بسم الله الرحمن الرحيم

Pharmacology of mineralocorticoids & their antagonists

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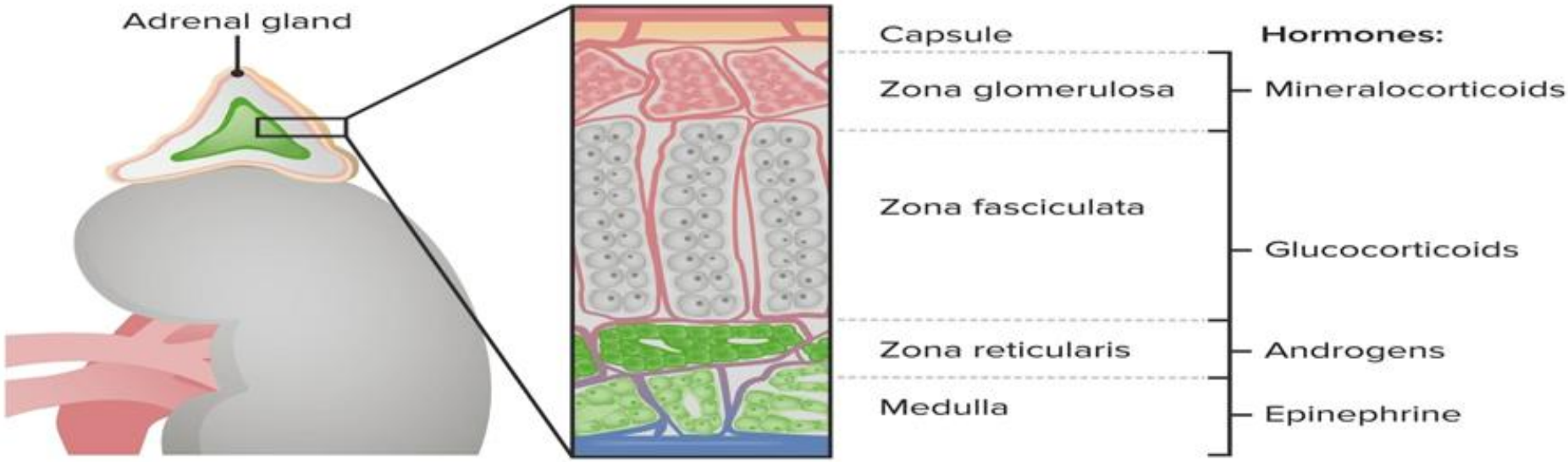
INTRODUCTION

❑The adrenal cortex releases a large number of steroids (corticosteroids) into the circulation. The hormonal steroids may be classified as:

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, their release is regulated by:

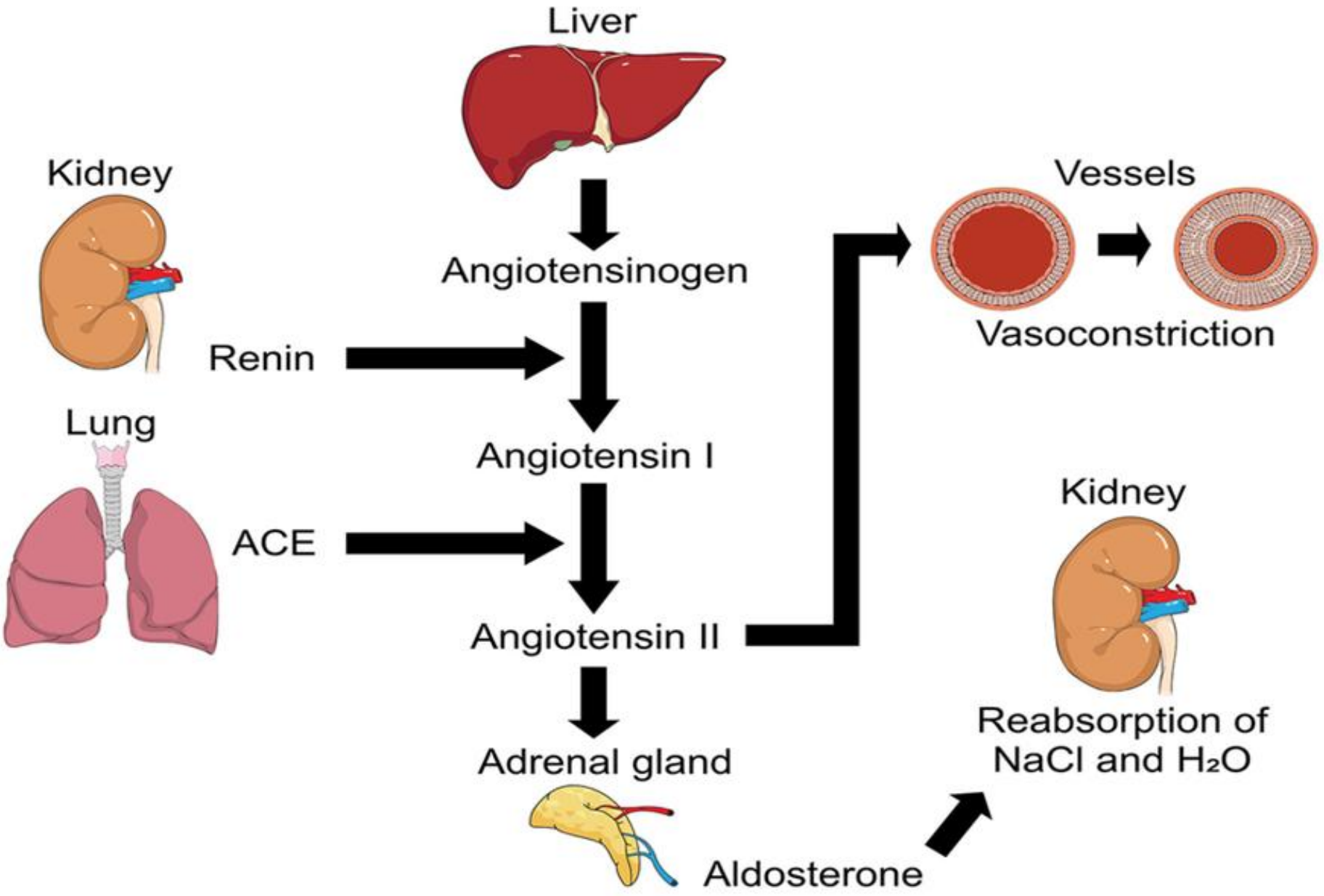
1-**ACTH** produces a moderate stimulation of Aldosterone release, but aldosterone doesn't cause any significant feedback control of ACTH secretion.

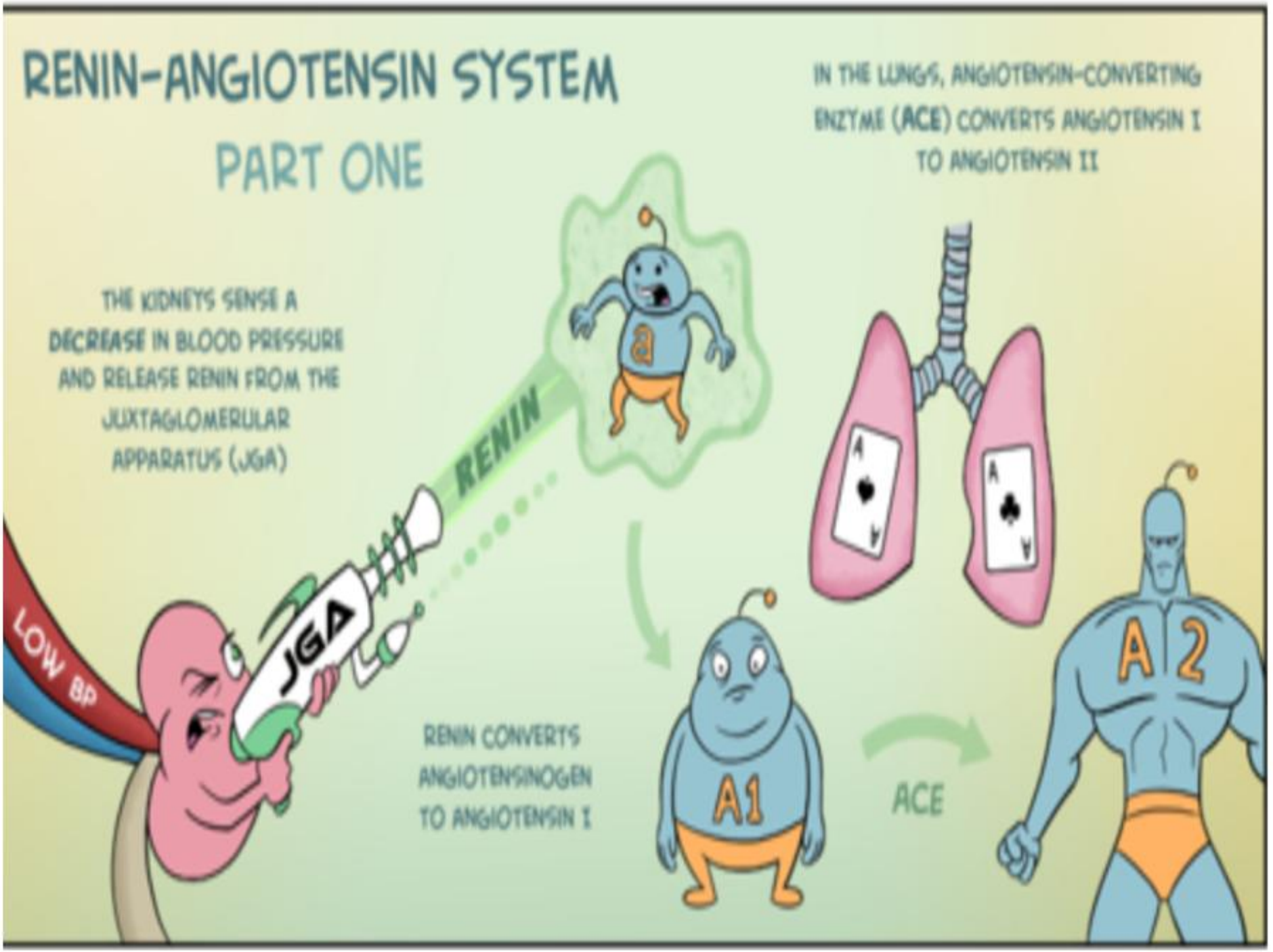
- Without ACTH, aldosterone secretion falls to about half the normal rate, indicating that other factors.

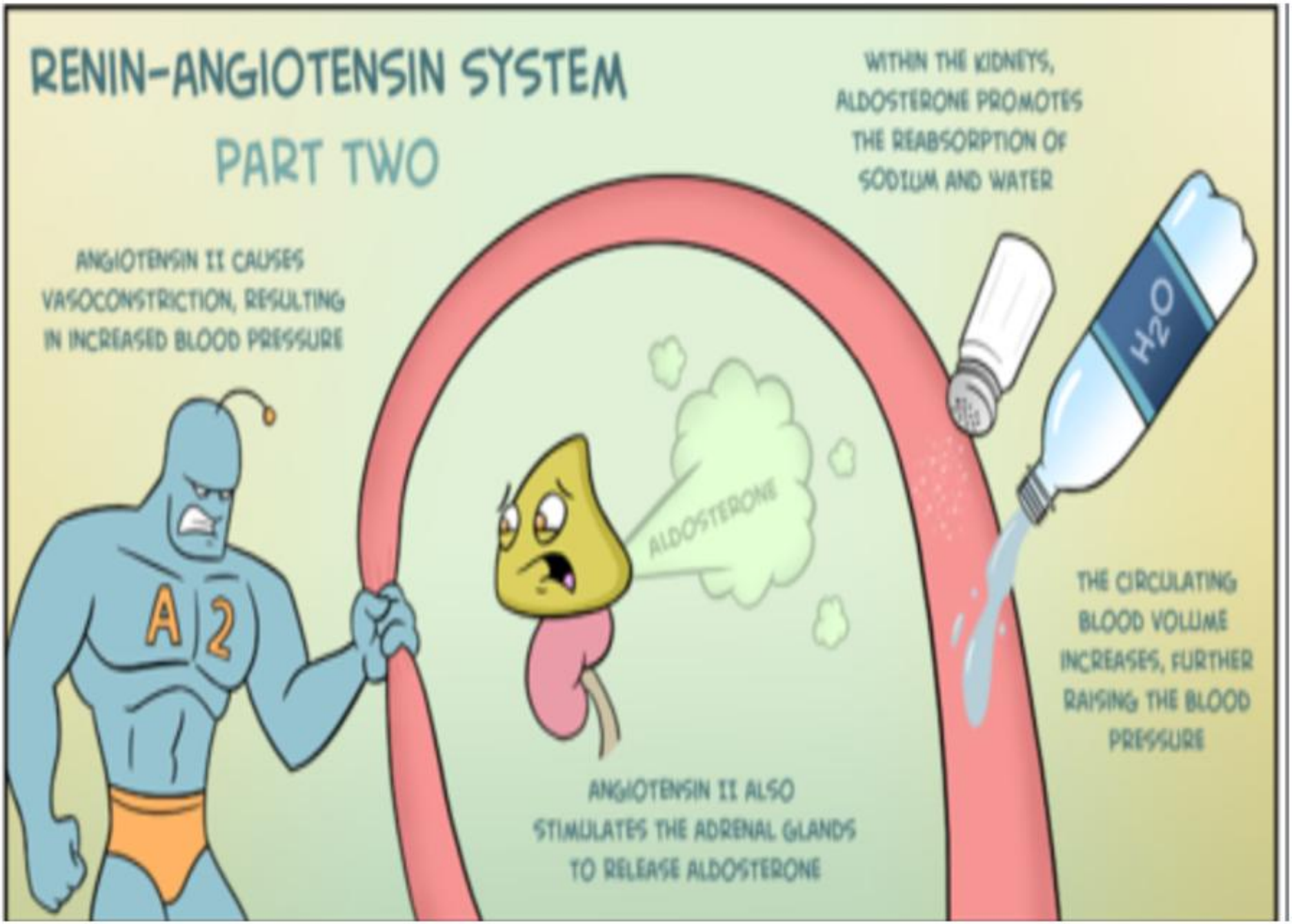
2- **Angiotensin II**, regulate aldosterone secretion. See **Renin Angiotensin Aldosterone system** (RAAS).

3- Local **potassium** levels.

Renin Angiotensin Aldosterone system (RAAS)

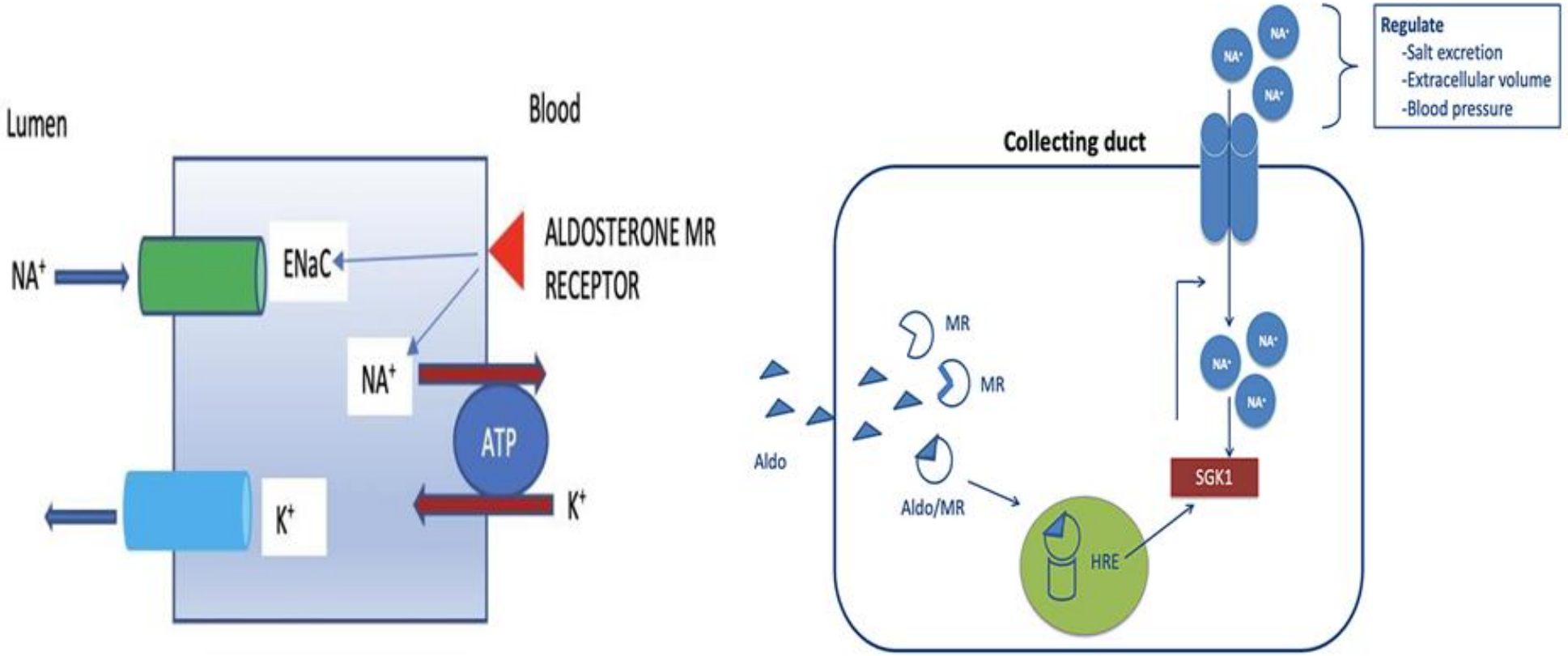



RENIN-ANGIOTENSIN SYSTEM
PART ONE
THE KIDNEYS SENSE A DECREASE IN BLOOD PRESSURE AND RELEASE RENIN FROM THE JUXTAGLOMERULAR APPARATUS (JGA)
LOW BP
JGA
RENIN
a
RENIN CONVERTS ANGIOTENSINOGEN TO ANGIOTENSIN I
A1
ACE
IN THE LUNGS, ANGIOTENSIN-CONVERTING ENZYME (ACE) CONVERTS ANGIOTENSIN I TO ANGIOTENSIN II
A2


RENIN-ANGIOTENSIN SYSTEM
PART TWO
ANGIOTENSIN II CAUSES VASOCONSTRICTION, RESULTING IN INCREASED BLOOD PRESSURE
WITHIN THE KIDNEYS, ALDOSTERONE PROMOTES THE REABSORPTION OF SODIUM AND WATER
A2
ALDOSTERONE
H2O
ANGIOTENSIN II ALSO STIMULATES THE ADRENAL GLANDS TO RELEASE ALDOSTERONE
THE CIRCULATING BLOOD VOLUME INCREASES, FURTHER RAISING THE BLOOD PRESSURE

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) on 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) Aldosterone stimulates 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.

Medications affecting aldosterone

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

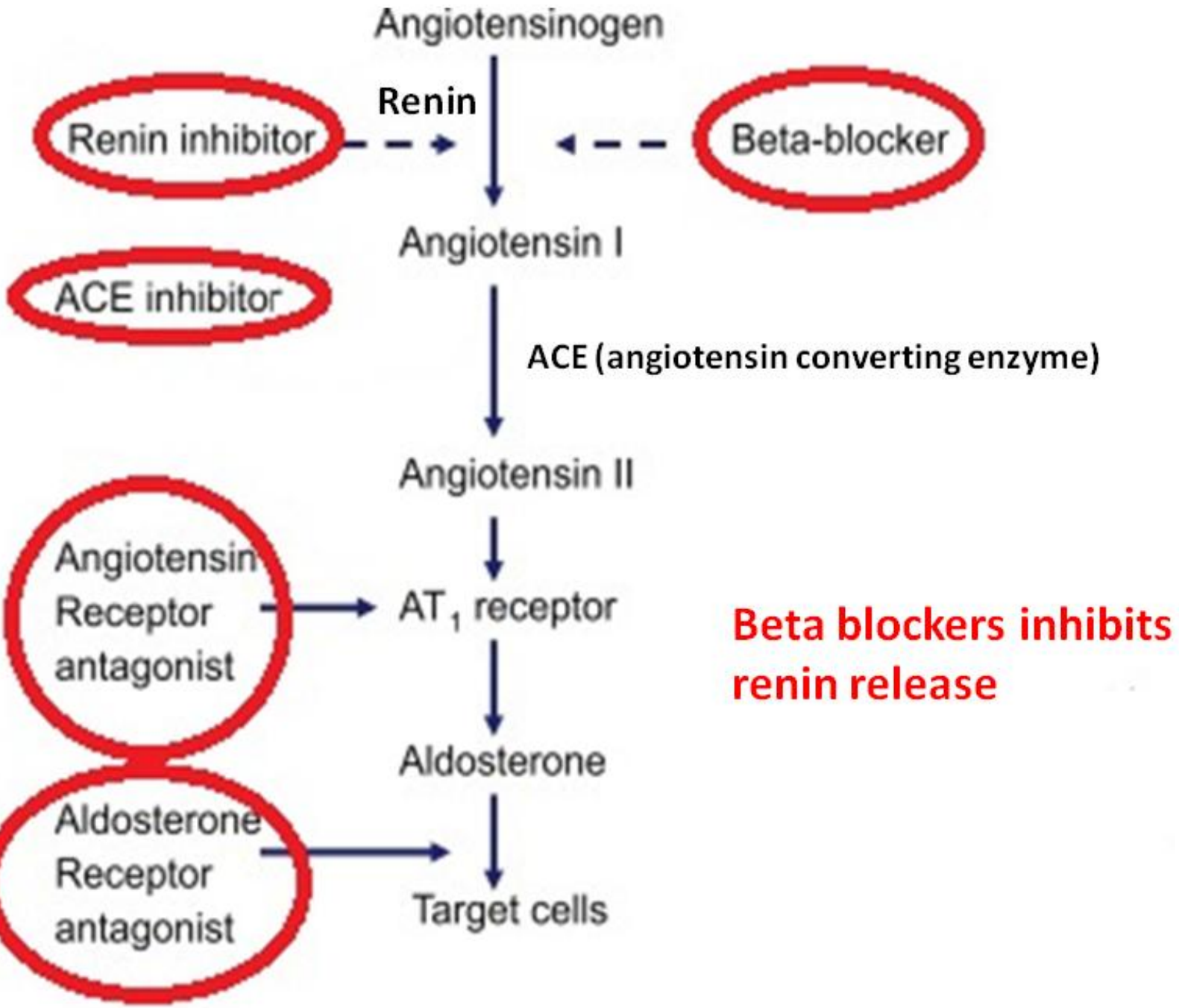
2- **Direct renin inhibitors** will decrease both angiotensin and aldosterone.

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**.

❑ Elevation of aldosterone levels occurs with continuous activation of (RAAS System), in patients suffering from **heart failure**.

❑ Elevated levels of aldosterone had growth-promoting effects and can activates fibroblasts and can cause **fibrosis** (remodeling) in many organ systems including the **heart and blood vessels**.

➢ Elevated aldosterone levels in patients suffering from liver failure can lead to edema and ascites.

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- Treatment of congenital adrenal hyperplasia (**Adrenogenital syndrome**).

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

3- Pharmacotherapy of orthostatic **hypotension**, , the use of synthetic mineralocorticoids, such as fludrocortisone acetate which reduces sodium loss and promotes water retention. IV fluids and sympathomimetics can help also.

	Glucocorticoid	Mineralocorticoid
Cortisol (hydrocortisone)	1	1
Prednisolone	4	0.8
Dexamethasone	30	Negligible
Betamethasone	30	Negligible
Aldosterone	0	80
Fludrocortisone	10	125

Fludrocortisone

It is the most widely used mineralocorticoid therapeutically.

Pharmacokinetics

- Oral absorption of fludrocortisone is rapid and complete.
- The volume of distribution of fludrocortisone is **80 – 85 L.**
- Distribution into CSF appears minimal.
- Fludrocortisone is **70-80% protein bound** in plasma, mostly to **albumin** and corticosteroid-binding globulin.
- Fludrocortisone is a metabolized by the CYP3A family. Strong inhibitors/inducers of CYP3A should be avoided.
- About 80% of an administered dose of fludrocortisone is excreted in the urine, & the other 20% is eliminated biliary in stool.

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.** Spironolactone decrease potassium loss in urine induced by other diuretics.

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**.

4- Gastrointestinal disturbances.

5- Skin rashes.

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. It has beneficial **anti-inflammatory**, **anti-remodeling** & **anti-fibrotic properties** in the kidneys, heart, and blood vessels.

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.

N.B-Drospirenone, a progestin, is an oral contraceptive and also antagonizes the effects of aldosterone.


THANK YOU!