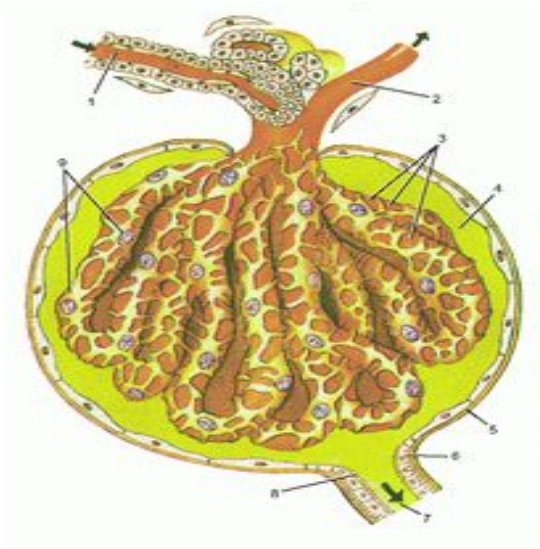
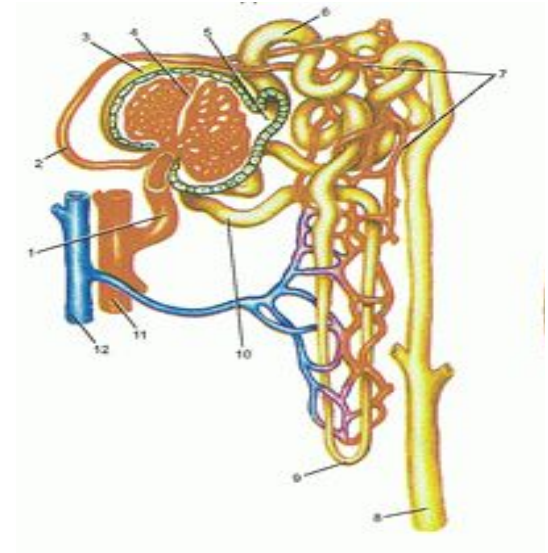




Drugs affecting water-salt metabolism

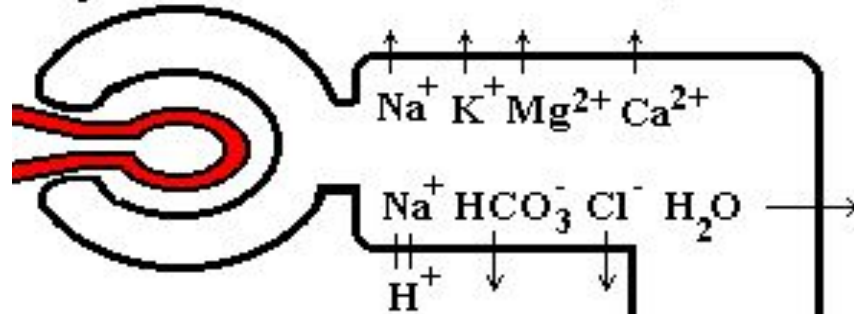
Diuretics



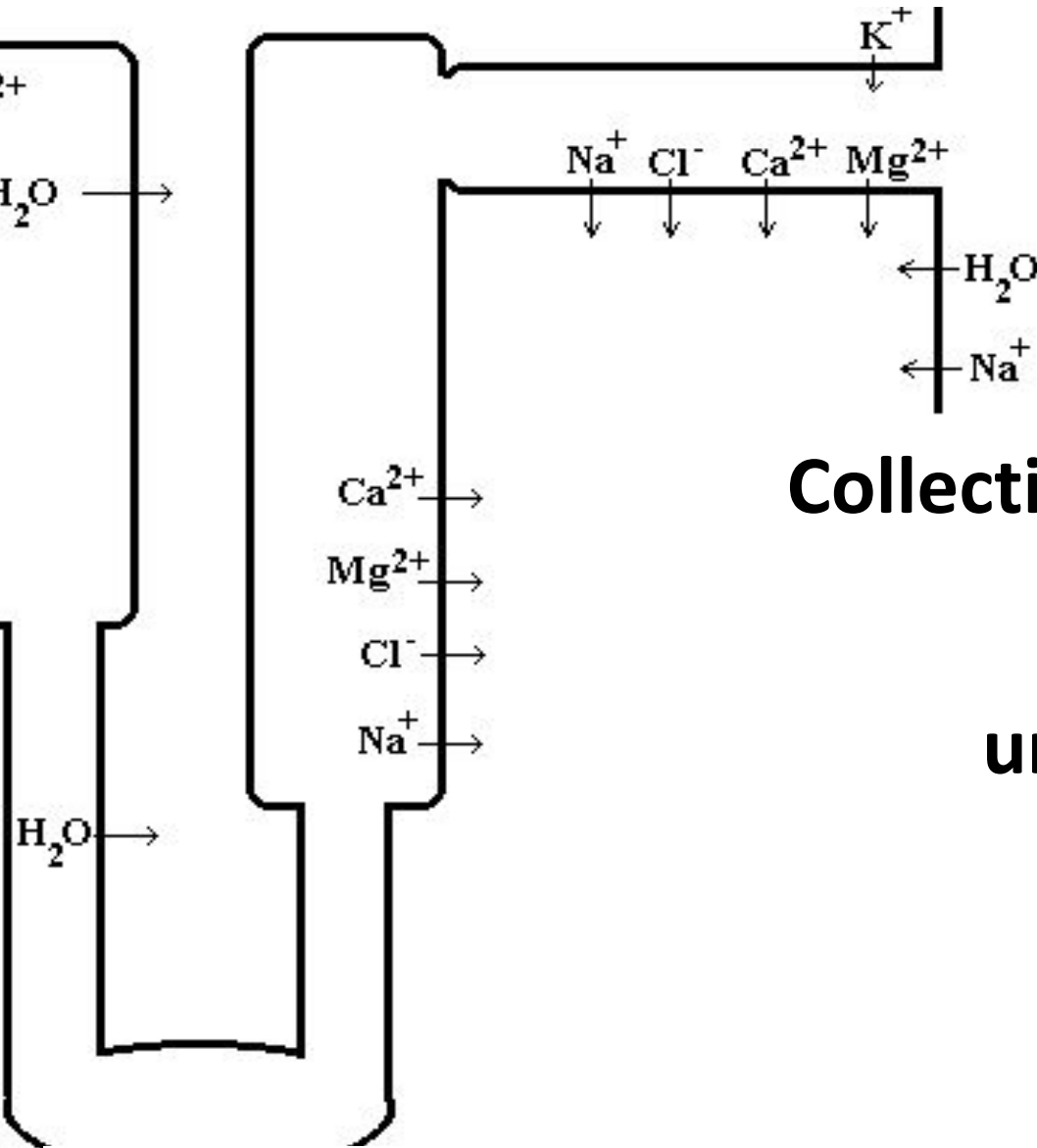
- ❑ Diuretics excrete excess water and ions from the body. They increase diuresis. Urine formation includes 3 processes: glomerular filtration, tubular reabsorption and secretion.
- ❑ Filtration of blood plasma takes place in capillary glomerulus and its capsule. Almost all components of plasma pass through the pores, but proteins, substances bound to these proteins and lipids can not pass. The daily volume of glomerular filtrate is about 170 l. Only 1.5 l is excreted as urine.
- ❑ The process of reabsorption and secretion occurs throughout all segments of the nephron: proximal tubules, Henle's loop, distal tubules and collecting tubules/ducts.

glomerulus

Distal convoluted tubules



Proximal convoluted tubules



Henle's loop

Collecting tubules

urine

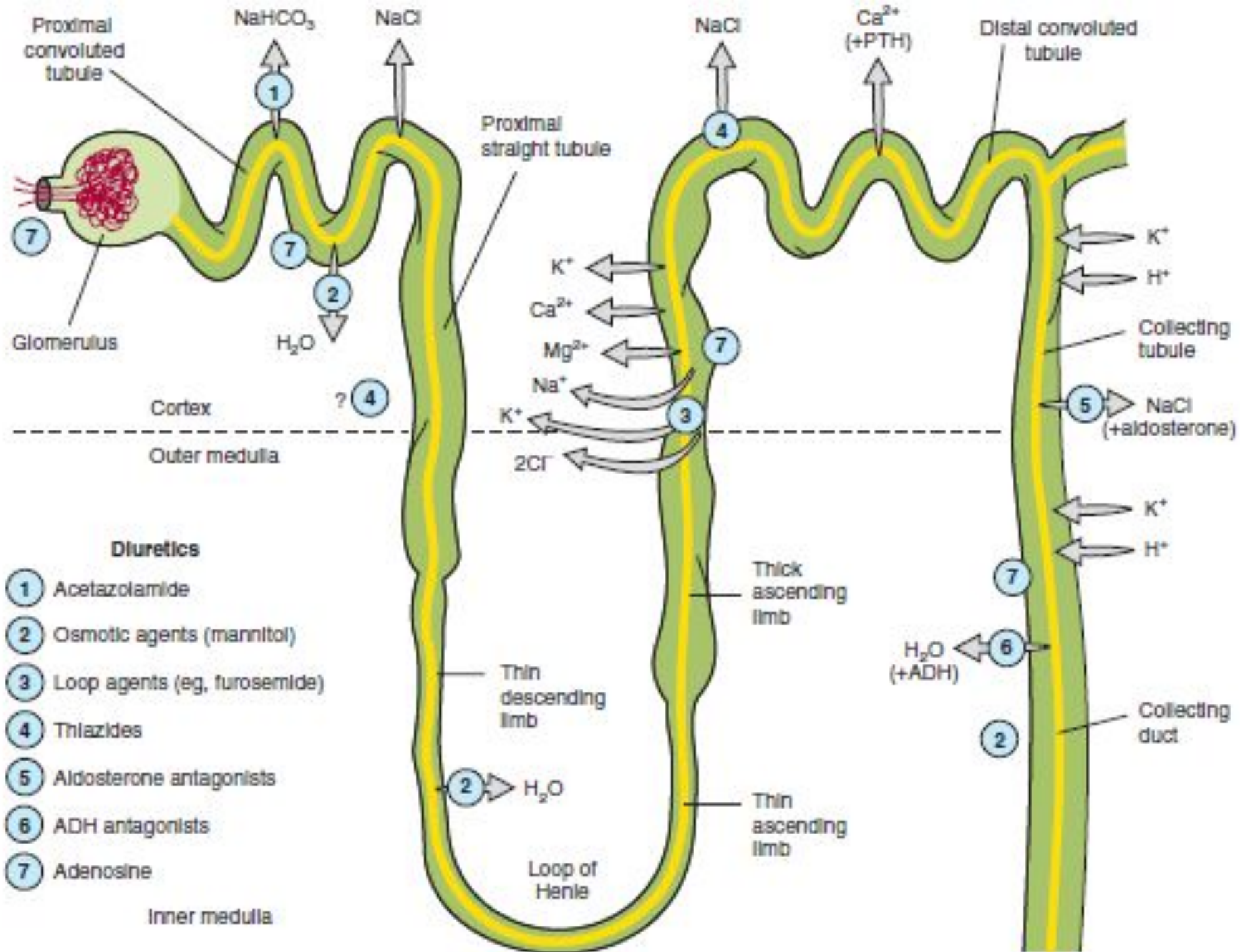
Mechanisms of reabsorption of Na and H₂O

- ATP-dependent membrane pump sodium in the proximal and distal tubules.
- Exchange sodium for H⁺, formed with the participation of carbonic anhydrase ($\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2$) and dehydrogenases in the proximal and distal tubules.
- Energy-dependent chloride pump in the thick segment of the ascending part of loop of Henle
- Aldosterone-dependent sodium reabsorption in the distal tubule and collecting tubule/ducts.
- The vasopressin-dependent reabsorption of water in collecting tubules/ducts.

Classification according to the localization and mechanism of action

1. Drugs that increase glomerular filtration (hydruretics):
aminophylline, cardiac glycosides
2. Drugs affecting the epithelium of the tubules –
saluretics (↓ reabsorption of ions):
 - Proximal convoluted tubules: **acetazolamide** (blocker of carbonic anhydrase)
 - Loop diuretics: **furosemide** (Lasix), **torasemid**

- ❑ Proximal and distal convoluted tubules:
hydrochlorothiazide, clopamide, cyclomethiazidum, indapamide
- ❑ Potassium-sparing diuretics (distal convoluted tubule and collecting tubules/ducts): **triamterene, spironolactone** (antagonist of aldosterone)
- ❑ Drugs affecting most of the segments of the renal tubules: **mannitol** (osmotic diuretic)



Classification according the power of action

- **The most active diuretics** (reduce the reabsorption of sodium by 10-25%): loop diuretics, osmotic diuretics
- **Less active diuretics** (reduce the reabsorption of sodium by 5 – 10%): thiazides, indapamide
- **Weak diuretics** (decrease reabsorption of sodium by 1 - 3%): spironolactone, triamterene

Classification

according speed of onset and duration of action:

- ❑ **Rapid and short-acting** (the effect after a few minutes, lasts several hours): loop diuretics, osmotic diuretics.
- ❑ **The average speed and the duration of effect** (1-2 hours, lasts up to a day): thiazides, “non-thiazide”, triamterene.
- ❑ **Slow and long-acting** (the action in a few days, lasts for several days): spironolactone.

Indications for diuretics

Emergency:

- ☐ Pulmonary edema, edema of brain, larynx
- ☐ Acute heart failure
- ☐ Acute renal failure
- ☐ Hypertensive crisis
- ☐ An acute attack of glaucoma
- ☐ Forced diuresis in acute poisoning

Non-emergency:

- Chronic heart, renal failure (chronic kidney disease)
- Glaucoma, increased intracranial pressure
- Hypertensive disease
- Epilepsy
- Cirrhosis

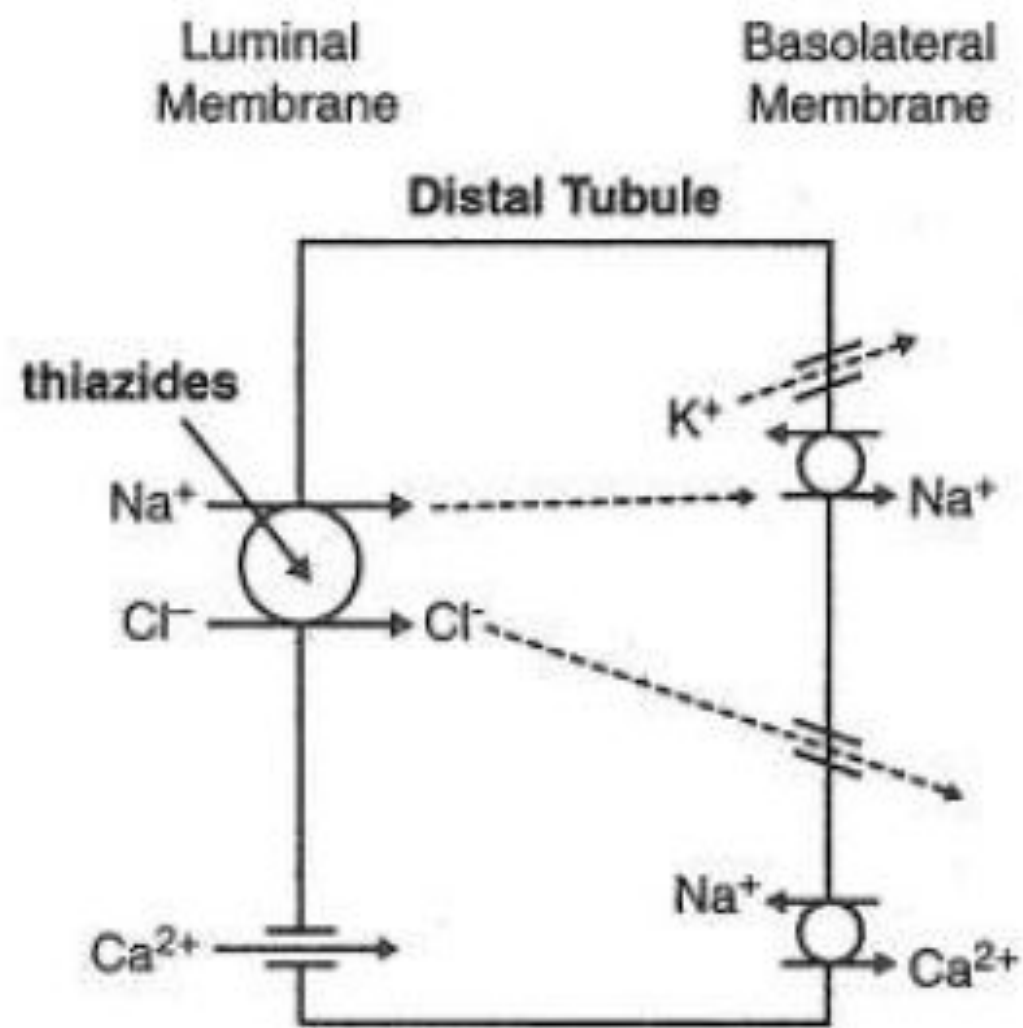
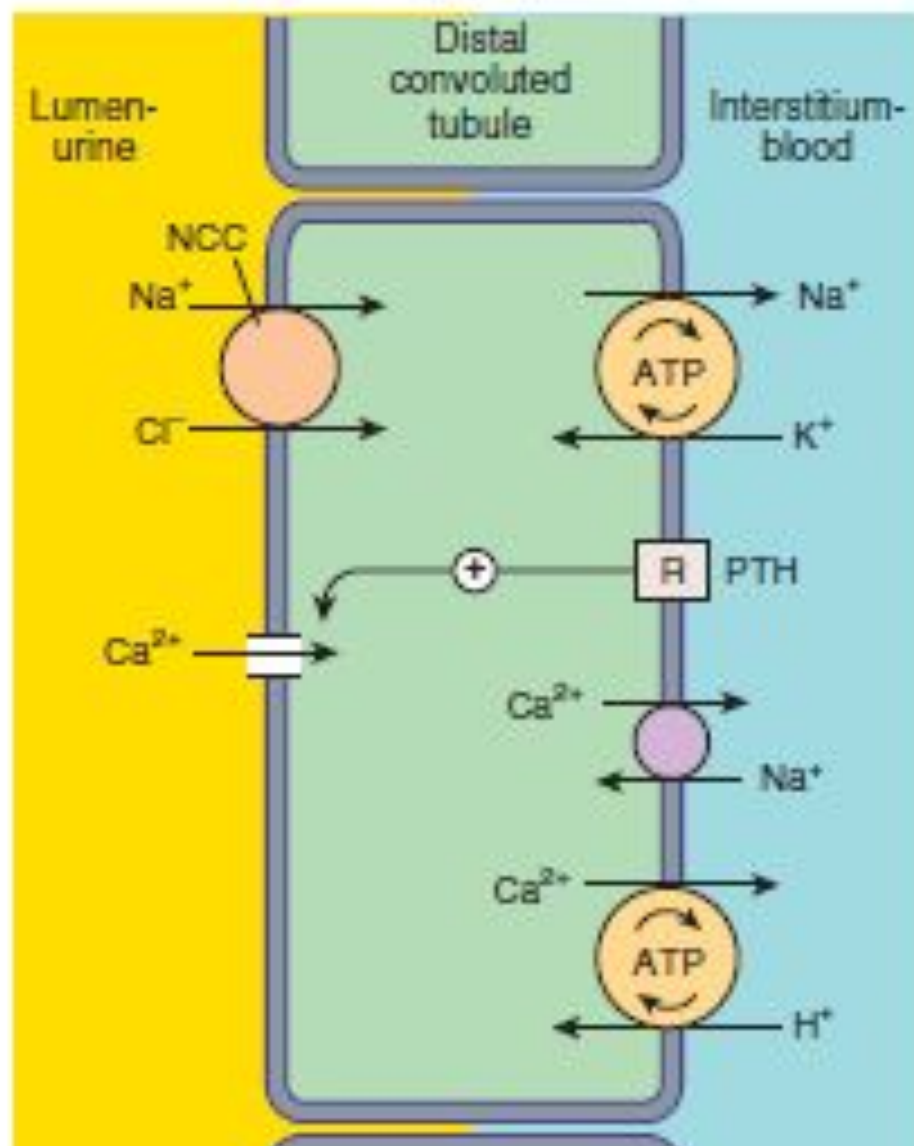
❑ **Hydrochlorothiazide** is a derivate of thiazide. It suppresses reabsorption of sodium and chlorine ions mostly in the early part of the distal tubules, because it inhibits Na^+/Cl^- transport system. It slightly inhibits carbonic anhydrase in the proximal tubules and decreases the reabsorption of bicarbonate.

❑ It enhances potassium and magnesium secretion, but delays excretion of calcium ions.

❑ It decreases blood pressure because it reduces blood volume and increases the elasticity of the vascular wall.

❑ It is used orally as a diuretic and hypotensive agent. It is used also for the treatment of glaucoma, hypercalcuria, in the treatment of diabetes insipidus.

THIAZIDES

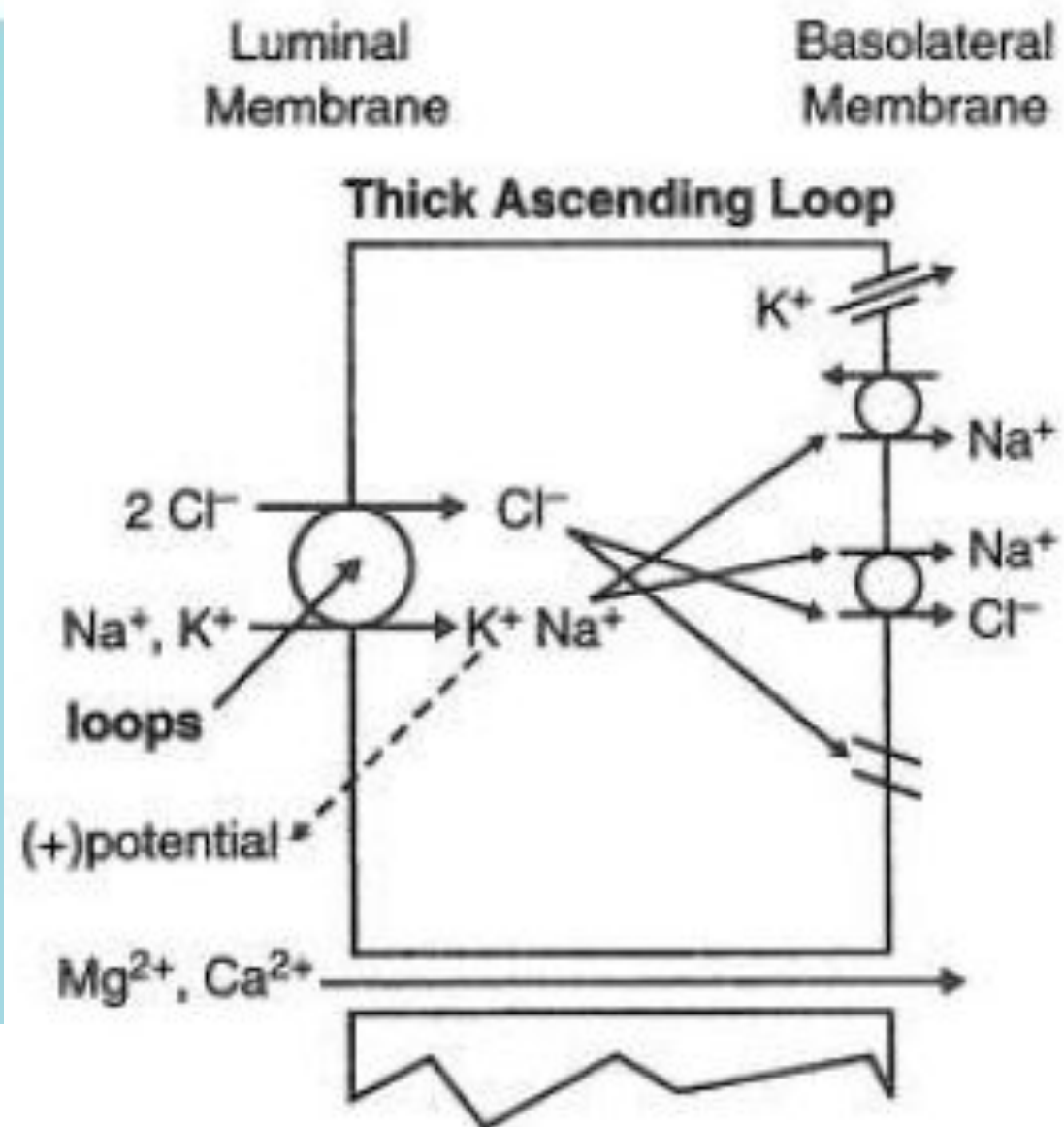
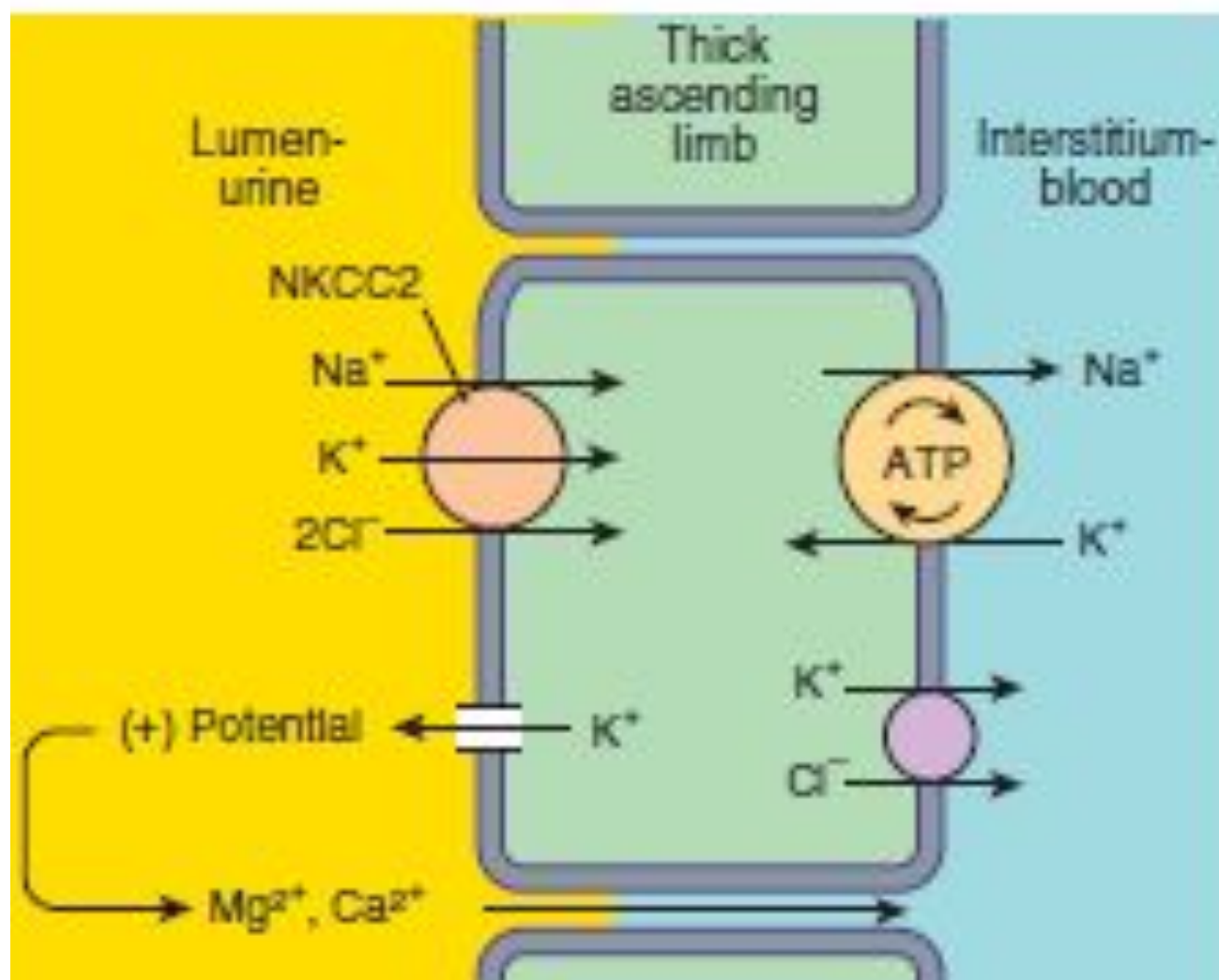


- ❑ The speed of onset of action – 0.5-1 h, duration of action – 8-12 h.
- ❑ The main side effects are hypokalemia, hypomagnesemia. Prevention and treatment of these condition are based on administration of drugs containing K^+ and Mg^{2+} (potassium chloride, “Asparcam”, “Pananginum”).
- ❑ Other adverse effects: hypochloraemic metabolic alkalosis, hyperuricaemia, hyperglycaemia, hyperlipidemia, nausea, vomiting, fatigue.

- ❖ **Cyclomethiazidum** is 50 times as active as hydrochlorothiazide.
- ❖ **Clopamide** acts slowly but longer. The drug begins to act in 1-2 h, and its effect lasts for 24 h.
- ❖ **Indapamide** is used orally once a day for the treatment of arterial hypertension. **Indapamide** decreases blood pressure. The effect develops slowly. Possible side effects include hypokalemia, prolongation of Q-T (on ECG), allergic reaction. It does not cause hyperlipidemia.

- ❖ Furosemide is a very efficacious agent. Its effect begins in glomerulus because it increased the concentration of prostaglandins there. Furosemide inhibits active reabsorption of chlorine and sodium ions in the thick ascending limb of Henle's loop by blocking $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ transport system.
- ❖ Furosemide also reduces sodium absorption in the proximal tubules. It also enhances excretion of calcium and magnesium. It increases diuresis.
- ❖ It possesses moderate hypotensive activity.

LOOP DIURETICS



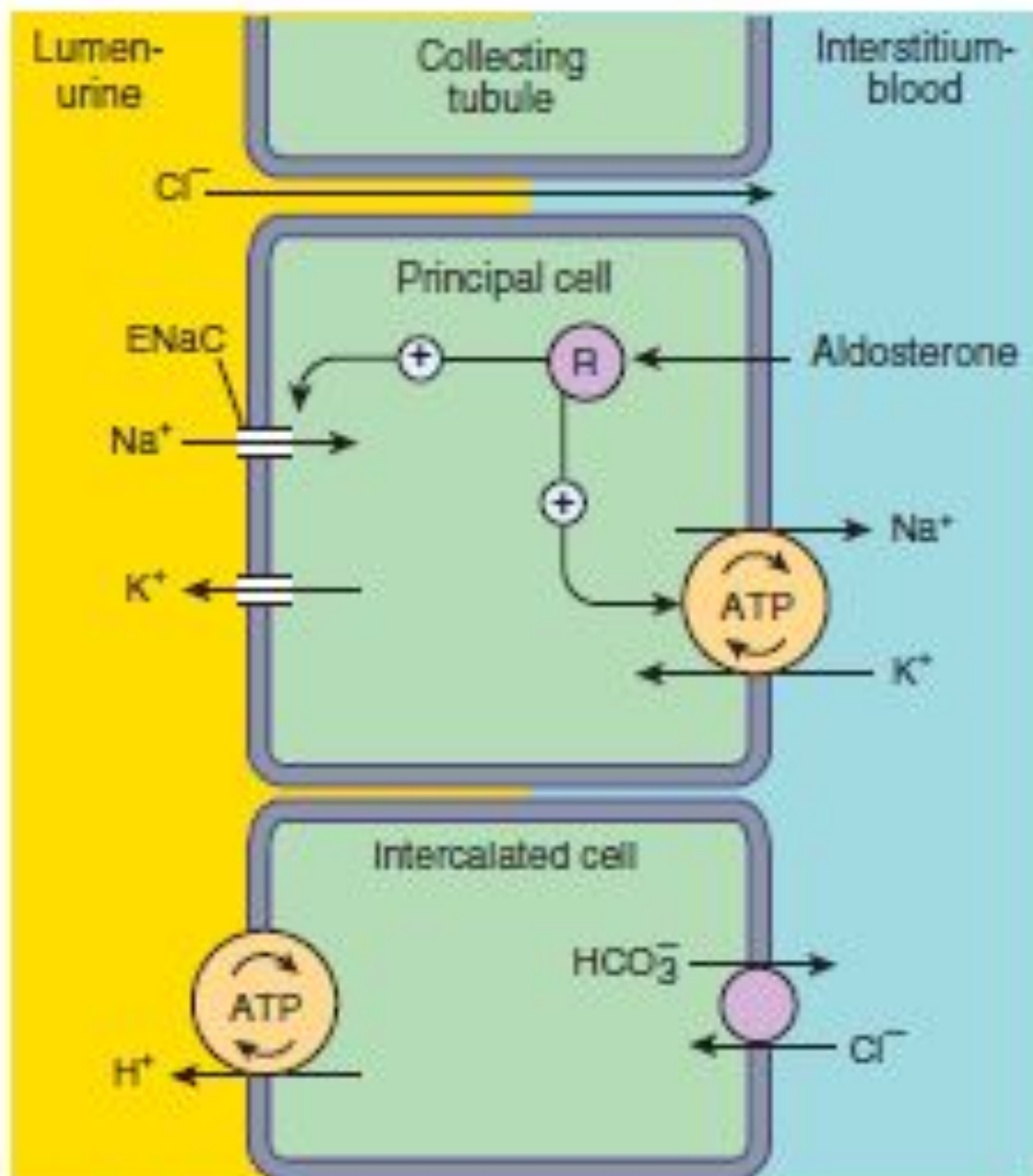
- ❖ When administered intravenously, the drug begins to act in 3-5 min after infusion. The effect lasts 1-2 h. In case of oral use the effect is observed after 20-30 min and is maintained for 3-4 h.
- ❖ It is used as a diuretic, antihypertensive drug.
- ❖ Indications for use: the treatment of pulmonary edema, brain edema, hypercalcaemia in case of ergocalciferol overdose or hyperparathyroidism. It is used to provide forced diuresis in cases of acute poisoning.
- ❖ Adverse effects: potassium depletion, hypomagnesemia, hypokalemic metabolic alkalosis, dyspepsia, headache, hearing disorder, hyperglycemia, hyperuricemia, dizziness, allergic reactions.

- Torasemide's effect lasts longer. Maximal effect develops in 2-3 h. The duration of effect is 6-8 h.
- It is prescribed when edema are caused by chronic heart failure, kidneys failure, hepatic failure. It is used for the treatment of arterial hypertension. It is taken orally once a day.
- Adverse effects: hypokalemia, hyperuricemia, increased creatinine and urea in blood plasma, thrombocytopenia, dryness in a mouth, vertigo, allergic reaction.

- **Triamterene** is a “potassium-and magnesium-sparing diuretic”. It retain potassium and magnesium in the body.
- The main sites of action are the collecting tubules and the distal tubules. The agent reduces permeability of sodium channels. So it decreases the reabsorption of sodium and chlorine ions. It increases the elimination of uric acid also. It is mild diuretic. It is usually administered in a combination with the potent potassium depleting drugs.
- Side effects: dyspepsia, headache, dizziness, hyperkalemia, azotemia, leg cramps.

✓ Spironolactone is an antagonist of mineralocorticoid aldosterone. It eliminates its effects on renal tubular function. Aldosterone decreases sodium ion excretion but increases potassium secretion. These processes take place in the distal renal tubules and the collecting ducts. Spironolactone blocks receptors of aldosterone. It enhances excretion of sodium and chlorine ions and water.

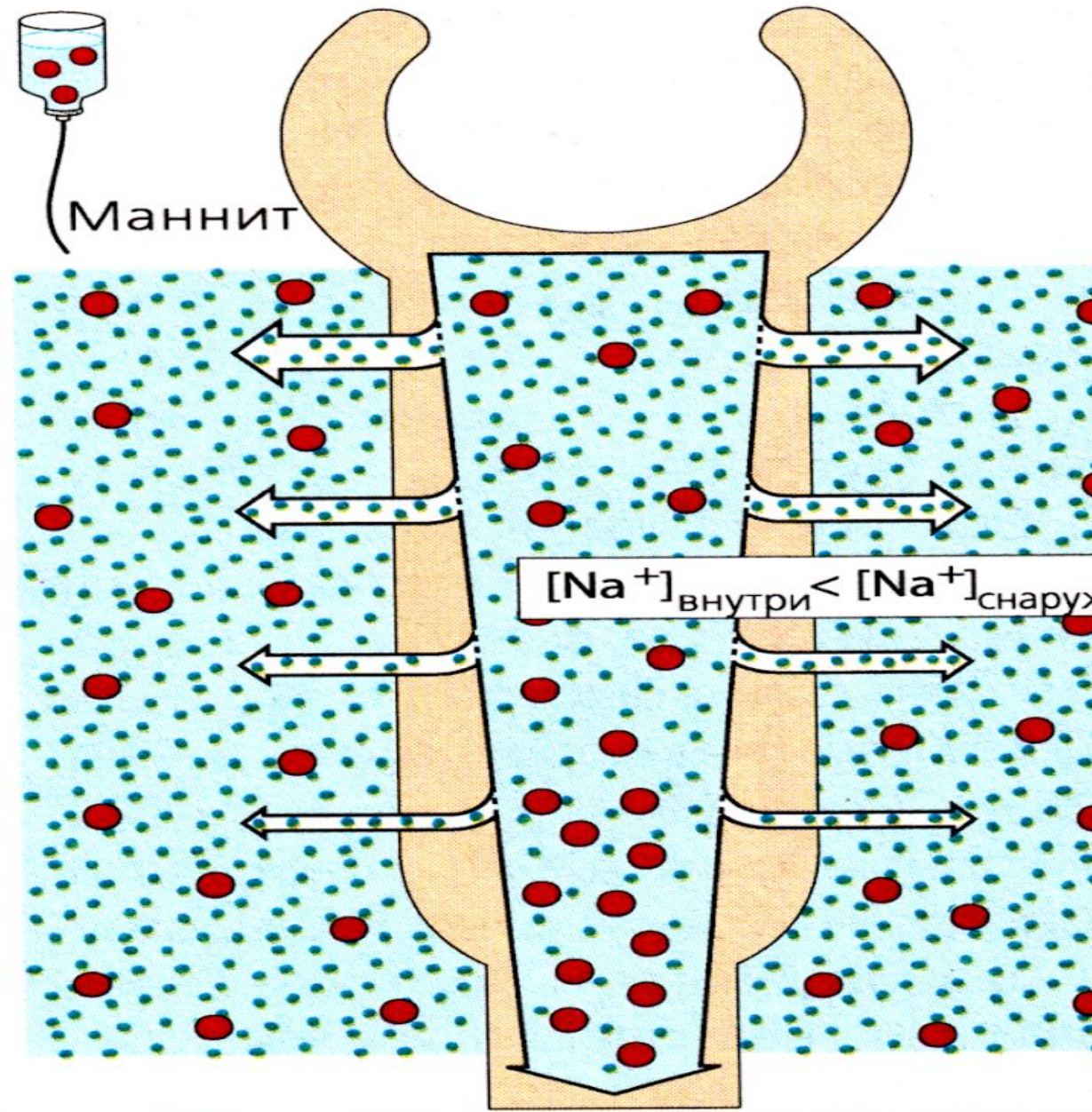
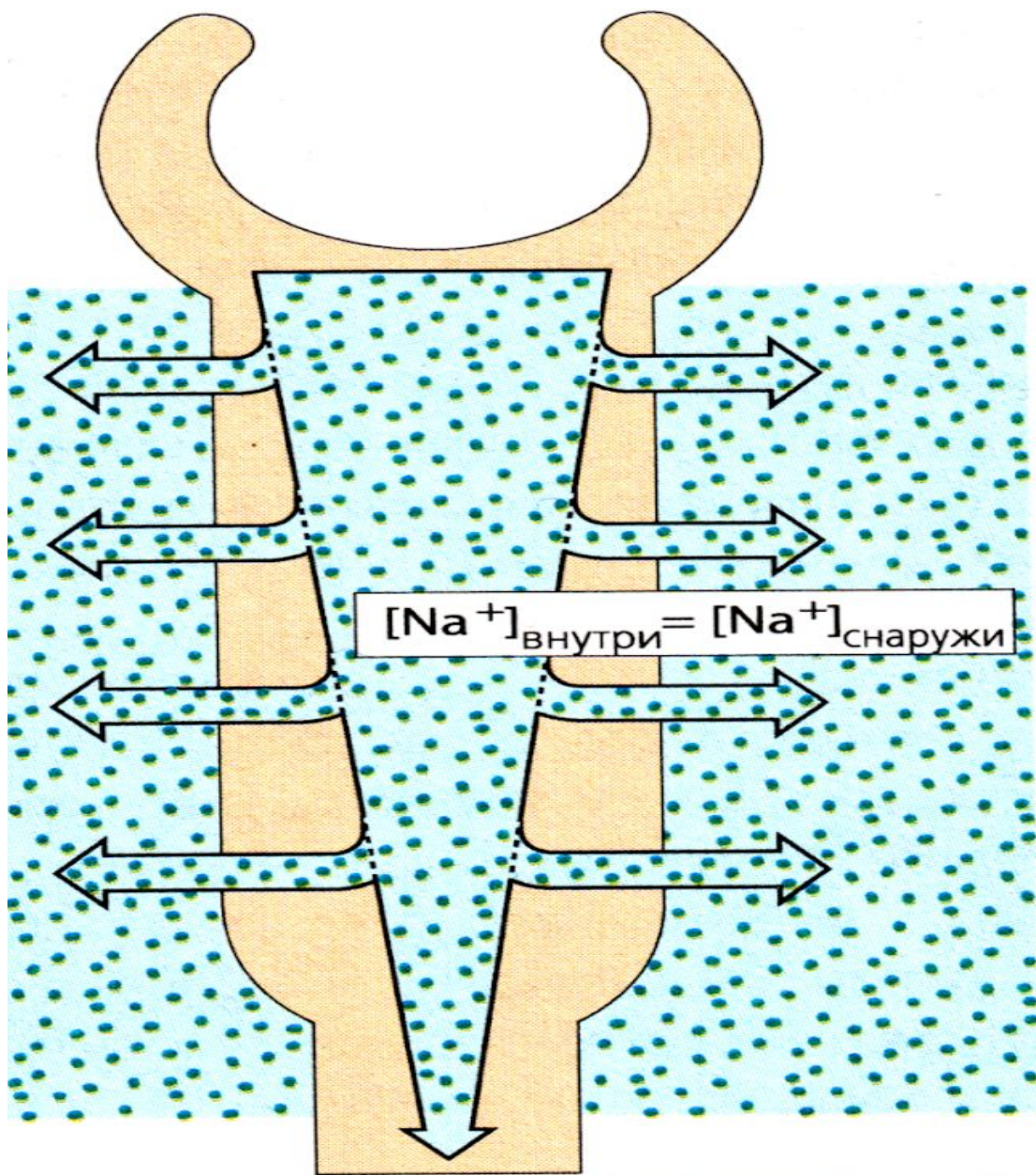
✓ Spironolactone diminishes secretion of potassium ions. It also spares magnesium.



- ✓ It is a weak diuretic. It is effective in cases of edema that resulted from aldosterone overproduction.
- ✓ Its effect develops slowly. It is administered orally together with diuretics causing hypokalemia.
- ✓ Side effects: dizziness, sleepiness, skin rashes, hyperkalemia, gynecomastia.

- **Mannitol** is osmotic diuretic. Its effect begins in blood. It is injected intravenously and it increases osmotic pressure in the blood. So fluid from the tissues enters the bloodstream. Mannitol increases the circulating blood volume.
- Mannitol reaches renal tubules lumen, causes a rise of osmotic pressure. The reabsorption of the water is considerably diminished. So reabsorption of sodium is diminished also. Mannitol acts in the proximal, distal tubules, descending limb of Henle's loop.

- Mannitol is used as a diuretic, as a dehydrating agent in the treatment of brain edema, glaucoma (reducing intraocular pressure), in the treatment of acute poisoning.
- The side effects: headache, nausea, vomiting, dizziness, chest pain.
- Mannitol is contraindicated in patients with impaired renal function, high blood pressure, heart failure.



- Euphylline is xanthine derivate. It has a vasodilating effect. It increases renal blood flow and glomerular filtration rate.
- It impairs reabsorption of sodium and chlorine ions in the proximal and distal tubules, slightly increases calcium excretion. It is a weak diuretic, and it is used as broncholytic.

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