

Odessa National Medical University

**Department of general and clinical pharmacology
and pharmacognosy**

DIURETICS

EDEMA

- ➡ **Edema, also spelled oedema,**
- ➡ **fluid retention, dropsy, hydropsy and swelling, is the build-up of fluid in the body's tissue**
- ➡ **Most commonly, the legs or arms are affected**
- ➡ **Symptoms may include skin which feels tight, the area may feel heavy, and joint stiffness**
- ➡ **Other symptoms depend on the underlying cause**

EDEMA

Causes may include

- ➔ venous insufficiency
- ➔ heart failure
- ➔ kidney problems
- ➔ low protein levels
- ➔ liver problems
- ➔ deep vein thrombosis
- ➔ **infections, angioedema**
- ➔ **certain medications**
- ➔ lymphedema
- ➔ **It may also occur after prolonged sitting or standing and during menstruation or pregnancy**
- ➔ **The condition is more concerning if it starts suddenly, or pain or shortness of breath is present**

EDEMA



EDEMA

Treatment depends on the underlying cause

If the underlying mechanism involves sodium retention, decreased salt intake and a diuretic may be used

Elevating the legs and support stockings may be useful for edema of the legs

Older people are more commonly affected

The word is from the Greek οίδημα oídēma meaning 'swelling'

EDEMA

Examples of edema in specific organs:

Peripheral edema (dependent edema of legs) is extracellular fluid accumulation in the legs. This can occur in otherwise healthy people due to hypervolemia or maintaining a standing or seated posture for an extended period of time

It can occur due to diminished venous return of blood to the heart due to congestive heart failure or pulmonary hypertension

It can also occur in patients with increased hydrostatic venous pressure or decreased oncotic venous pressure, due to obstruction of lymphatic or venous vessels draining the lower extremity

Certain drugs (for example, amlodipine) can cause pedal edema

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EDEMA

Examples of edema in specific organs:

Cerebral edema is extracellular fluid accumulation in the brain. It can occur in toxic or abnormal metabolic states and conditions such as systemic lupus or reduced oxygen at high altitudes. It causes drowsiness or loss of consciousness, leading to brain herniation and death.

Pulmonary edema occurs when the pressure in blood vessels in the lung is raised because of obstruction to the removal of blood via the pulmonary veins.

This is usually due to failure of the left ventricle of the heart. It can also occur in altitude sickness or on inhalation of toxic chemicals. Pulmonary edema produces shortness of breath. Pleural effusions may occur when fluid also accumulates in the pleural cavity.

EDEMA

Examples of edema in specific organs:

Edema may also be found in the cornea of the eye with glaucoma, severe conjunctivitis, keratitis, or after surgery. Affected people may perceive coloured haloes around bright lights.

Edema surrounding the eyes is called periorbital edema (puffy eyes) .

The periorbital tissues are most noticeably swollen immediately after waking, perhaps as a result of the gravitational redistribution of fluid in the horizontal position.

Common appearances of cutaneous edema are observed with mosquito bites, spider bites, bee stings (wheal and flare), and skin contact with certain plants such as poison ivy or western poison oak the latter of which are termed contact dermatitis.

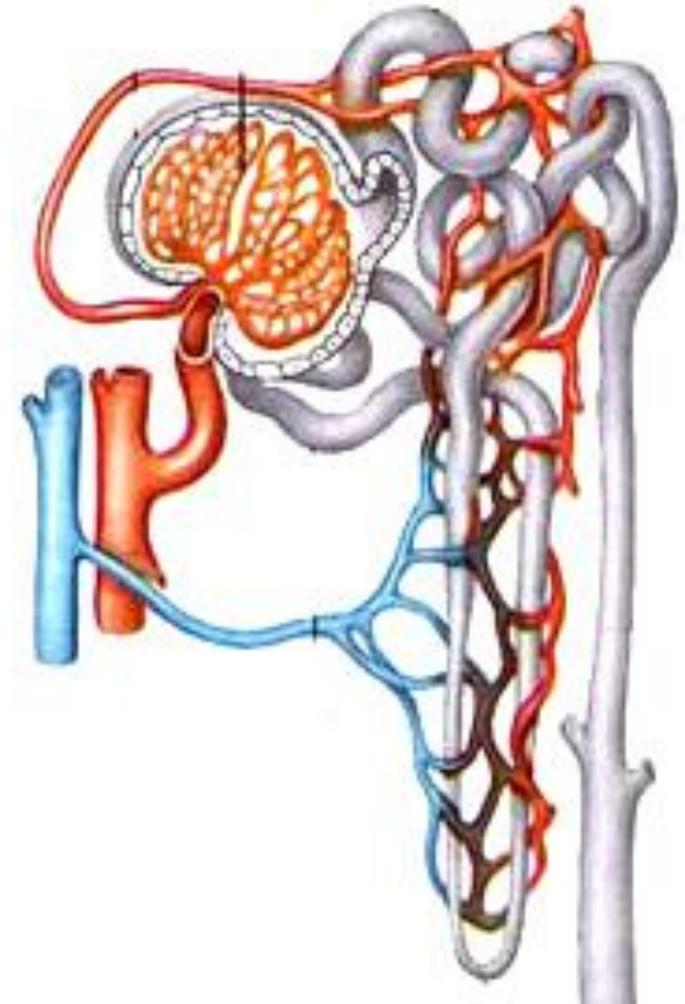


DIURETICS

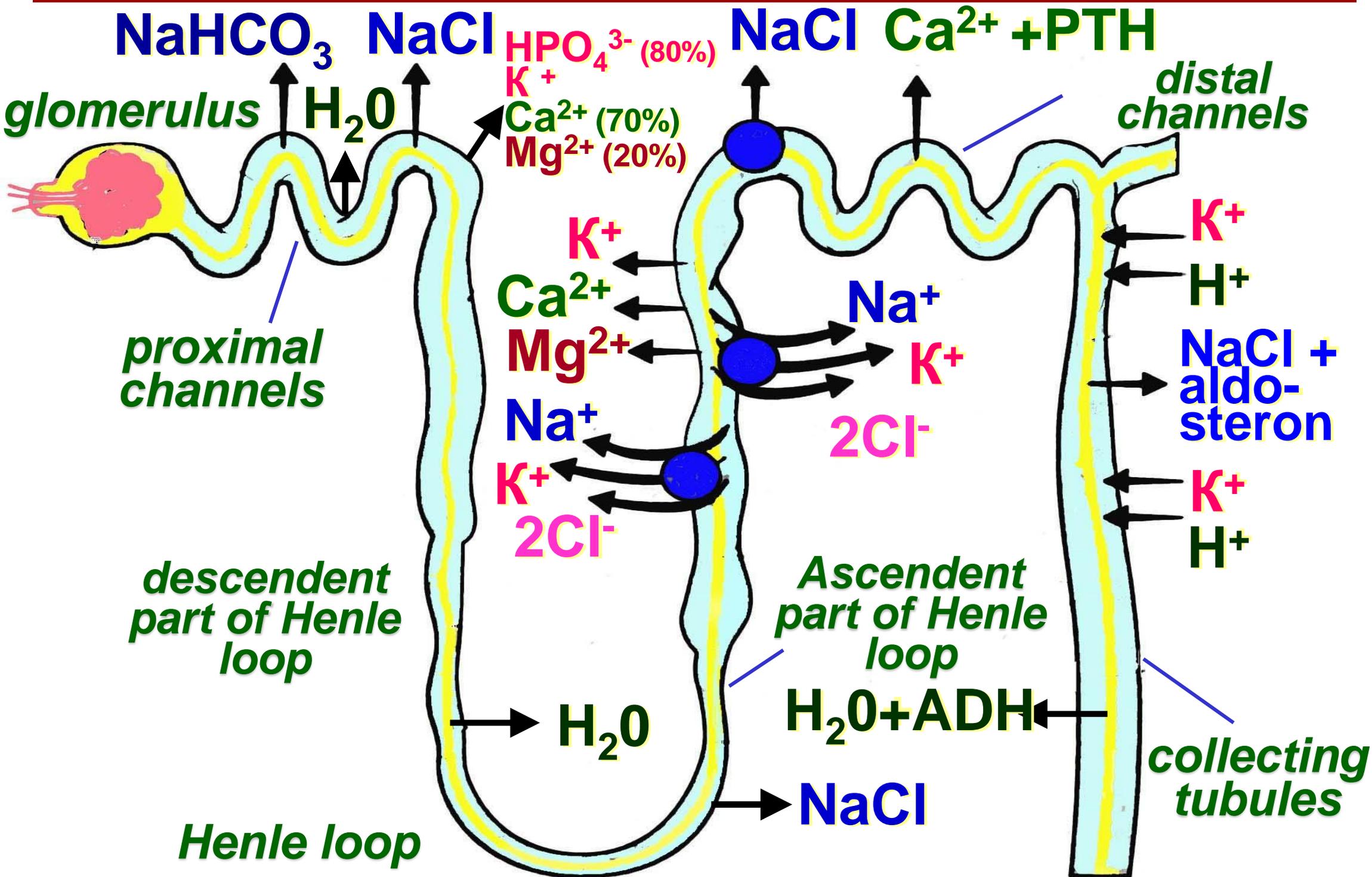
Agents of plant origin, non-organic and organic
increase diuresis

via:

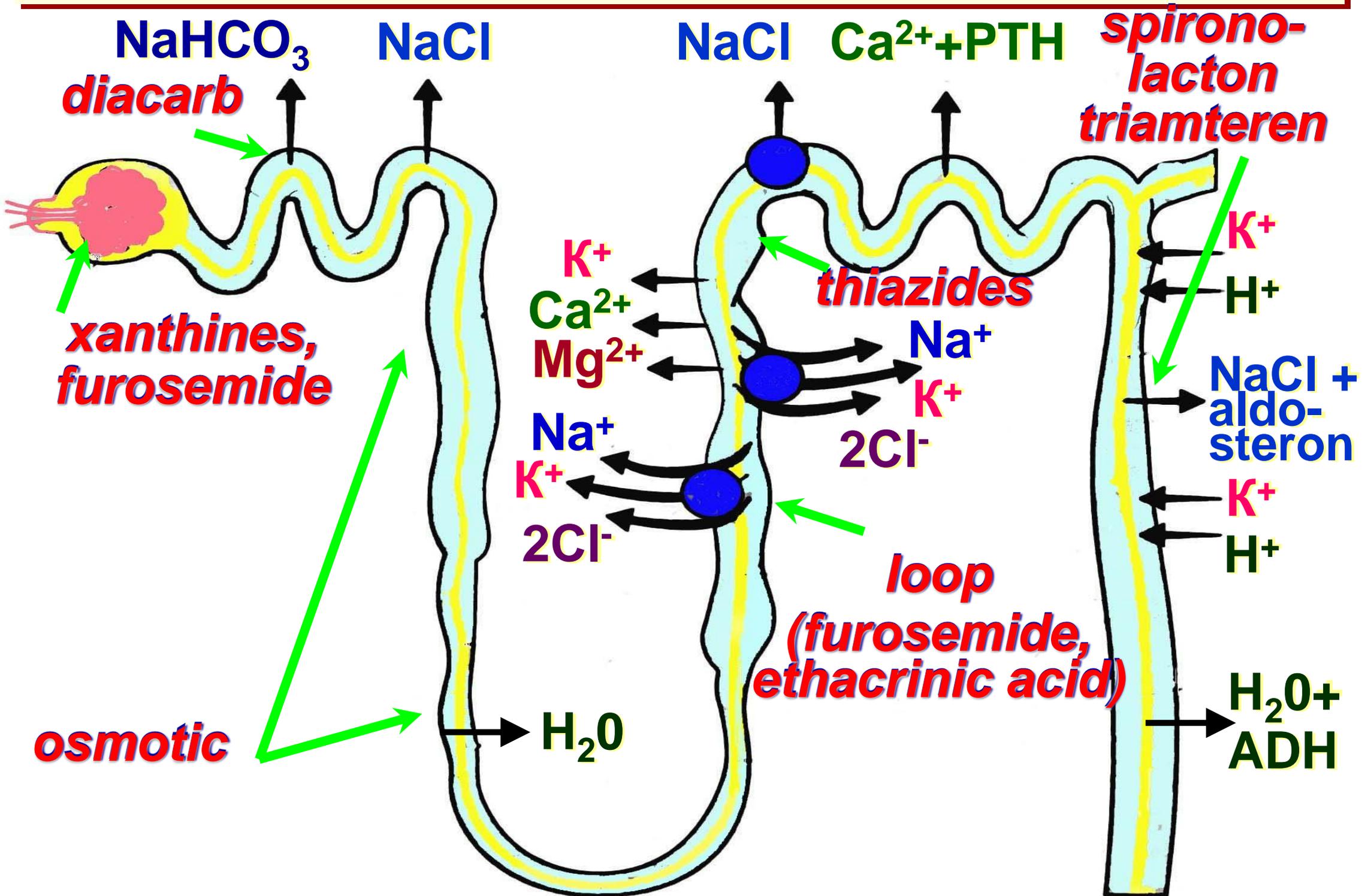
enhancement of filtration
(production of primary urine),
inhibition of reabsorption
electolites (first of all Na^+ and Cl^-) and water in renal
channels (production of
secondary urine)



CANALICULUS SYSTEM OF KIDNEY



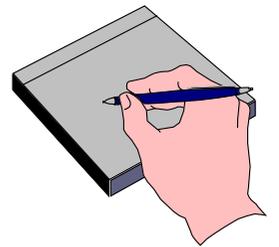
SITES OF DIURETICS ACTION



CLASSIFICATION OF DIURETICS

according to power of action (Na excretion,%):

- ▶ **strong acting:**
 - loop (15-25 %) – furosemide (lasix), ethacrinic acid (uregit), bufenox (brinaldix), torasemide
- ▶ **intermediate acting:**
 - ✓ thiazides and thiazide-like (5-10 %) – hydrochlorothiazide (hypothiazide), cyclomethiazide (navidrex), clopamide, indapamide
 - ✓ osmotic (5-8 %) – mannitol
- ▶ **weak acting (3-5 %):**
 - ✓ potassium-sparing – spironolacton, triamteren, amilorid
 - ✓ carbonic anhydrase inhibitors – diacarb (acetazolamide)
 - ✓ miscellaneous – xanthines, plant-origin



Xanthines

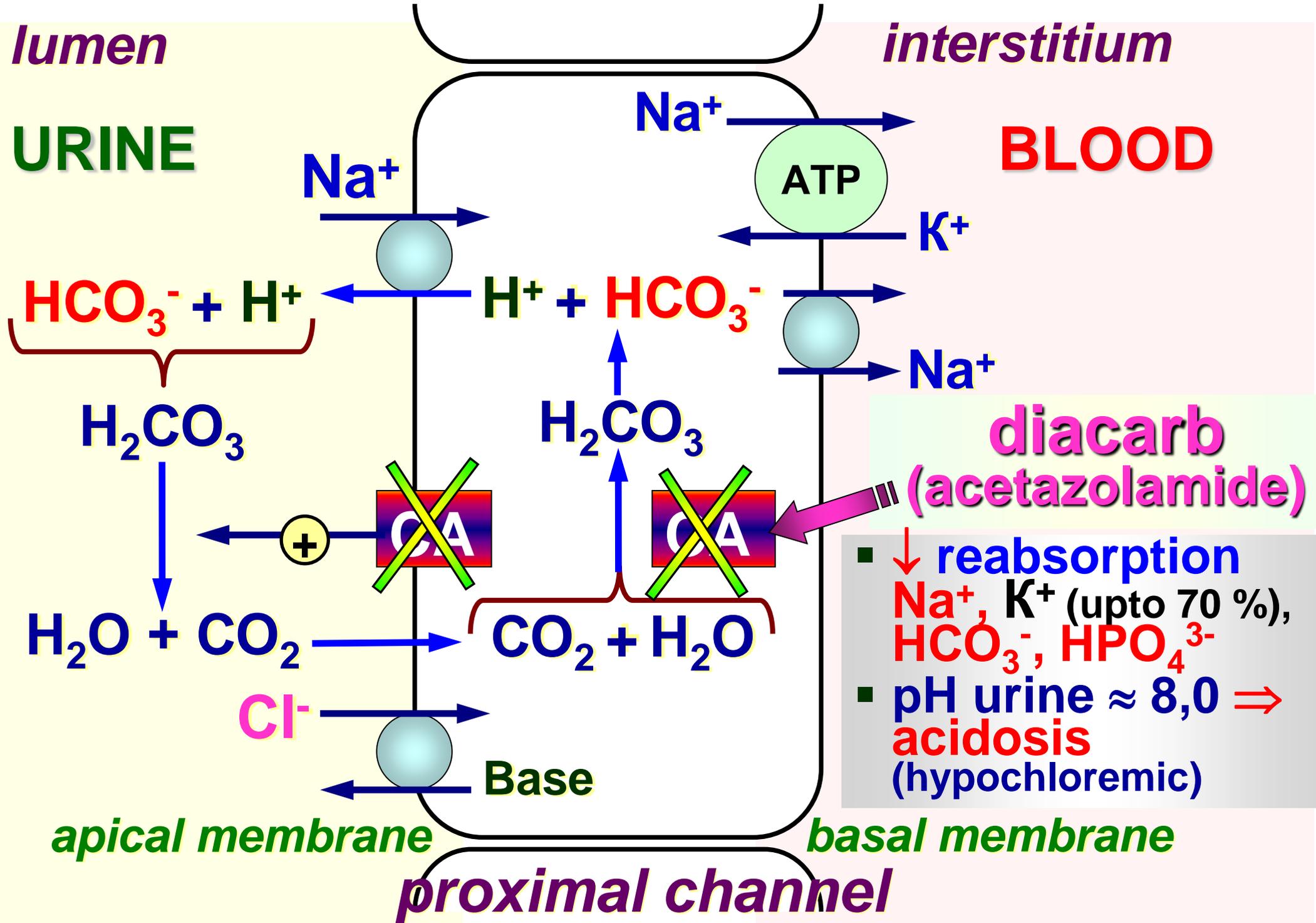
Aminophyllin (euphyllin), teophyllin

Mechanism of diuretic action:

- ❖ ↑ systemic and renal hemodynamics, remove spasm of renal arterioles, removing of renal arterioles spasm
- ❖ ↑ renal bloodflow
- ❖ ↑ glomerular filtration
- ❖ decreasing of contacts nephrocytes with urine, ↑ its flow through canaliculus
- ❖ ↑ number of functioning glomeruli
- ❖ ↓ reabsorption of sodium in proximal channels and water in descendent part of loop

Also possesses cardiostimulant, vasodilating, spasmolytic, broncholytic actions

CARBONIC ANHYDRASE INHIBITORS



CARBONIC ANHYDRASE INHIBITORS

indications:

- hypochloremic alkalosis
- Glaucoma
- hydrocephaly, epilepsy
- mountain sickness



adverse effects:

- hypokaliemia ! (drowsiness, paresthesia, paralytic ileus, nephropathy, arrhythmia)
- hyperchloremic acidosis
(3-4 days vacations in therapy !)
- Formation of phosphate stones in kidneys
- ↓ stomach acidosis
- allergy, agranulocytosis



OSMOTIC DIURETICS

mannit (mannitol), urea

mechanism of action

- **↑ renal bloodflow** (↑ production of vasodilator factor – prostoglandin E2, prostocyclin)
- **↑ osmotic pressure of urine** ⇒ **↓ reabsorbtion of water**
- **acts mainly in proximal channels, descendent part of Henle loop, as well as in collecting tubules**
- **moderately ↑ excretion Na^+ , H^+ , K^+ , Mg^{2+} , Ca^{2+} , Cl^- , HCO_3^- , phosphates**, could cause alkalosis and acidosis
- **dehydrative effect** ⇒ **↑ circulated blood volume**, that decreases in association with raising diuretic effect

OSMOTIC DIURETICS

Indications for mannit

- **cerebral edema** (almost immediate – on 60-90 % ↓ intracranial pressure)
- **acute poisoning** (enforced diuresis)
- **acute necrosis of renal channels** (in result of shock, hemolysis, poisoning)
- **acute glaucoma attack**

adverse effects

- ✓ **urea**, passes through histo-hematologic barriers (including BBB) and mannit in case of cranial trauma – **rebound phenomenon** (secondary cerebral edema, ↑ intracranial pressure)
- ✓ **urea** – irritating action on vein, necrosis at s.c. administration
- ✓ **overdosing** – significant dehydration with ↓ BP, thrombosis, thirsty, hallucinations

LOOP DIURETICS

URINE

Ascendant part
of Henle loop

BLOOD

symport

Na^+

K^+

2Cl^-

Na^+

ATP-
ase

K^+

furosemide,
ethacrinic acid

K^+

K^+

Cl^-

Mg^{2+} , Ca^{2+}

- ↓ reabsorption Na^+ , Cl^- , K^+ , Mg^{2+} , Ca^{2+} , H^+ , HCO_3^-
- ↓ tissue respiration
- ↑ synthesis of prostaglandins
- ⇒ ↑ renal bloodflow
- vasodilation of veins and arteries ⇒ ↓ BP and unloading of left ventriculus (like nitroglycerin)



INDICATIONS OF LOOP DIURETICS

- ❖ acute and chronic heart failure
- ❖ pulmonary edema
- ❖ cerebral edema
- ❖ liver cirrhosis with portal hypertension and ascites
- ❖ acute and chronic renal failure
- ❖ arterial hypertension, hypertonic emergency
- ❖ poisoning (enforce diuresis)
- ❖ glaucoma attack
- ❖ hypercalcemia crisis

ADVERSE EFFECTS OF LOOP DIURETICS

- hypokaliemia, hypocalciemia
- hypochloremic **alkalosis**
- dehydration, abrupt increasing of diuresis (6-10 l)
- orthostatic hypotension
- hyperglycemia
- ototoxicity (**disturbance of endolymph content**)
- gout relapse
- interstitial nephritis
- atherogenic
- acute pancreatitis (**rarely**)
- allergy, photosensibility
- leucopenia, thrombocytopenia

THIAZIDE DIURETICS

URINE

distal channels

BLOOD

symport

PTH

Na^+

P

Cl^-

Na^+

~~ATP-ase~~

K^+

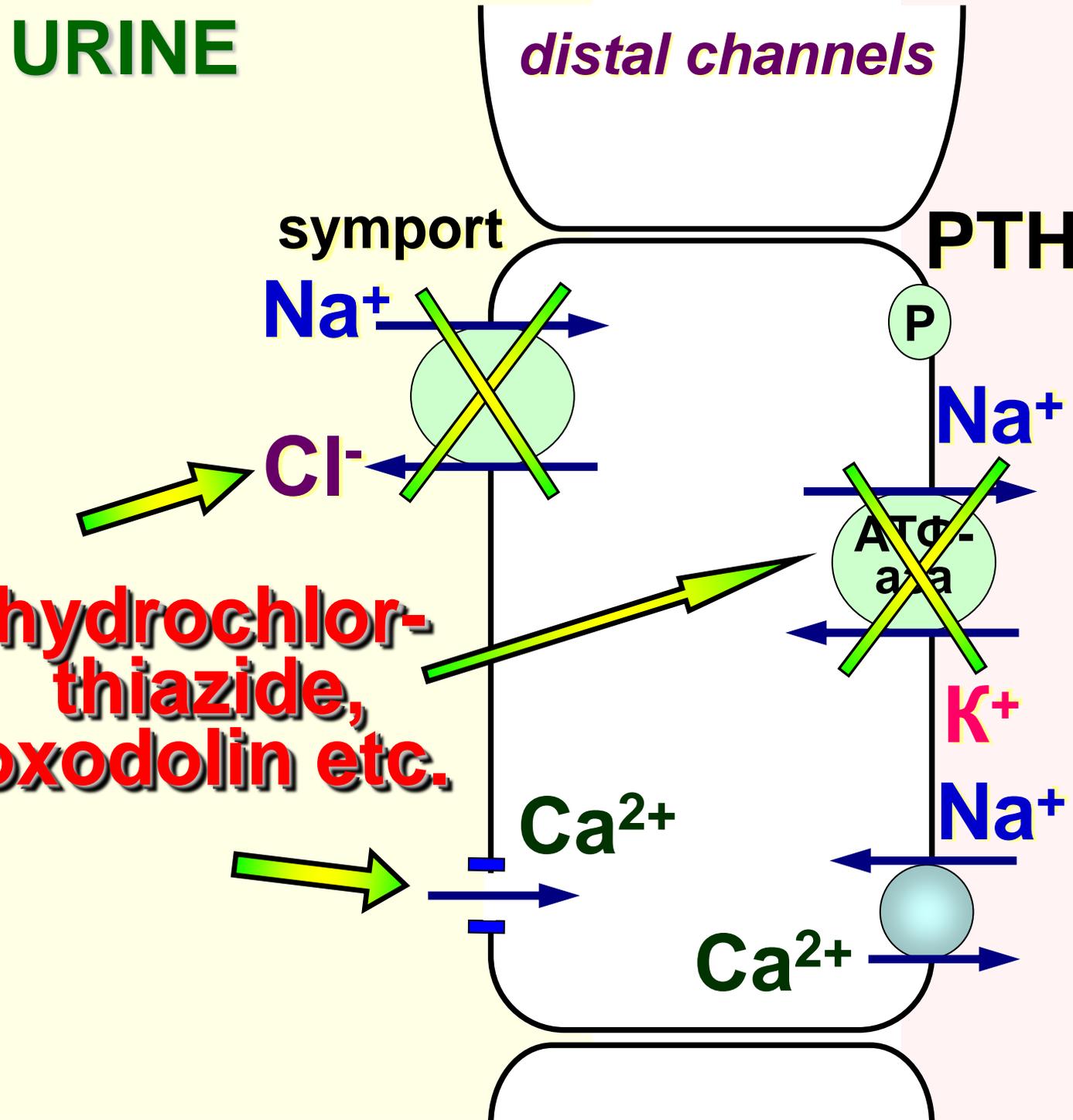
Na^+

Ca^{2+}

Ca^{2+}

hydrochlor-
thiazide,
oxodolin etc.

- ↓ reabsorption Cl^- , Na^+ , H^+ , K^+ , Mg^{2+}
- ↑ Ca^{2+} in blood
- Insignificantly ↓ HCO_3^- and phosphates
- disturbance of renal bioenergy
- ⇒ don't alter (worsen) renal bloodflow
- ↑ renin secretion ⇒ ↑ aldosteron
- ↑ ADH





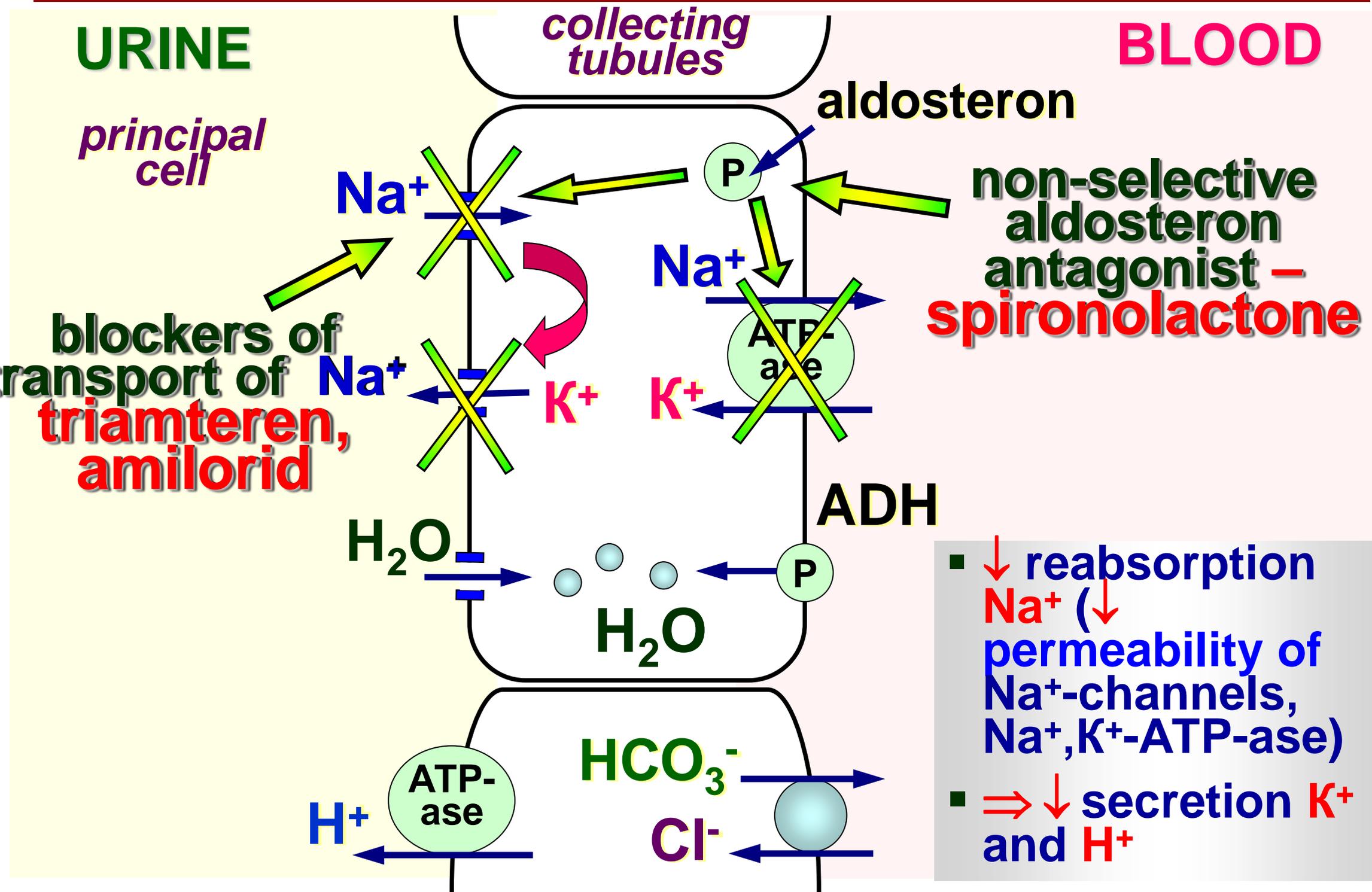
INDICATIONS OF THIAZIDE DIURETICS

- ❖ **chronic heart failure (↓ pre-load)**
- ❖ **arterial hypertension (in complex therapy)**
- ❖ **liver cirrhosis with portial hypertension and ascites**
- ❖ **nephrosis**
- ❖ **toxicosis during pregnancy**
- ❖ **hypocalciemia**
- ❖ **diabetes insipidus**
- ❖ **bromism (↓ binding with Br)**

ADVERSE EFFECTS OF THIAZIDE DIURETICS

- hypokaliemia, hypomagniemia
- Hyponatremia (↑ ADH, ↑ thirsty)
- hypercalciemia
- metabolis alkalosis
- hyperlipidemia (atherogenic)
- diabetes mellitus
- hyperurecemia
- orthostatic hypotension
- allergy, photodermatitis, thrombocytopenia, agranulocytosis
- anorexia, pancreatitis relapse, cholecystitis
- tiredness, paresthesia, xantopsia

POTASSIUM-SPARING DIURETICS



INDICATIONS FOR POTASSIUM-SPARING DIURETICS

- hypokaliemia
- heart failure
- arterial hypertension (in combination with thiazides)
- primary (tumor etc.) and secondary hyperaldosteronism (heart failure, liver cirrhosis etc.) – spironolacton
- lithium overdosing – triamteren, amilorid

ADVERSE EFFECTS OF POTASSIUM-SPARING DIURETICS

- hyperkalemia
- acidosis
- gynecomastia, impotence, dysmenorrhea (spironolactone)
- diarrhea, gastritis, peptic ulcer of stomach with bleeding (spironolactone)
- skin rash, thrombocytopenia
- tremor, ataxia (spironolactone)
- hypotension (triamteren)
- Acute renal failure, nephritis (triamteren)
- macrocytic anemia (triamteren)

GENERAL PRINCIPLES OF DIURETICS APPLICATION

- ▶ daily diuresis should not exceed **2-2,5 l**
- ▶ rational choice consider:
 - ✓ intensity of edemas syndrome
 - ✓ hemodynamic disturbances
 - ✓ initial electrolytes status
 - ✓ pharmacological features of the diuretics, their adverse effects (**intake before noon!**)
 - ✓ индивидуальной переносимости
- ▶ intermittent course
- ▶ combination of diuretics
- ▶ adequate drinking
- ▶ in urgent cases – administration of strong diuretics I.V.
- ▶ supervising and correction of electrolyte and acid-alkaline balance

THERAPY OF CONGESTIVE HEART FAILURE

■ basic:

- ✓ ACE inhibitors
- ✓ diuretics and selective antagonists of aldosterone's receptors: eplerenone (inspra)
- ✓ cardiac glycosides
- ✓ β -adrenoblockers (with ACE inhibitors):
bisoprolol, carvedilol, metoprolol-retard

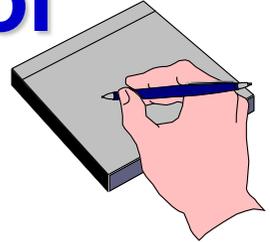
■ supplementary: angiotensin receptors antagonists, calcium channel blockers (amlodipine)

■ additional (for special clinical occasions): vasodilators (nitrates, calcium channel blockers), anti-arrhythmics, anti-aggregants, indirect anticoagulants, glucocorticoids, cardiac glycosides synergists – vitamins (thiamine, pyridoxine, nicotinic acid, tocopherol), cardiotropic agents (glucose, steroidal and non-steroidal anabolic agents)

ANTI-GOUT AGENTS

● ↓ *uric acid synthesis:*

- ✓ xanthine oxidase inhibitors – allopurinol
- ✓ with different mechanism of action – benzbromaron



● ↑ *uric acid excretion (uricosuric agents):*

- ✓ ↓ uric acid reabsorption in renal channels – benzbromaron, probenecide
- ✓ modifying urine pH to alkaline side – uralit
- ✓ combined – allomarone

● *in acute gout attack:* NSAIDs (butadione, indomethacine), colchicine, glucocorticoids