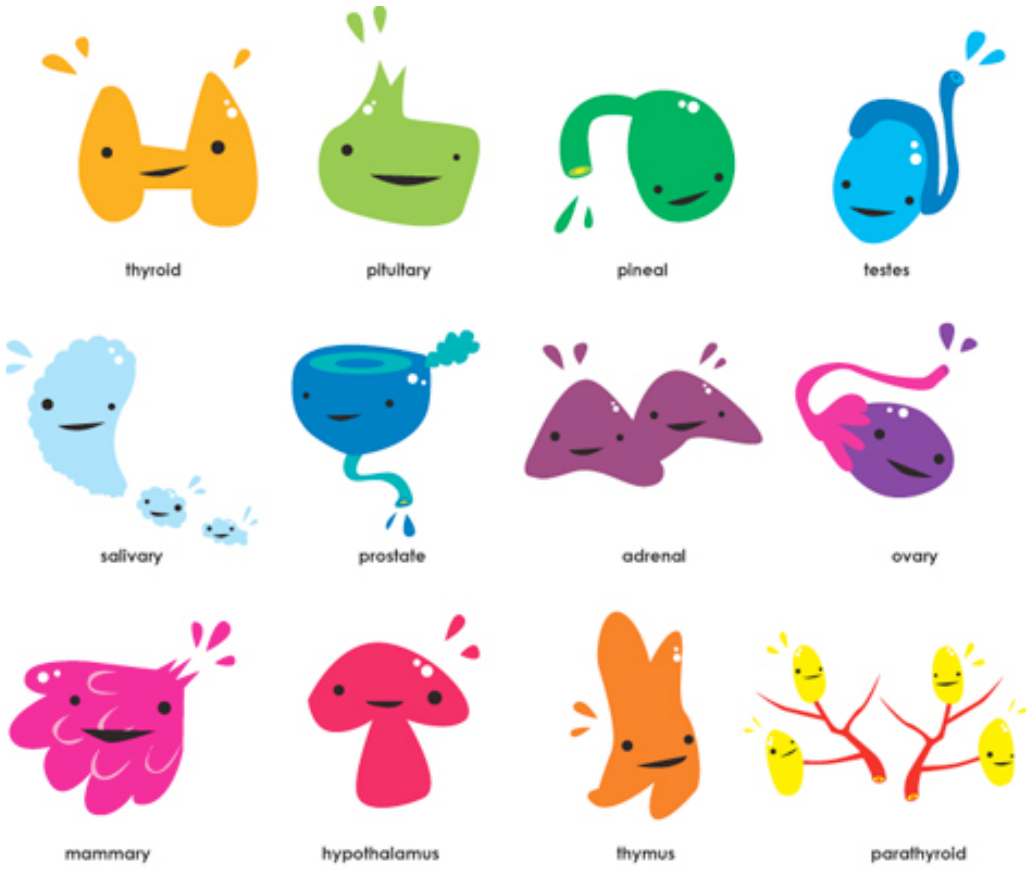
Lecture 10: Physiology of Mineralocorticoids



Note: 1) This is a rearrangement of the slides + Few notes

2) Focus on every figure and graph. Do not ignore them!

notes are in purple

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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 give rise to 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. 3. The zona reticularis secretes the adrenal **androgens [**mainly **DHEA]** as well as small amounts of estrogens and some glucocorticoids.

	CORTEX	MEDULLA
Percent Mass	80 %	20 %
Origin	Mesoderm	Ectoderm (neural crest)
Regeneration Capacity	Yes	No
Zones	3 concentric zones	Chromaffin cell
Hormones	Glucocorticoids Mineralocoricoids	Ep and NE
Organelles	Large Smooth ER	Relatively Smaller

Chemical Nature of Adrenocortical Hormones.

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

Mineralocorticoids

They affect the electrolytes 'minerals' of ECF, namely Na & K, hence, the name mineralocorticoids.

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: **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%).

Synthesis

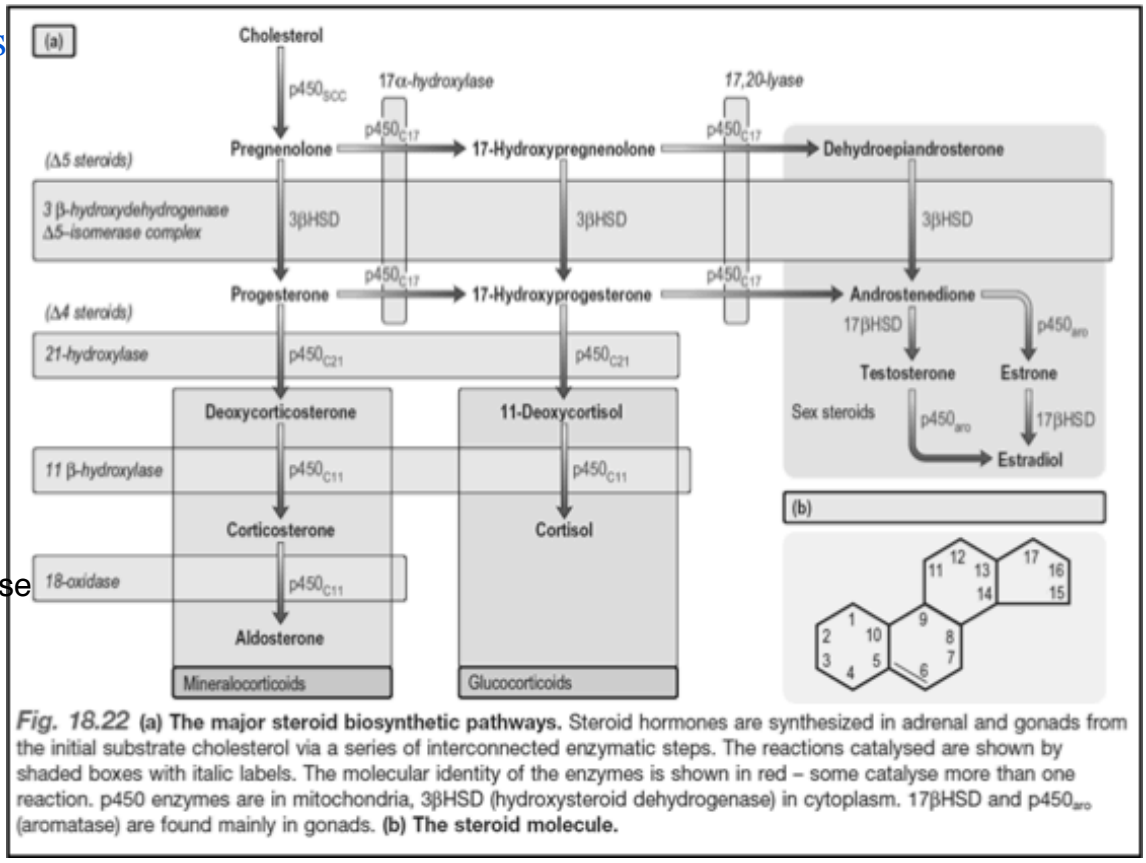


Fig. 18.22 **(a) The major steroid biosynthetic pathways.** Steroid hormones are synthesized in adrenal and gonads from the initial substrate cholesterol via a series of interconnected enzymatic steps. The reactions catalysed are shown by shaded boxes with italic labels. The molecular identity of the enzymes is shown in red – some catalyse more than one reaction. p450 enzymes are in mitochondria, 3βHSD (hydroxysteroid dehydrogenase) in cytoplasm. 17βHSD and $p450_{aro}$ (aromatase) are found mainly in gonads. **(b) The steroid molecule.**

Aldosterone synthase

✦ As noted earlier, each layer of the adrenal cortex synthesizes and secretes predominantly one type of steroid: glucocorticoid, mineralocorticoid, or androgen. The *basis for this specialization* is the presence or absence of the enzymes that catalyze various modifications of the steroid nucleus. For example, the zona reticularis and zona fasciculata produce androgenic steroids because they contain 17,20-lyase; on the other hand, the zona glomerulosa produces aldosterone because it contains aldosterone synthase.

✦ The precursor for all adrenocortical steroids is **cholesterol.** Most of the cholesterol is provided to the adrenal cortex via the circulation, and small amounts are synthesized *de novo* within the adrenal cortical cells. Cholesterol circulates bound to LDL. There are receptors for these lipoproteins in the membranes of adrenocortical cells; the lipoprotein-cholesterol complex binds and is transferred into the cell by endocytosis. Inside the cells, cholesterol is esterified and stored in cytoplasmic vesicles until it is needed for synthesis of steroid hormones.

✦ The first step in the synthesis of all adrenocortical hormones is the conversion of cholesterol to pregnenolone, catalyzed by **cholesterol desmolase.** Thus, all layers of the adrenal cortex contain cholesterol desmolase. Cholesterol desmolase is the rate-limiting enzyme in the pathway, and it is stimulated by **ACTH**

✦ **Pregnolone** itself is not a hormone, but is the **immediate precursor for the synthesis of all steroid hormones**

✦ Mineralocorticoids are produced in zona glomerulosa where **aldosterone synthase** converts corticosterone to aldosterone. If aldosterone synthase is deficient corticosterone, which have glucocorticoid and mineralocorticoid activity is secreted. So symptoms may not appear.

Relative Potencies of Corticosteroids Compared with Cortisol

TABLE 34.2 Comparison of Shared Activities of Adrenal Cortical Hormones

Hormone	Glucocorticoid Activity[a]	Mineralocorticoid Activity[b]
Cortisol	100	0.25
Corticosterone	20	0.5
Aldosterone	10	100

[a]Percentage activity, with cortisol being 100%
[b]Percentage activity, with aldosterone being 100%

Actions:

the aim of aldosterone actions is to ↑ plasma Na and, consequently, increasing ECF volume. Also, ↓ plasma K.

1- Renal Effects:

- Aldosterone acts on collecting tubule **principal cells**

1. ↑ Na+ permeability of the luminal plasma membrane
   >> ↑ Na reabsorption >> ↓ Na excretion
2. Increase the number and activity of basolateral plasma membrane Na+/K+-ATPase pumps. >> ↓ Na excretion & ↑ K excretion
3. Increase the luminal plasma membrane K+ permeability. >> ↑ K excretion
4. Increase cell metabolism.

- Aldosterone also act on **intercalated cells**:

Increase H+ secretion by increasing the activity of H/K- ATPase pump.

2- 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.

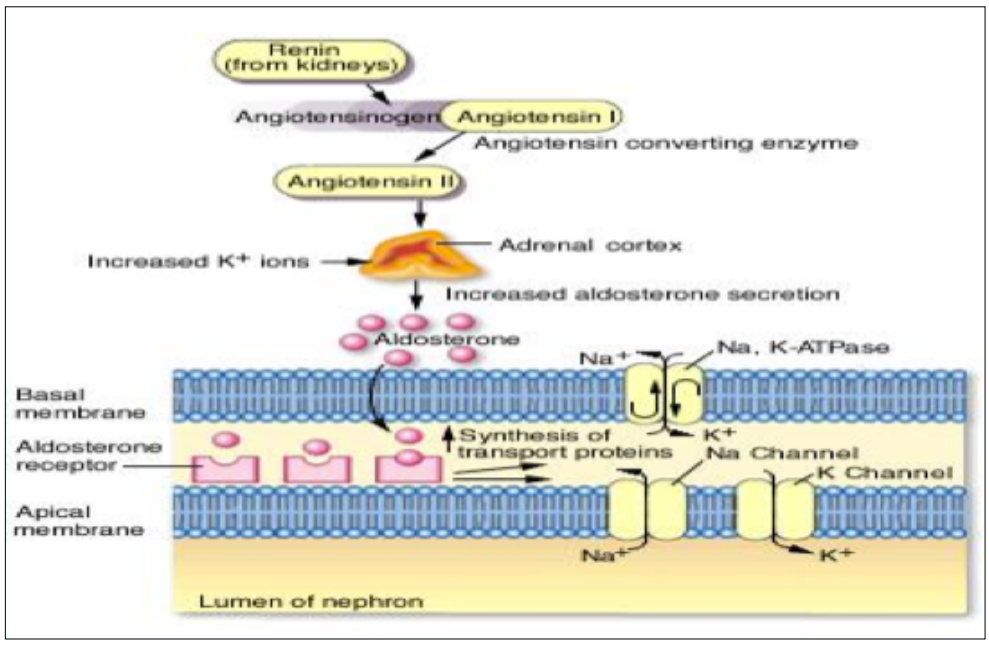
• The effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva are lost.

3- Effects on Intestinal Epithelial Cells

• 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 >> diarrhea.

Cellular Mechanism of Aldosterone Action:



It has steroid MoA.

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

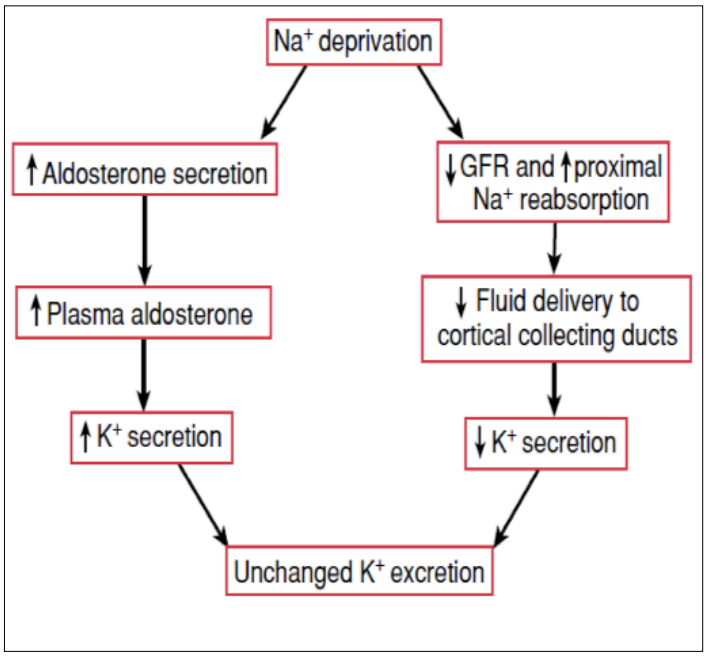
2- Aldosterone combines with a highly specific cytoplasmic receptor protein.

3- The aldosterone- receptor complex diffuses into the nucleus, where it induce transcription of one or more genes into mRNA.

4- The mRNA diffuses back into the cytoplasm, where it causes protein formation of 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.

✳ In case of **low Na**, aldosterone secretion levels will be high to restore Na levels. However, this doesn't effect K excretion. So, 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.



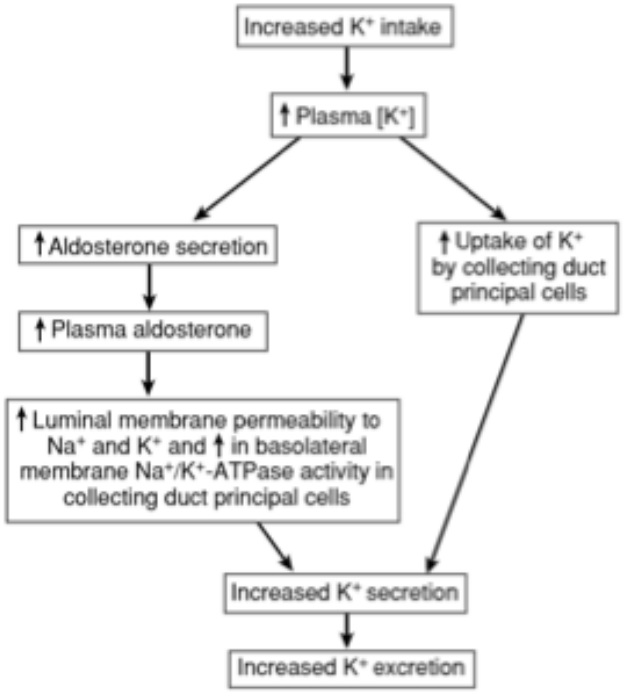
Therefore we can consider increasing the activity of H/K- ATPase transporter as one of aldosterone actions.

H/K- ATPase absorb K and secrete H ions to the lumen of tubules. This transporter is located on the apical membrane of **intercalated cells** of collecting tubules.

Recall that **I cells** are responsible for maintaining **acid-base** balance.

In cases of hyperaldosteronism, alkalosis occur as a result of hyperactivity of this pump, as we'll see later.

✳ On the other hand high K dietary intake activate aldosterone secretionleading to ↑ K excretion



MINERALOCORTICOID ESCAPE

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

So, large doses of aldosterone will lose their action. This probably due to Atrial Natriuretic Peptide which will cause Na excretion.

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

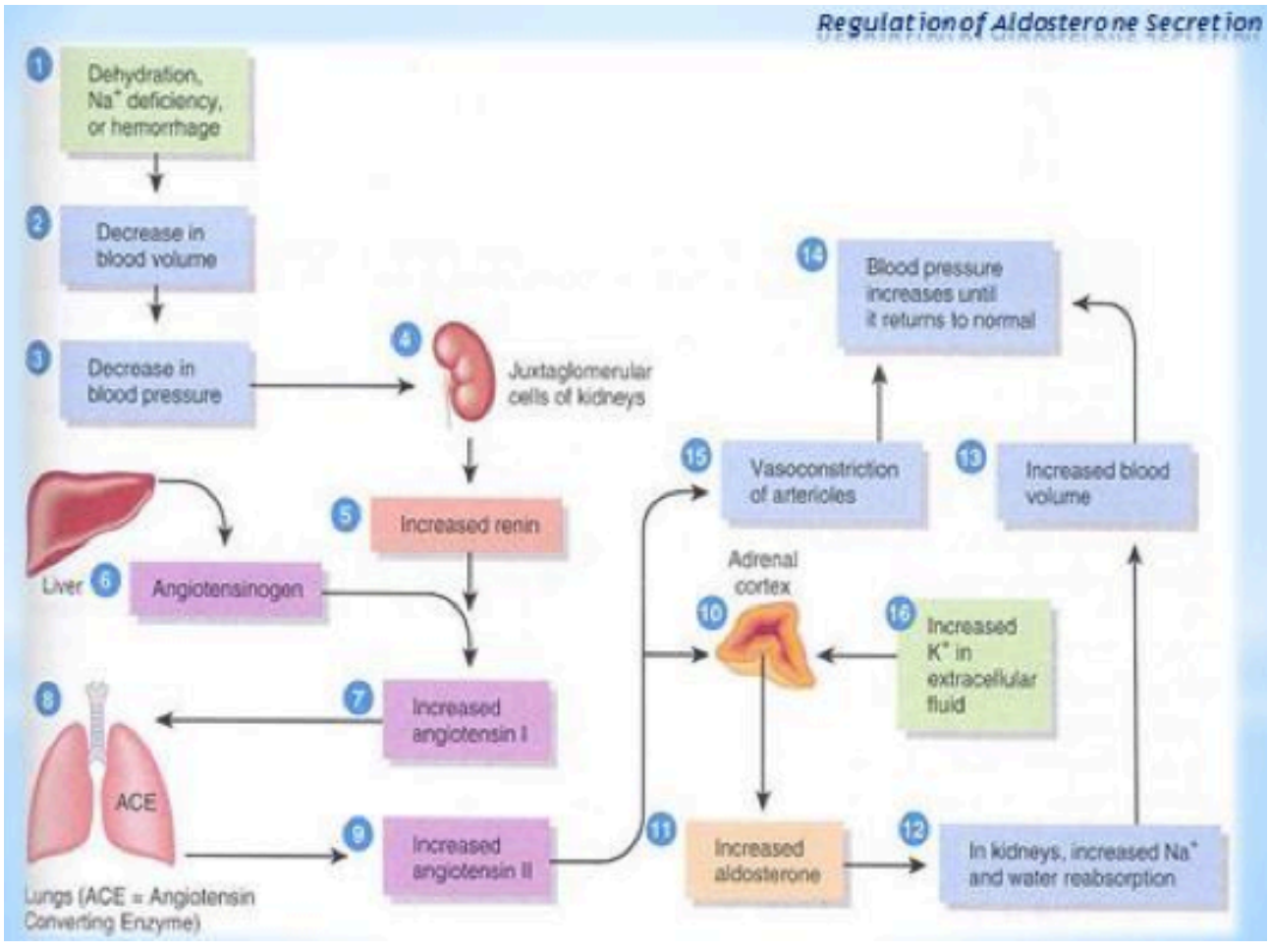
Inhibitory agents

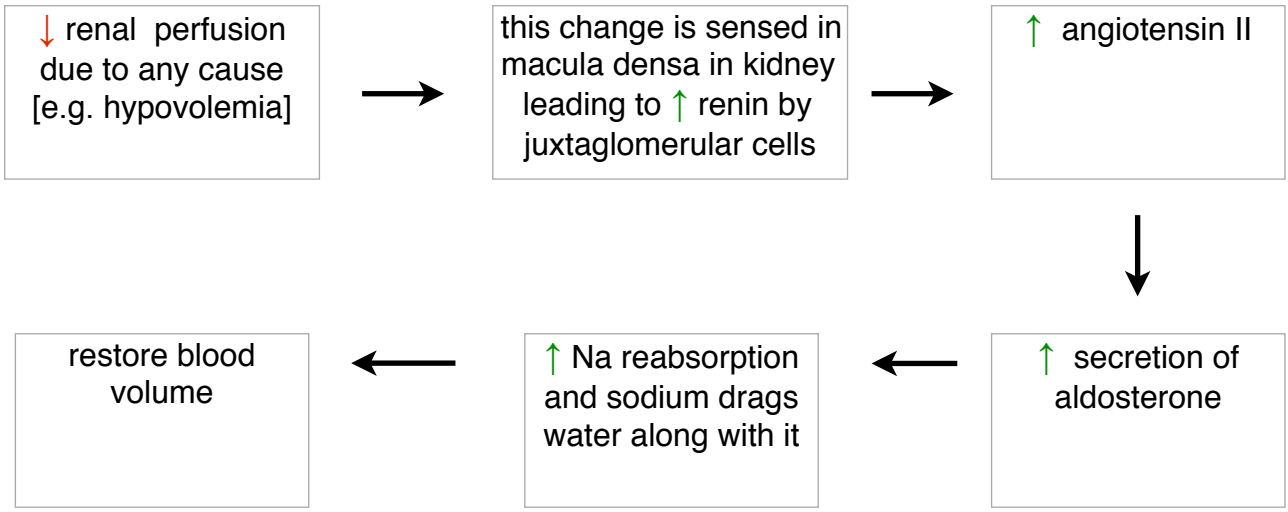
- Atrial natriuretic hormone
- High Na+ concentration
- K+ deficiency

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

✦ Recall that activation of the renin- angiotensin system happens in response to diminished blood flow to the kidneys or to sodium loss.

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





Disturbance in mineralocorticoids

1- Mineralocorticoid Deficiency as seen in Addison's disease

❖ 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. [cardiac arrest]

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.
❖ high aldosterone >> ↓ renin by negative feedback [low-renin hypertension]

low renin is one of the diagnostic criteria of primary hyperaldostreonism