Adrenal Gland

Mineralocorticoids

(Lecture-1)

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Objectives

By the end of this lecture, students should be able to describe:

- The structure of adrenal cortex consisting of the zona glomerulosa, zona fasciculate and zona reticularis and list the adrenocortical hormones secreted by each zone.
- The chemical nature of the hormones.
- Mechanism of action of aldosterone
- The effects of aldosterone on:
  - Renal tubules
  - Body fluids
  - Sweat and salivary glands
  - Intestinal cells.
- Control of secretion of aldosterone.
- Describe clinical correlates of Addison's diseases and Conn's syndrome.

Keywords: aldosterone, mineralocorticoids, hypokalemia, hyperkalemia, rennin-angiotensin system

The Adrenal Gland

The two adrenal glands, lie at the superior poles of the two kidneys, each gland is composed of two distinct parts, the adrenal medulla and the adrenal cortex.

A- The adrenal medulla (the central 20 %)

- Derived from embryonic neural crest ectoderm (same tissue that produces the sympathetic ganglia).
- Functionally related to the sympathetic nervous system.
- It synthesizes and secretes catecholamines (mainly epinephrine but some norepinephrine).

B- The adrenal cortex

- Does not receive neural innervation.
- Must be stimulated hormonally (ACTH).
- It secretes corticosteroids (adrenocortical hormones):
  - Mineralocorticoids
  - Glucocorticoids
  - Androgens

These hormones have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

The adrenal cortex has three distinct layers:

1. The zona glomerulosa (15 % of the adrenal cortex) secretes mineralocorticoids (aldosterone is the principal).

2. The zona fasciculate (75 % of the adrenal cortex) the middle and widest layer, secretes the glucocorticoids: cortisol (the principal glucocorticoid) and corticosterone, as well as small amounts of adrenal androgens and estrogens.

3. The zona reticularis secretes the adrenal androgens as well as small amounts of estrogens and some glucocorticoids.

Chemical nature of Adrenocortical Hormones.

They are steroid hormones synthesized in the mitochondria and the endoplasmic reticulum from cholesterol.

Mineralocorticoids

The mineralocorticoids have gained this name because they especially affect the electrolytes (the "minerals") of the ECF, Na+ and K+, in particular.

Mineralocorticoids include:

- Aldosterone (very potent, accounts for about 90 % of mineralocorticoid activity, the major mineralocorticoid secreted by the adrenals).
- Desoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted).
- Corticosterone , cortisol and cortisone have slight mineralocorticoid activity.

Aldosterone

- Source: Zona Glomerulosa
- Chemistry: Steroid
- Transport: Only about 40% free & 60 % bound to Albumin
- Half Life: 20 min
- Plasma basal levels: 6.0 ng/dl
- Daily Output: 150-250 mg/24 Hours
- Fate: Conjugated in Liver and then Excreted in urine (75%) or bile then in the feces (25%).

Functions of the Mineralocorticoids

1- *Renal Effects*

Aldosterone acts on collecting tubule & duct principal cells

- Increase the Na+ permeability of the luminal plasma membrane.
- Increase the number and activity of basolateral plasma membrane Na+/K+-ATPase pumps.
- Increase the luminal plasma membrane K+ permeability.
- Increase cell metabolism.

All of these changes result in increased Na+ absorption and K+ secretion.

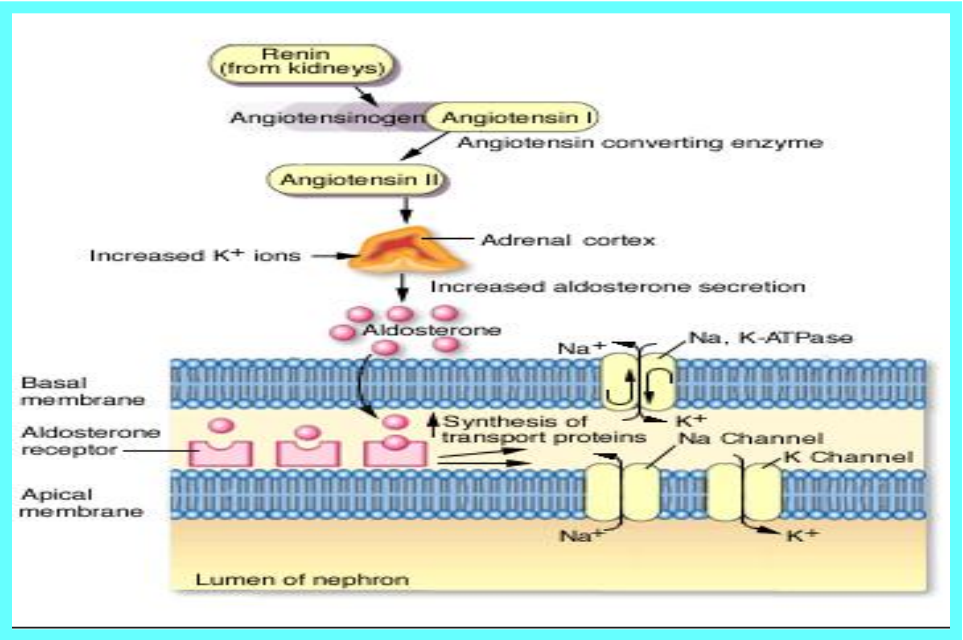
Effects on Sweat Glands and Salivary Glands

- Aldosterone greatly increases the reabsorption of NaCl and the secretion of K^+ by the ducts of sweat glands and salivary glands.
- The effect on the sweat glands is important to conserve body salt in hot environments.
- The effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva are lost.

2- *Effects on Intestinal Epithelial Cells*

- Aldosterone also greatly enhances Na^+absorption by the intestines, especially in the colon, which prevents loss of Na^+ in the stools.
- Conversely, in the absence of aldosterone, Na^+ absorption can be poor, leading to failure to absorb chloride and other anions and water as well.
- The unabsorbed NaCl and water then lead to diarrhea, with further loss of salt from the body.

Cellular Mechanism of Aldosterone Action



1- Aldosterone diffuses readily to the interior of the tubular epithelial cells because of its lipid solubility in the cellular membranes.

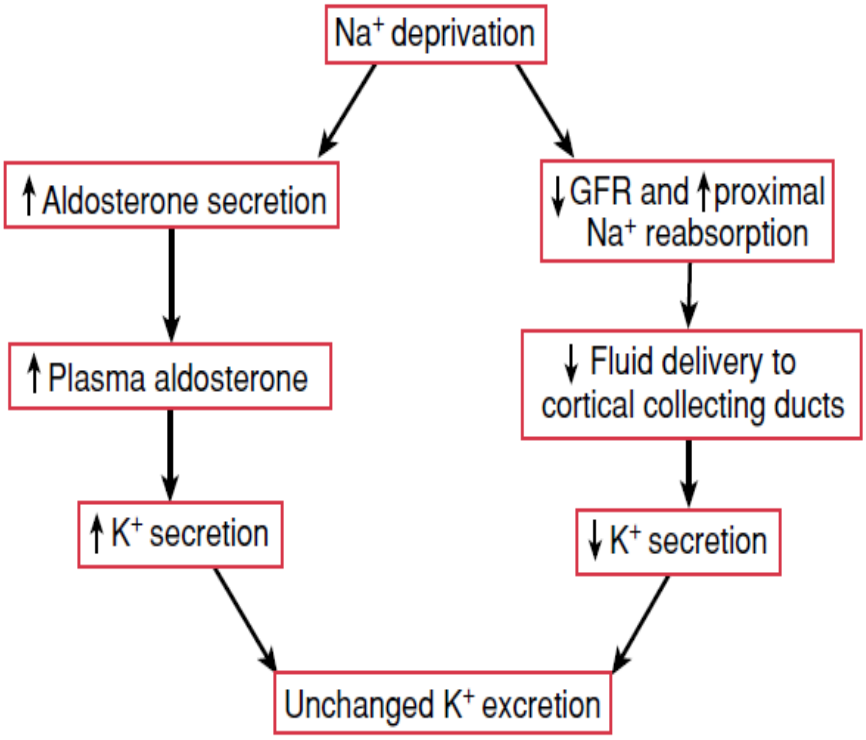
2- Aldosterone combines with a highly specific cytoplasmic receptor protein.

3- The aldosterone-receptor complex or a product of this complex diffuses into the nucleus, where it induce formation of one or more types of messenger RNA related to the process of Na^+, K^+ transport.

4- The messenger RNA diffuses back into the cytoplasm, where it causes protein formation of membrane transport proteins that are required for Na^+, K^+, and H^+ transport through the cell membrane as Na^+ K^+ ATPase, which serves as the principal part of the pump for Na^+ and K^+ exchange at the basolateral membranes of the renal tubular cells.

WHY Na+ DEPLETION DOES NOT LEAD TO ENHANCED K+ EXCRETION?

In cases of decreased dietary Na+ intake or Na+ depletion, the activity of the luminal plasma membrane H/K-ATPase found in intercalated cells is increased. This promotes K reabsorption by the collecting ducts.



MINERALOCORTICOID ESCAPE

" Large doses of a potent mineralocorticoid result in "escape" from the salt-retaining action of the steroid".

The fact that the person will not continue to accumulate Na^+ and water is due to the existence of numerous factors that are called into play when ECF volume is expanded; (probably due to increased secretion of ANP).

These factors promote renal Na^+ excretion and overpower the salt-retaining action of aldosterone.

Regulation of Aldosterone Secretion

Stimulatory agents

- Increased K+ concentration in the ECF
- increased levels of angiotensin II
- Decreased Na+ concentration
- ACTH from the anterior pituitary gland

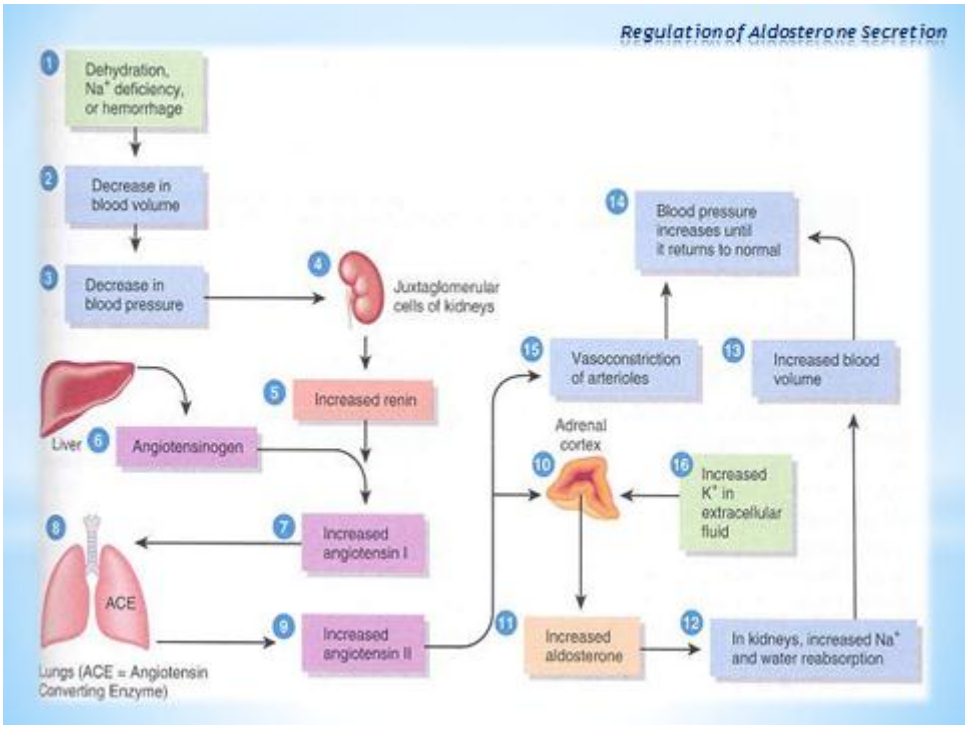
Inhibitory agents

- Atrial natriuretic hormone
- High Na+ concentration
- K+ deficiency

1. Increased K^+ concentration in the extracellular fluid:

A small percentage increase in K^+ concentration can cause a several fold increase in aldosterone secretion.

2. Increased activity of the renin-angiotensin system (increased levels of angiotensin II)



It also greatly increases aldosterone secretion. Activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss,

can cause a several fold increase in aldosterone secretion.

In turn, the aldosterone acts on the kidneys (1) to help them excrete the excess potassium ions and (2) to increase the blood volume and arterial pressure, thus returning the renin angiotensin system toward its normal level of activity. These feedback control mechanisms are essential for maintaining life.

3. Decreased Na^+ concentration:

A 10 to 20 % decrease in extracellular fluid Na^+ concentration can perhaps double aldosterone secretion.

4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion.

Of these factors, K^+ concentration and the renin-angiotensin system are by far the most potent in regulating aldosterone secretion.

Disturbance in mineralocorticoids

1- Mineralocorticoid Deficiency

- Lack of aldosterone secretion decreases renal tubular Na+ reabsorption and allows Na+, Cl+, and water to be lost into urine this leads to:
  - Decreased ECF volume.
  - Decreased plasma volume.
  - RBCs concentration rises markedly
  - Decreased cardiac output.
  - Circulatory shock may develop rapidly.
- Hyperkalemia and mild acidosis develop because of failure of K+ and H+ to be secreted in exchange for Na+ reabsorption. Hyperkalemia can lead to serious cardiac toxicity including weakness of heart contraction and arrhythmia.

Death usually occurs in the untreated patient 4 days to 2 weeks after cessation of mineralocorticoid secretion.

2- Primary Aldosteronism (Conn's Syndrome)

Occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldosterone.

The most important effects are:

- Decrease in Na+ loss in the urine with increase of Na+ in ECF & hypertension.
- Occasional periods of muscle paralysis as a result of hypokalemia.
- Decrease in H+ concentration in the ECF which leads to alkalosis.
- Decreased plasma renin concentration. This results from feedback suppression of renin secretion caused by the excess aldosterone or by the excess ECF volume and arterial pressure resulting from the aldosteronism.