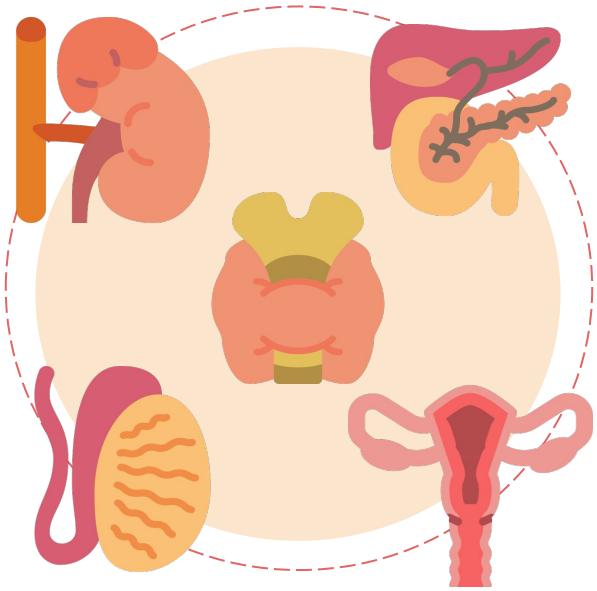

Mineralocorticoids

Objectives:

- The cellular arrangements and functional components of the adrenal gland.
- The hormones secreted by the medulla and cortex of the adrenal gland.
- The synthesis of the adrenocortical steroids.
- The physiological actions of aldosterone.
- The regulation of aldosterone secretion.
- The major stimuli for aldosterone secretion.

Revised By
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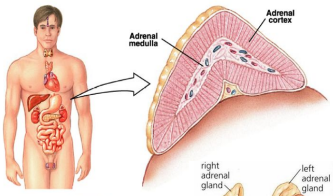
  - Nora AlKadi

Colour index:
- Important
- Numbers
- Extra

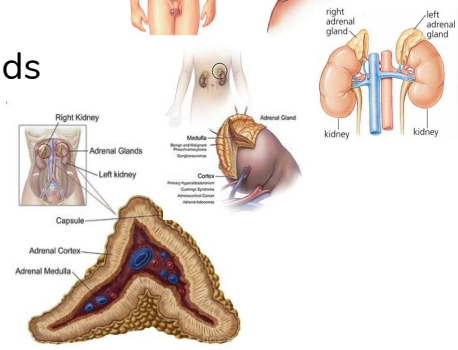
Adrenal Gland

- There are two adrenal (suprarenal) glands that lie at the superior pole of the two kidneys
- Small, pyramid-shaped
- Weigh 6-10 g
- Divided into two morphologically and distinct regions:



Adrenal cortex:

- Secrete group of hormones called corticosteroids
- All synthesized from the steroid cholesterol
- Have different functions.

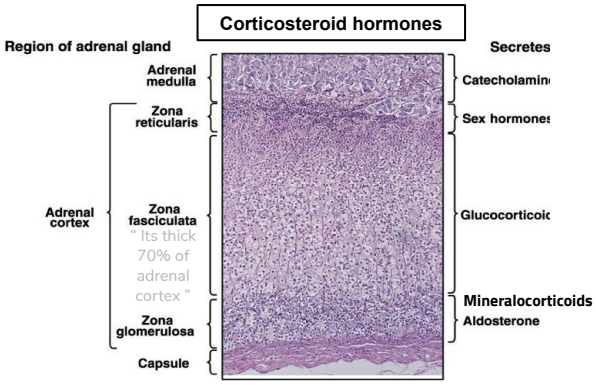


Adrenal medulla:

- It is the central region
- 20% of the gland
- Secretes EPN and NEPN (related to sympathetic nervous system).

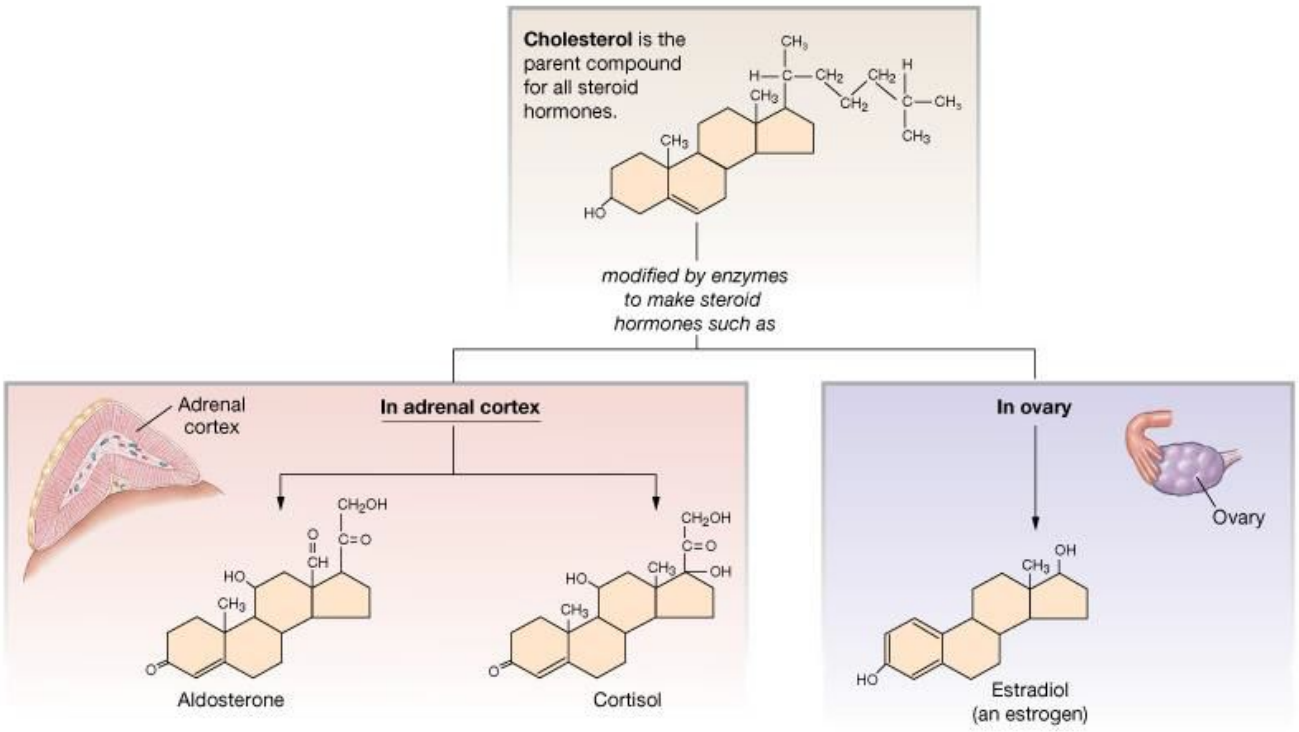
Adrenal Cortex

•Adrenal Cortex: Synthesizes and releases steroid hormones (corticosteroids)
•Different corticosteroids are produced in each of the three layers.

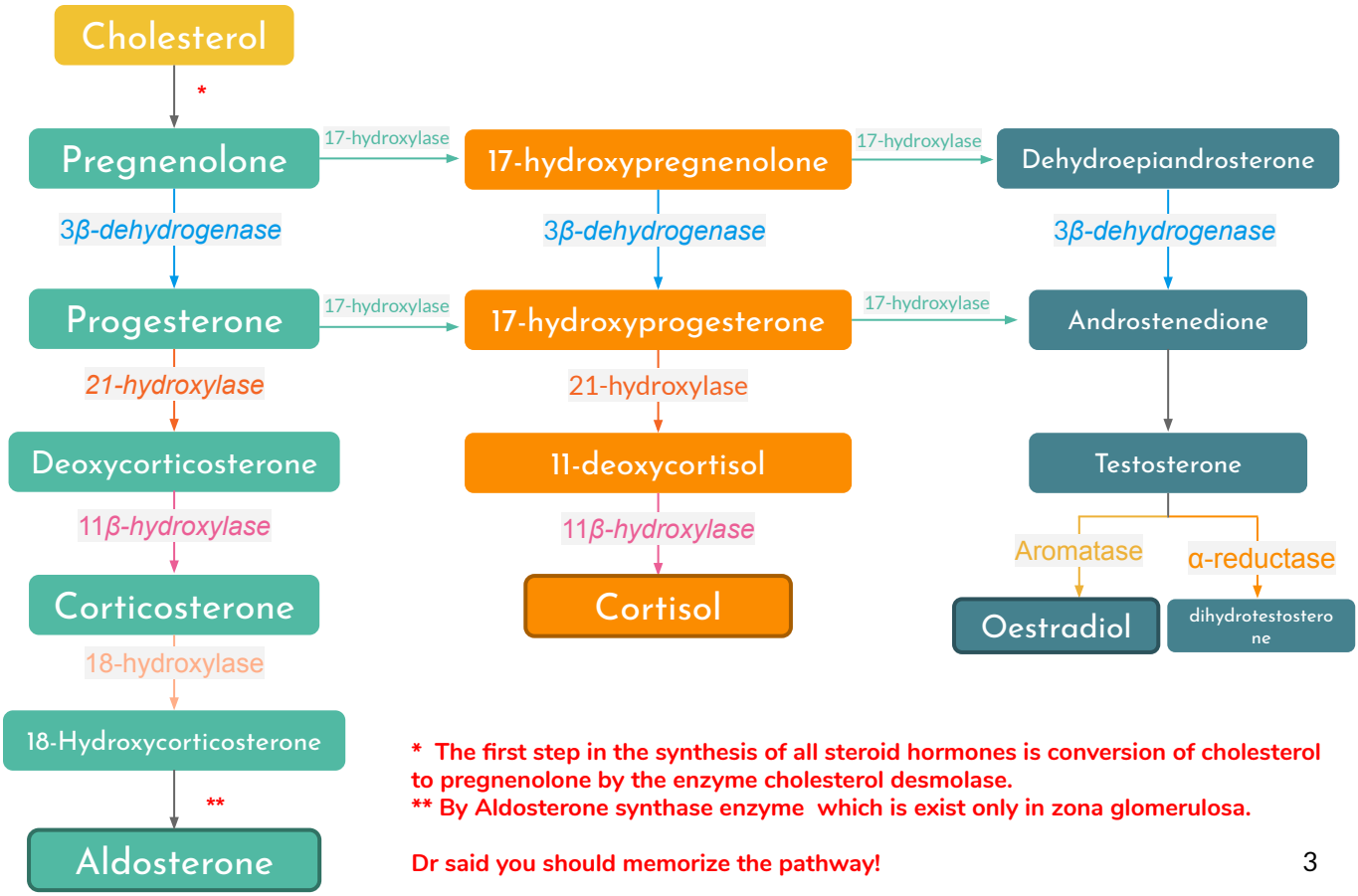


Region	Types	Hormones
Zona glomerulosa	Mineralocorticoids	Aldosterone only!
Zona fasciculata	Glucocorticoids	Cortisol (mainly) Corticosterone Androgens (small amount) Estrogens (small amount)
Zona reticularis	Gonadocorticoids	<u>Androgens</u> DHEA Androstenedione Estrogen (small amount) <u>Glucocorticoids</u> small amounts.

Structure of Steroid Hormones



Synthesis of Steroid Hormones



* The first step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone by the enzyme cholesterol desmolase.
** By Aldosterone synthase enzyme which is exist only in zona glomerulosa.

Dr said you should memorize the pathway!

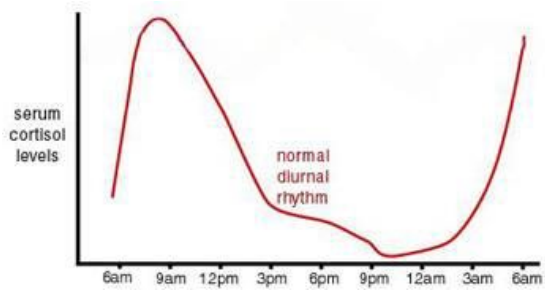
Because they are lipophilic, they can diffuse easily through cell membrane."This proves that steroid hormones cannot be stored or trapped in vesicles"

Aldosterone

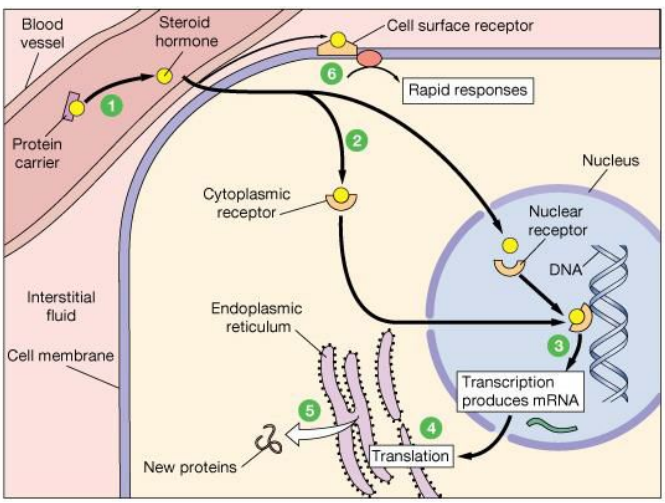
Steroid hormones are mainly produced in adrenal cortex, ovaries and testes.

- The main mineralocorticoid produced by the adrenal gland.
- A steroid hormone.
- Synthesized in zona glomerulosa.
- Aldosterone exerts 90% of all the mineralocorticoid activity.
- Target cells are called “principal (P) cell”.
- 60% of aldosterone bound to plasma protein. 40% is free form.
- Half life: 20 min
- Much of secreted aldosterone is metabolized by the liver and converted to **tetrahydro-glucuronide** derivative.

- Aldosterone levels fluctuate diurnally - highest concentration being at 8 AM, lowest at 11 PM, in parallel to cortisol rhythms.

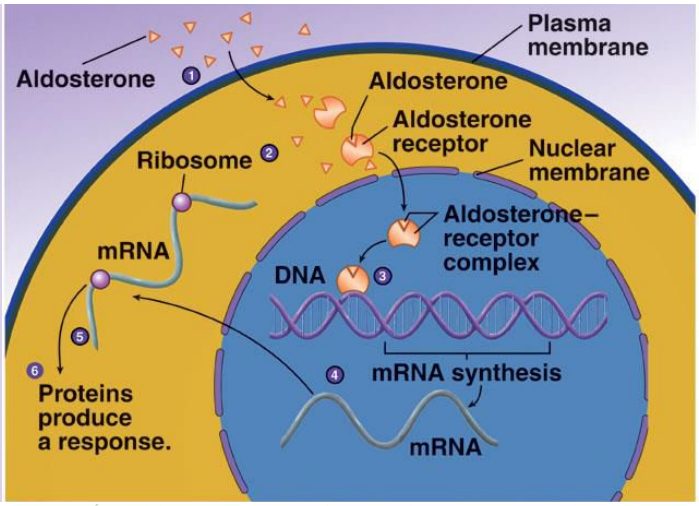


Steroid Hormones: MOA



1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins for cell processes.
6. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

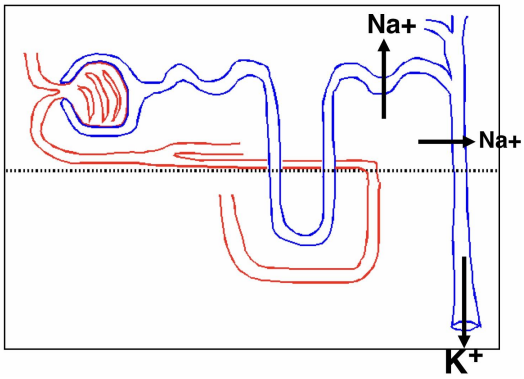
- Increases transcription of **Na^+/K^+ pump**
- Increases the expression of **apical Na^+ channels** and **$Na^+/K^+/Cl^-$ cotransporter.**



تخيلوه مغناطيس يسحب الصوديوم كل ماشافه، يسحبه من الكلية والأمعاء والقولون وال salivary and sweat glands.
.How? it diffuses into the cell as aldosterone to make the Na/K pump and protein channels

Actions of Aldosterone

Acts mainly on the cells of the **collecting ducts and distal tubules.**



Increases Renal Tubular **Reabsorption of Na^+ and Secretion of K^+ and H^+**

1) **Renal action**: Aldosterone causes sodium to be conserved in the ECF while increasing potassium excretion in the urine.
2) **Circulatory Actions of Aldosterone**: Increases ECF volume and Arterial Pressure.
3) It also affects **Na+ reabsorption** by sweat, salivary and intestinal cells. (Stimulates synthesis of more Na/K-ATPase pumps)
   "beside basolateral membrane in renal tubules"

Control of Aldosterone secretion:

- ↑ K+ concentration in the ECF
- ↓ Na+ concentration in the ECF
- Increased activity of the renin- angiotensin system
  - (increased levels of angiotensin II)
- Hypovolemia
- Hypotension
- ACTH:ACTH also stimulates aldosterone synthesis. However the ACTH stimulation is more transient than the other stimuli and is diminished within several days "ACTH stimulates mainly cortisol secretion followed by sex hormone and lastly aldosterone".
- Stress, surgery.

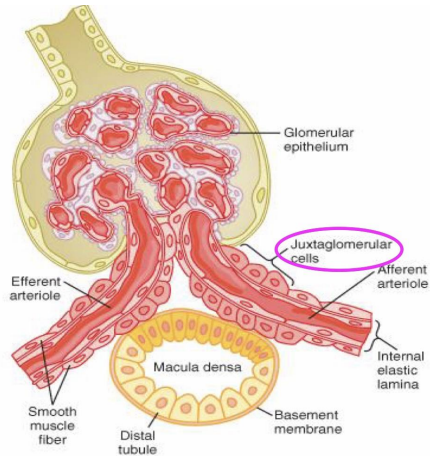
Hyperkalemia is more potent stimulus in compared to RAS which is more important physiologically.

↑ **Aldosterone secretion**

Control of Aldosterone secretion:

Renin:

- is a enzyme released by the kidneys when the arterial pressure falls.
- Renin is synthesized and stored in in the juxtaglomerular cells (JG cells) of the kidneys.
- The JG cells are modified smooth muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli.
- Renin acts on another plasma protein (angiotensinogen), to release angiotensin I which is converted to angiotensin II (in the lungs).

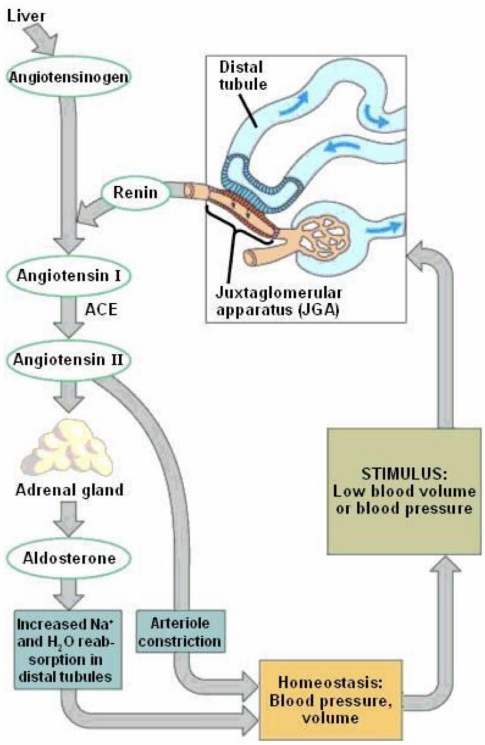


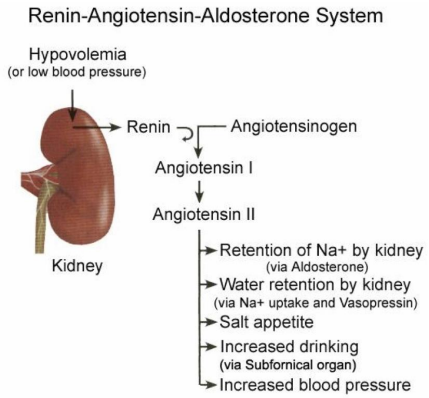
Angiotensin II:

Angiotensin II increases the blood pressure through:

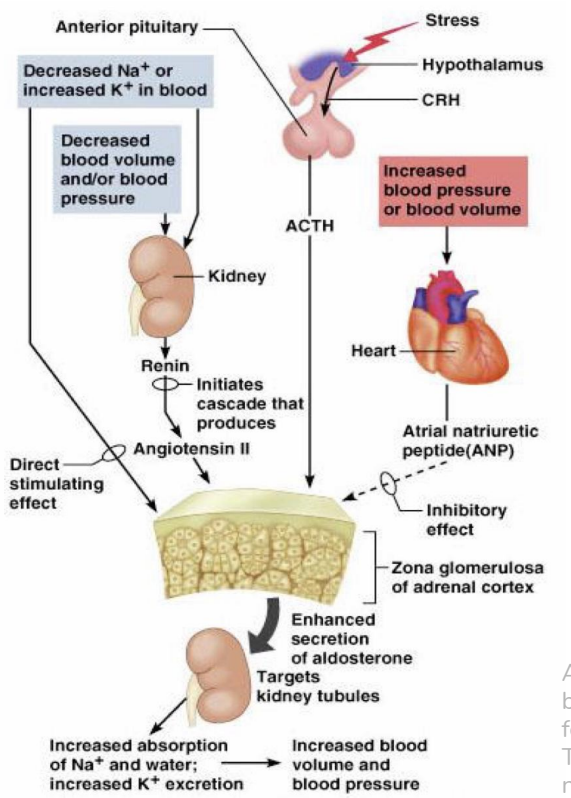
1) Vasoconstriction occurs intensely in the arterioles & much less so in the veins. Constriction of the arterioles increases the total peripheral resistance, thereby raising the arterial pressure.
2) Decrease excretion of both salt and water by the kidneys.
   This slowly increases ECF volume, which then increases the arterial pressure during subsequent hours and days.

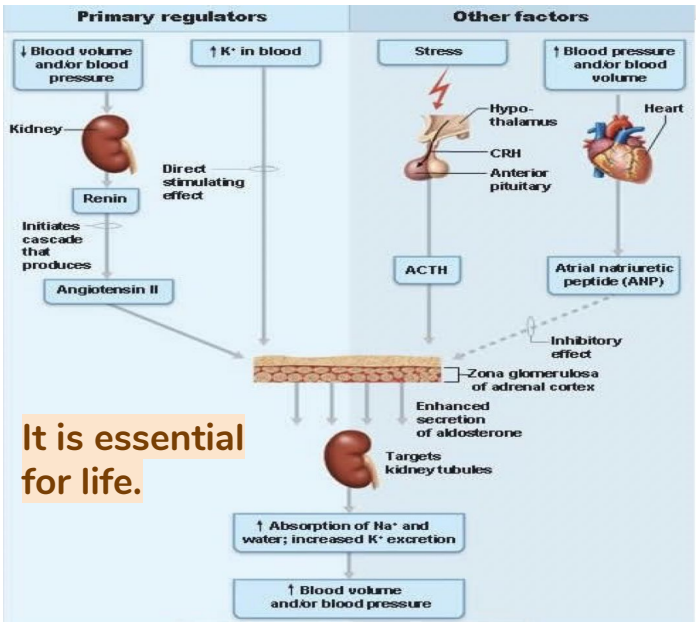
- Angiotensin II acts on the zona glomerulosa to stimulate aldosterone synthesis.
- Angiotensin II acts via increased intracellular cAMP to stimulate aldosterone synthesis.





Regulation of Aldosterone secretion:





Androgens unlike cortisol that has a regulatory mechanism mediated by negative feedback mechanism. Androgens does not have a negative feedback mechanism on hypothalamus to reduce ACTH secretion. That's why in case of congenital adrenal hyperplasia, there will be numerous amount of androgens without been regulated.

Hormones of Adrenal Secretion:

	production mg/day	concentr. ng/ml	activity MINERAL.	activity GLUCO.
Aldosterone	0.05-0.15	0.15	90%	
Deoxycorticosterone	0.6	0.15	1/15	
Corticosterone	1-4	2-4	1/50	4%
Cortisol	8-25	40-180	1/400	95%
DHEA	7-15	5		

→ **Notes:**

1) Cortisol is at 1000 fold higher concentrations than aldosterone
2) Corticosterone >>>> aldosterone
3) Cortisol binds well to the mineralocorticoid receptor.

Abnormalities

Primary hyperaldosteronism (increase secretion of mineralocorticoids)	→	Conn's Syndrome
Complete failure to secrete aldosterone	→	• Dehydration • Low blood volume • Low blood pressure • Death

What will happen if we removed the zona glomerulosa? Hyponatremia this leads to Low blood volume and low blood pressure, and eventually death.

Primary Aldosteronism (Conn's Syndrome)

Cause	Tumor of the zona glomerulosa cells (adenoma) → secretes large amounts of aldosterone.
Effects	❑ **Hypokalemia** ❑ **Hypertension** ❑ Slight increase in ECF volume and blood volume. ❑ **Hypernatremia** Very slight increase in plasma sodium concentration ❑ Neuromuscular manifestations, weakness, paresthesia and intermittent paralysis caused by the hypokalemia. ❑ Nocturnal polyuria & polydipsia ❑ Increased tubular (intercalated cells) hydrogen ion secretion, with resultant mild alkalosis. ❑ Decreased plasma renin concentration (from feedback suppression of renin secretion caused by the aldosterone) or by the excess ECF volume and arterial pressure. Because the renin is acting as a feedback mechanism
Treatment	Usually surgical removal, Spironolactone .

Na reabsorption will increase which leads to higher blood pressure and this manifests to hypertension and hypernatremia. Also K **excretion** will increase which leads to hypokalemia.

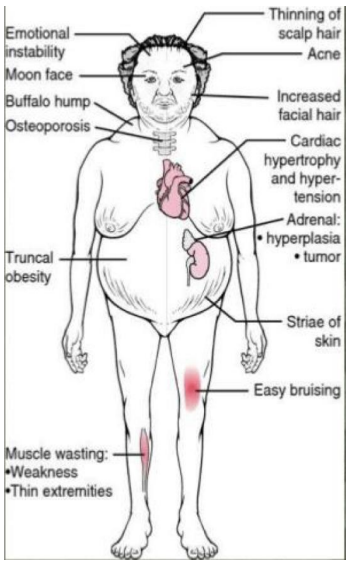
Sometimes a patient will be treated for hypertension only, not dealing with the cause of the manifestation which is a tumor of the adrenal gland. That's why it is better to do an ultrasound test to see if the patient has a tumor or not.

Conn's Syndrome

Symptoms :

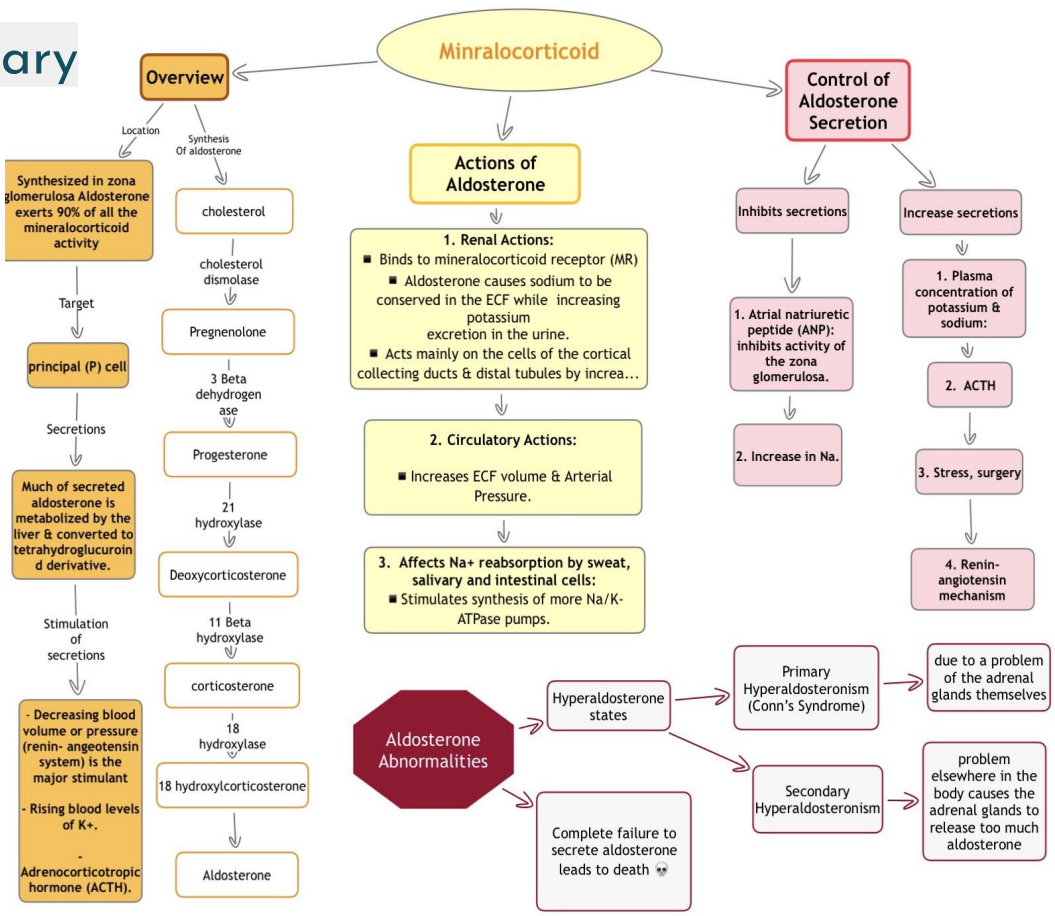
- frequent urination
- Increased thirst
- Weakness and fatigue
- Headache
- Muscle cramps
- Tingling in fingers
- Temporary paralysis
- Heart palpitations
- Hypertension (high blood pressure)

Treatment is surgical removal



Conn's syndrome (primary hyperaldosteronism)	Secondary hyperaldosteronism
↓ Plasma Renin	↑ Plasma Renin

Summary



MCQs

Q1: Aldosterone is secreted by:
A) Zona glomerulosa
B) Zona fasciculata
C) Zona reticularis
D) Adrenal medulla

Q2: Conn's syndrome leads to:
A) Decrease ECF volume
B) Acidosis
C) Hypokalemia
D) Hypotension

Q3: Renin-Angiotensin System is:
A) Direct inhibitor
B) Direct stimulus
C) Indirect inhibitor
D) Indirect stimulus

Q4: Aldosterone increases Na reabsorption by:
A) Increase synthesis of Na/K pump
B) Increase expression of apical K channels
C) Decrease Na/ K / Cl cotransporter
D) None of the above

Q5: The conversion of Cholesterol to Pregnenolone is catalyzed by which enzyme?
A) 21-hydroxylase
B) 3B- dehydrogenase
C) Cholesterol dismolase
D) Cholesterol hydroxylase

Answers
Q1: A
Q2: C
Q3: D
Q4: A
Q5: C