Pharmacology of mineralocorticoids & their antagonists

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INTRODUCTION

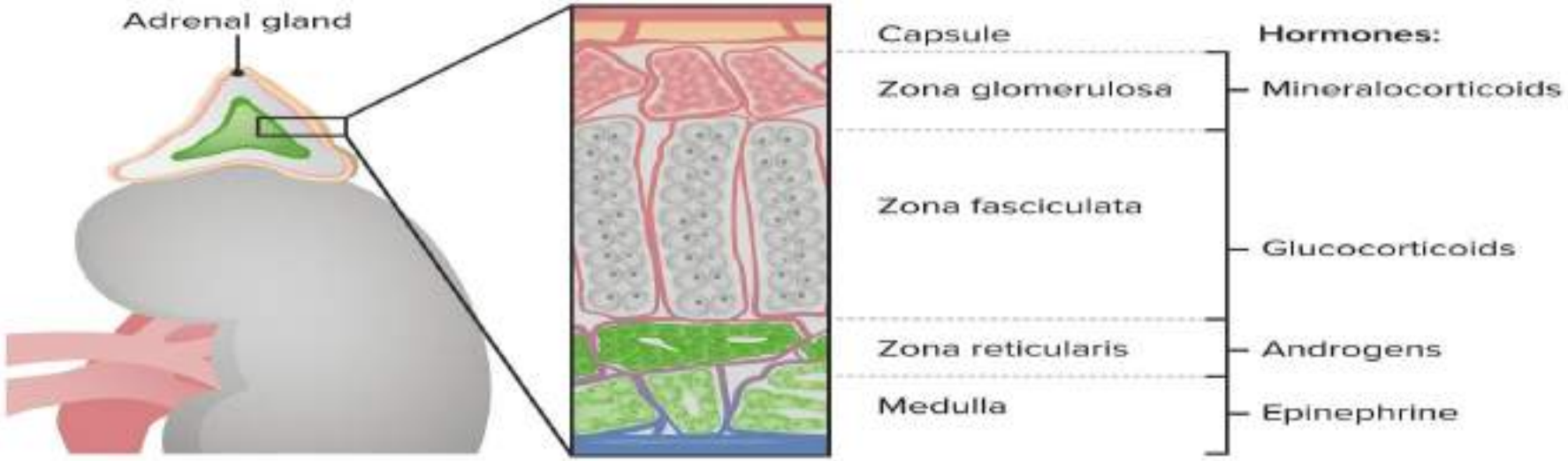
❑The **adrenal cortex** releases many **steroids (corticosteroids)** into the circulation.

❑**The hormonal steroids**:

1- Glucocorticoids (like cortisol) having important effects on **intermediary metabolism** and **immune function.**

2- Mineralocorticoids (aldosterone) having principally salt retaining activity.

3- Adrenal androgens like dehydroepiandrosterone (DHEA) in its sulfated form (DHEAS).



Mineralocorticoids

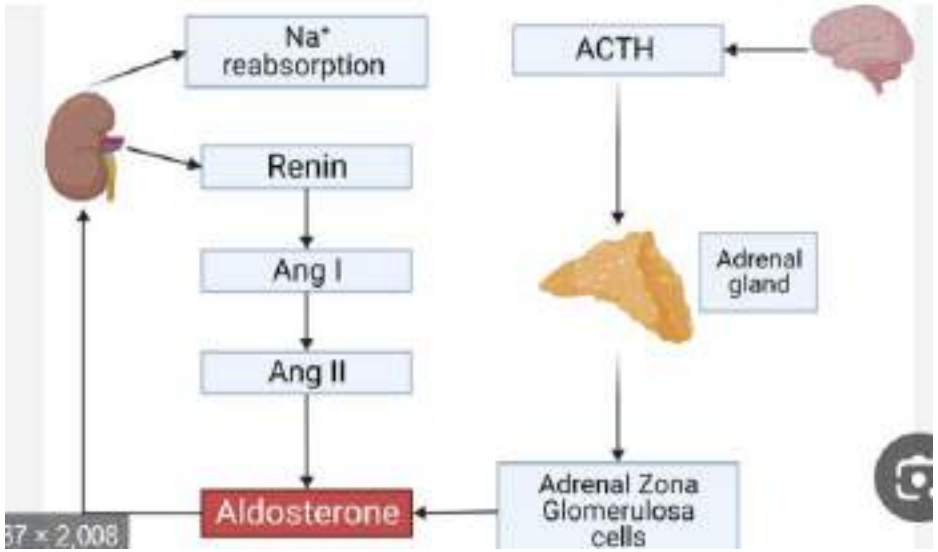
- **Mineralocorticoids:**
- (mainly **aldosterone** and small insignificant amounts of 11-deoxycorticosterone) are synthesized in the **zona glomerulosa** of the adrenal cortex
- **Mineralocorticoid release is regulated by:**

1-ACTH produces a **moderate stimulation of Aldosterone release**, but aldosterone doesn't cause any significant feedback control of ACTH secretion.

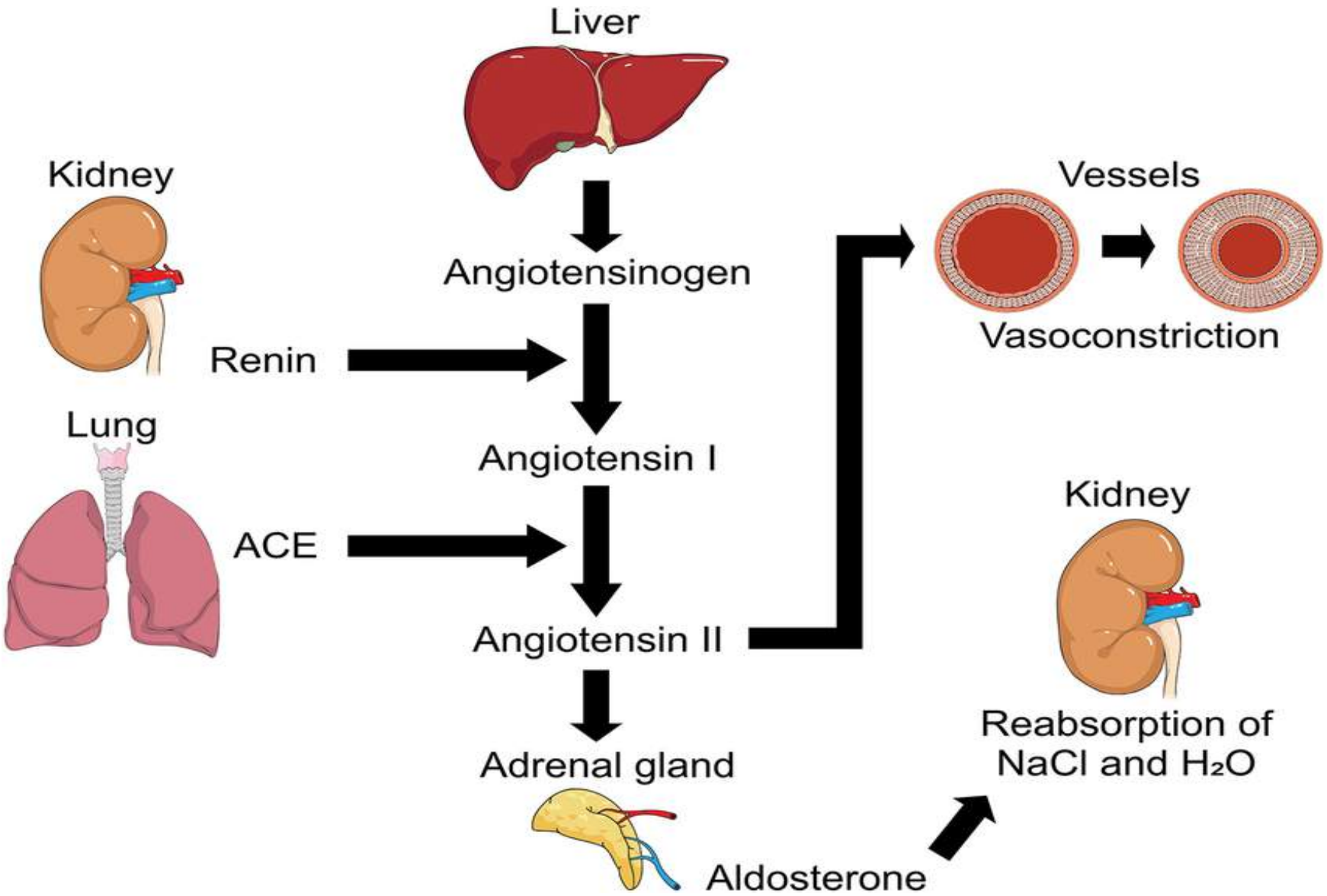
❑**Without ACTH, aldosterone secretion falls to about half the normal rate**

2- Angiotensin II, regulate aldosterone secretion. See **Renin Angiotensin Aldosterone system (RAAS).**

3- Local potassium levels.

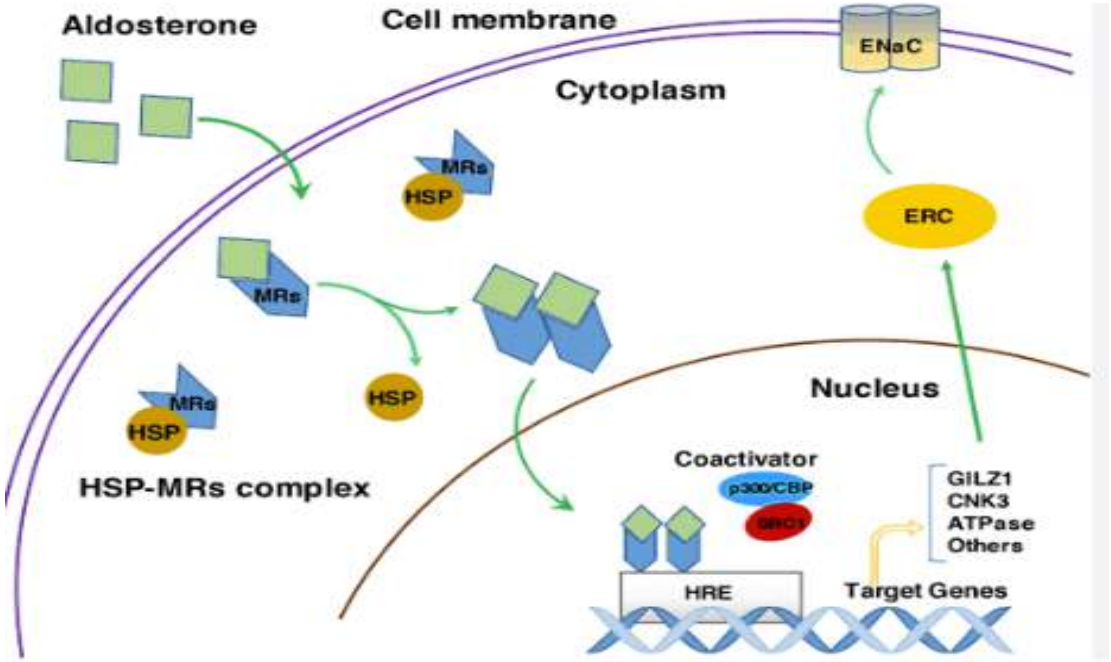


Renin Angiotensin Aldosterone system (RAAS)



Mechanism of action

- **Mineralocorticoids** act by:
- binding to the **Mineralocorticoid receptor** in the cytoplasm of target cells, especially principal cells of the distal convoluted and collecting tubules of the kidney.
- The **drug-receptor complex** activates a series of events ending by **protein synthesis.**



Pharmacodynamics

1) Aldosterone acts on mineralocorticoid receptors (MR) in cytoplasm of principal cells in the distal renal tubule, promoting reabsorbing sodium (Na+) ions and water into the blood, and secreting potassium (K+) ions into the urine.

2) Stimulation of H+ secretion by **intercalated cells** in the **collecting duct** into the urine, regulating acid/base balance.

3) Aldosterone may act on the central nervous system via the posterior pituitary gland to **release vasopressin** (**Anti-Diuretic-Hormone**) which **reabsorb water into the blood** by **direct actions on renal tubular cells**.

4) **Sodium re-absorption** in the sweat and salivary glands, in the gastrointestinal mucosa, and across cell membranes in general also is increased.

Drugs affecting aldosterone

1- **Beta-antagonists** can decrease of renin secretion, which decrease the secretion of aldosterone.

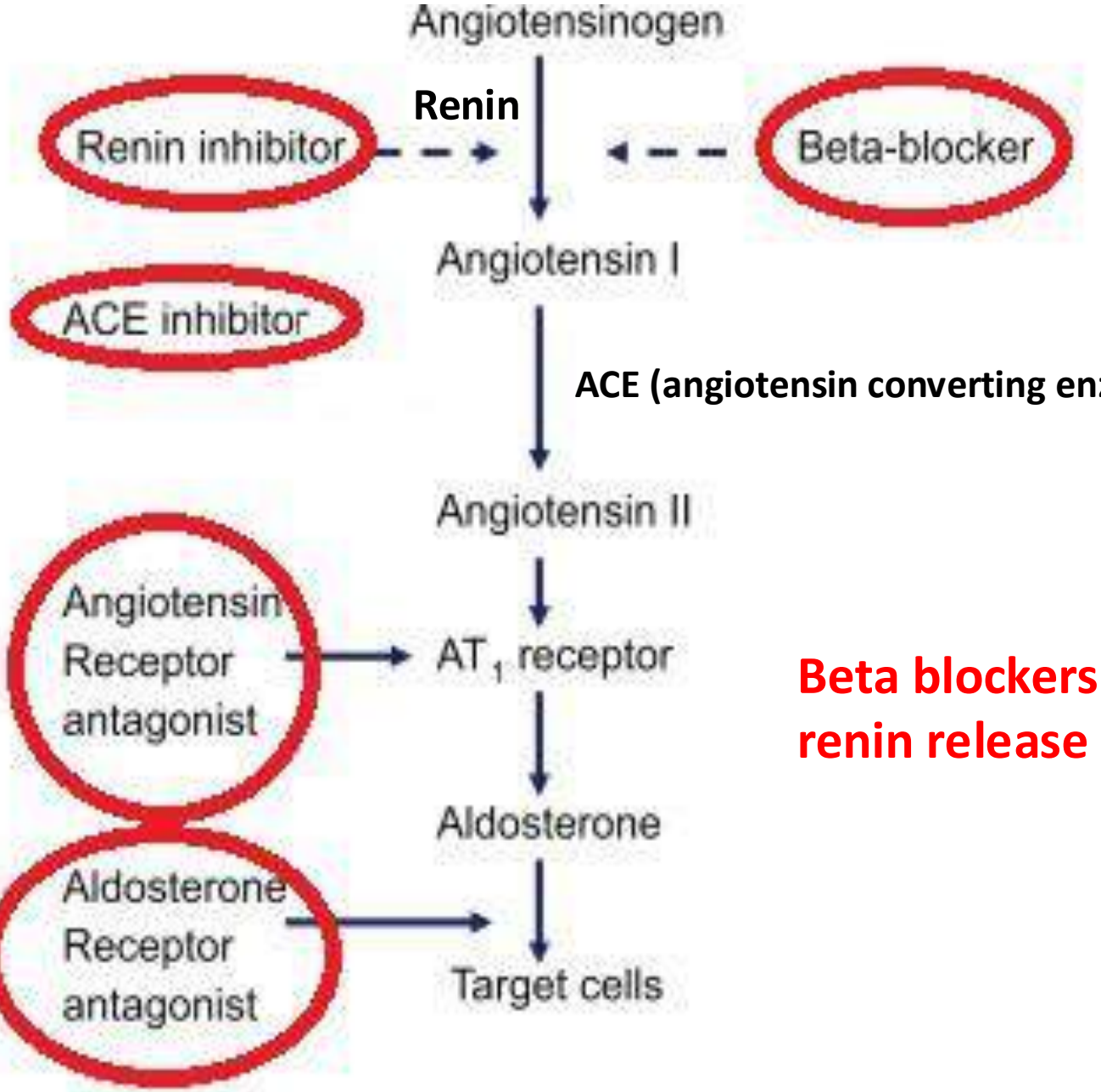
2- **Direct renin inhibitors** will decrease both angiotensin and aldosterone.

3-Angiotensin-converting enzyme inhibitors, which block ACE resulting in a decrease in angiotensin II and consequently aldosterone.

4-Angiotensin II receptor blockers (ARBs) block angiotensin II receptors which result in a decrease in aldosterone.

5**-Spironolactone** and other **aldosterone receptor blockers**, which prevents aldosterone from acting on its receptors.

❑**N.B. Sympathomimetics which activates renal beta receptors can cause increase in both angiotensin and aldosterone levels.**



Beta blockers inhibits renin release

Disorders in mineralocorticoid secretion

1- Mineralocorticoid deficiency (e.g., certain types of Addison's disease and congenital adrenal hyperplasia).

➢Hyponatremia, hyperkalemia, acidosis, muscle weakness, irregular heartbeat, and abnormal blood pressure.

2- Mineralocorticoid excess (Hyperaldosteronism) caused by **a primary tumor** in the adrenal gland (**Conn syndrome**) or over dosage of synthetic mineralocorticoids.

➢Hyperaldosteronism can lead to **hypokalemia**, metabolic **alkalosis**, increased plasma volume, and **hypertension**.

Mineralocorticoid agonists

❑ **Used mainly as hormonal replacement for adrenal insufficiency**

A- Natural:

1- **Aldosterone**; **potent** mineralocorticoid & negligible glucocorticoid activity.

2- **Cortisol** (**hydrocortisone**); it has mineralocorticoid activity equals to Glucocorticoid activity.

3- **Deoxycorticosterone** (a weak mineralocorticoid) had some importance therapeutic uses in the past. Not used now for humans.

B- Synthetic: Examples

1- Prednisolone; it has **more glucocorticoid** than mineralocorticoid effect (5:1).

2-Fludrocortisone has a very potent mineralocorticoid activity with **little glucocorticoid action.**

Therapeutic uses of mineralocorticoids:

1- **Congenital adrenal hyperplasia (Adrenogenital syndrome).**

2- **Addison's disease**: **Hydrocortisone** is used.

3- **Orthostatic hypotension**

Fludrocortisone

- It is the **most widely used mineralocorticoid** therapeutically.

Adverse effects:

_**Hypertension**, Hypernatremia, **Edema**, cardiac enlargement, and **Hypokalemia**

Mineralocorticoid antagonists

1- Spironolactone

- **It blocks both aldosterone and androgen receptors.**
- Its onset of action is slow, and the effects last for 2–3 days after the drug is discontinued.

Uses of spironolactone:

1-Treatment of **primary hyper-aldosteronism.**

2- Used as a **potassium sparing diuretic** (with other diuretics) in the treatment of **hypertension** and **edema.**

3- Treatment of **hepatic edema** and **ascites**.

4- Treatment of **heart failure** (**anti-remodeling action**). Spironolactone can decrease mortality in cardiac failure patients

5- Treatment of **acne** and **hirsutism**.

Adverse effects of spironolactone:

1- **Hyperkalemia (dangerous in renal impairment)**

2- Cardiac **arrhythmia**.

3- Hormonal disturbances like **menstrual irregularities**, **gynecomastia**, and **impotence.**

2- Eplerenone:

- It is **selective aldosterone receptor antagonist** with little effects on androgen receptors.
- The risk of hormonal disturbances like menstrual abnormalities, gynecomastia, and impotence is less than spironolactone.

3- **Finerenone**, **a novel non-steroidal aldosterone antagonist**, is approved for the treatment of hypertension & heart failure.

4- Amiloride and triamterene are medications that block the sodium channels on the luminal side of the principal cells within the kidney. They **block the functions of aldosterone**.

➢They prevents sodium absorption and prevent potassium excretion.

Therefore, possible side effects to all of these medications are Hyponatremia, hyperkalemia, and hypovolemia.


THANK YOU!