induced by autoimmune responses that will lead to decreased production of cortisol and, in some cases, also results in decreased production of aldosterone. If aldosterone levels are insufficient, characteristic electrolyte abnormalities are evident owing to increased excretion of Na+ and decreased excretion of K+ chiefly in urine but also in sweat, saliva, and the GI tract. This condition leads to isotonic urine and decreased blood levels of Na+ and Cl− with increased levels of K+. Left untreated, aldosterone insufficiency produces severe dehydration, plasma hypertonicity, acidosis, decreased circulatory volume, hypotension, and circulatory collapse.

Cortisol deficiency impacts carbohydrate, fat, and protein metabolism and produces severe insulin sensitivity. Gluconeogenesis and liver glycogen formation are impaired, and hypoglycemia results. As a consequence, hypotension, muscle weakness, fatigue, vulnerability to infection, and stress are early symptoms. A characteristic hyperpigmentation on both exposed and unexposed parts of the body is evident.

**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!
Quick quiz which of the following is negative statement for the actions of aldosterone
1. most potent and active mineralocorticoid
2. it retains Na+ and excretes K+
3. acts at loop of Henle of the kidney
4. it excretes H+ and NH₄+ ions

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: (refer to the clinical cases supplement)
1. 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. Primary aldosteronism (Conn's syndrome) is caused by the overproduction of aldosterone

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).

**Quick quiz:** glucocorticoids are transported in blood by:

1. Albumin
2. Transcortin
3. Free form
4. All the above

**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.

**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).
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** (refer to the clinical cases supplement)

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.
2. Hormones of the adrenal Medulla
Hormones secreted by the Adrenal Medulla

Objectives

1. List the hormones synthesized by the adrenal medulla and state their functions and clinical significance
2. Define phaeochromocytoma and the laboratory results obtained in the assessment of the disease

Cells in the adrenal medulla synthesize and secrete epinephrine and norepinephrine. Following release into blood, these hormones bind adrenergic receptors on target cells, where they induce essentially the same effects as direct sympathetic nervous stimulation.

Synthesis 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:

Norepinephrine and epinephrine are stored in electron-dense granules which also contain ATP and several neuropeptides. Secretion of these hormones is stimulated by
acetylcholine release. 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 (50%) by albumin and other serum proteins. Once secreted their half life in the circulation is short (approximately 12 min) but they have a large effect on heart, vessels, metabolism, brain, muscles etc. all as part of stress responses.

**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 signaling pathways.

There are two major classes of adrenergic receptors these are:

1. $\alpha$ adrenergic receptor (epinephrine and norepinephrine)
   a. $\alpha_1$
   b. $\alpha_2$

2. $\beta$ adrenergic receptor (epinephrine )
   a. $\beta_1$
   b. $\beta_2$

**Control of catecholamine release**

The release of the catecholinamines is controlled from nerve cells within the posterior hypothalamus which can ultimately stimulate acetylcholine release from nerve terminals of the sympathetic nerves. This induces depolarization of the chromaffin cells and exocytosis of the catecholamine containing granules following a rise in intracellular calcium concentration.
**Metabolic Effects of catecholamines 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.
- Glycogenolysis to provide extra sources of glucose
- Stimulation of lipolysis in fat cells to provide fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose.
- Increased metabolic rate due to increased oxygen consumption and heat production increase throughout the body in response to epinephrine binding beta receptors.
- Increased breakdown of glycogen in skeletal muscle to provide glucose for energy production.

**Water and electrolytes metabolism**

- Decreased sodium excretion and glomerular filtration due to direct effects on the kidney
- Effects on renin secretion leads to increased aldosterone production with effects on distal sodium handling
- Serum potassium may be increased

**Catecholamine Degradation**

All catecholamines are rapidly eliminated from target cells and the circulation by three mechanisms:

1. reuptake into secretory vesicles
2. uptake in non-neural cells (mostly liver)
3. degradation.

Degradation relies on two enzymes:

1. catechol O-methyltransferase (COMT) in non-neuronal tissues
2. monoamine oxidase (MAO) within neurons.

to produce metabolites (metanephrines and vanillylmandelic acid (VMA)) from free catecholamines.
Metabolites and free catecholamine are eliminated by direct filtration into the urine and excreted as:

1) free norepinephrine,
2) conjugated norepinephrine
3) metanephrines and
4) VMA

Phaeochromocytoma
Catecholamine-secreting tumors arise from the chromaffin cells of the adrenal medulla. The condition is relatively rare, occurring in up to 0.5% of hypertensive patients in hospital clinics. The symptoms are variable, and it is not uncommon for years to elapse before the diagnosis is made. Adrenal phaeochromocytomas secrete mainly noradrenaline. Episodes of increased catecholamine secretion cause hypertension, palpitation, headache and sweating.

The most widely used screening test is urinary metanephrines. Measurement of fractionated metanephrines (metadrenaline and normetadrenaline) has a sensitivity of 97% and a specificity of 69% for the diagnosis of phaeochromocytoma. Plasma free metaphrine and normetanephrine measurement has a sensitivity approaching 100% and specificity of 90%. Plasma catecholamine measurements should be undertaken in the resting state through an indwelling cannula.
Questions

1) Glucocorticoid receptors are in the cytoplasm. All of the following statements about the process by which the hormone influences transcription are correct except:
   a) The hormone must be in the free state to cross the cell membrane.
   b) Cytoplasmic receptors may be associated with heat shock proteins.
   c) **The receptor-hormone complex is not activated/transformed until it is translocated to the nucleus.**
   d) In the nucleus, the activated/transformed receptor-hormone complex searches for specific sequences on DNA called HREs (hormone receptor elements).
   e) The activated receptor-hormone complex may either activate or repress transcription of specific genes (only one activity per gene).

   C Dissociation of the heat shock protein from the receptor-hormone complex in the cytosol activates the complex. A: Steroid hormones travel bound to plasma proteins, but some is always free. D: These are consensus sequences in DNA. E: Activation is more common, but glucocorticoids repress transcription of the proopiomelanocortin gene.

2) All of the following are normal events leading to secretion of aldosterone from the adrenal gland except:
   a) Renin is released by the kidney in hypovolemia.
   b) **Angiotensinogen binds to membrane receptors.**
   c) Ca^{2+} levels in the cell rise.
   d) Aldosterone is secreted into the blood.

   B Angiotensinogen is cleaved by renin to angiotensin I, which must further be cleaved by converting enzyme to active angiotensin II. A: This is a major signal. C: This lead to increased Ca^{2+} and activation of protein kinase C.