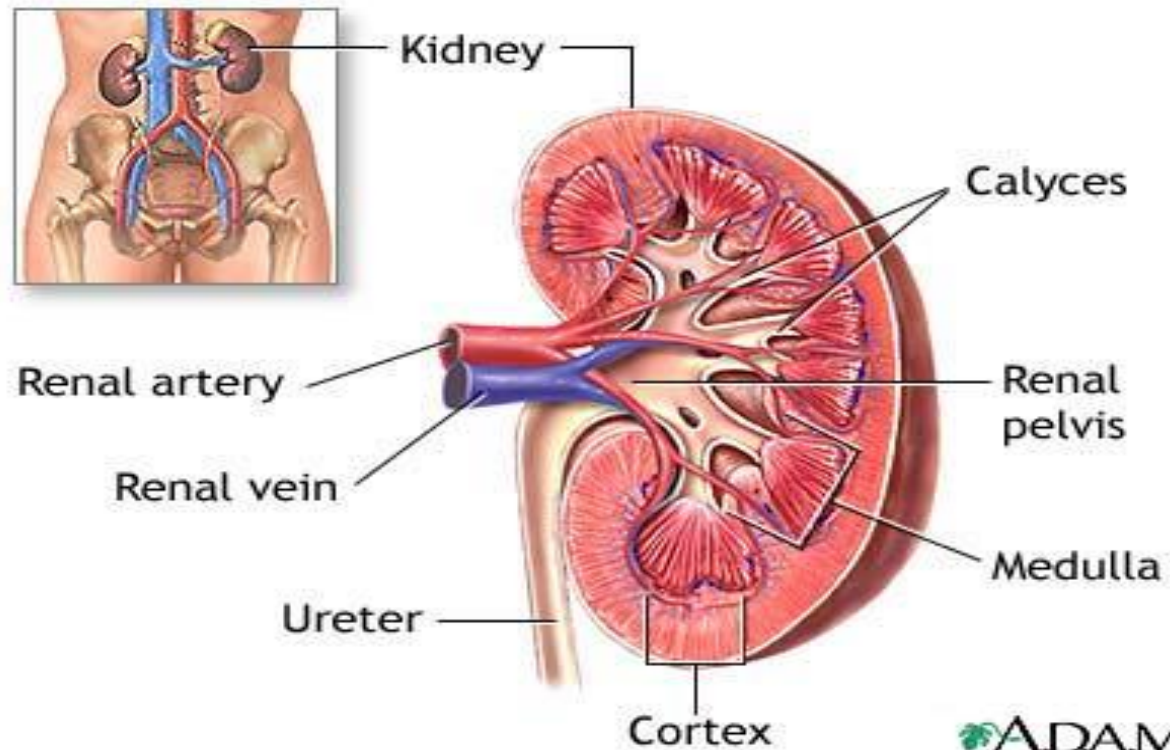


DIURETICS

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Thiazide diuretics

Drugs as:

- **Chlorothiazide**
- **Hydrochlorothiazide**
- **Chlorthalidone**
- **Metolazone**
- **Indapamide**



THIAZIDE DIURETICS

Chlorothiazide

Potency 0.1, $t^{1/2}$ 2h

Chlorthalidone

Potency 10, $t^{1/2}$ 26h

Metolazone

Potency 5, $t^{1/2}$ 5h

Hydrochlorothiazide

Potency 1, $t^{1/2}$ 3h

Indapamide

Potency 20, $t^{1/2}$ 16h

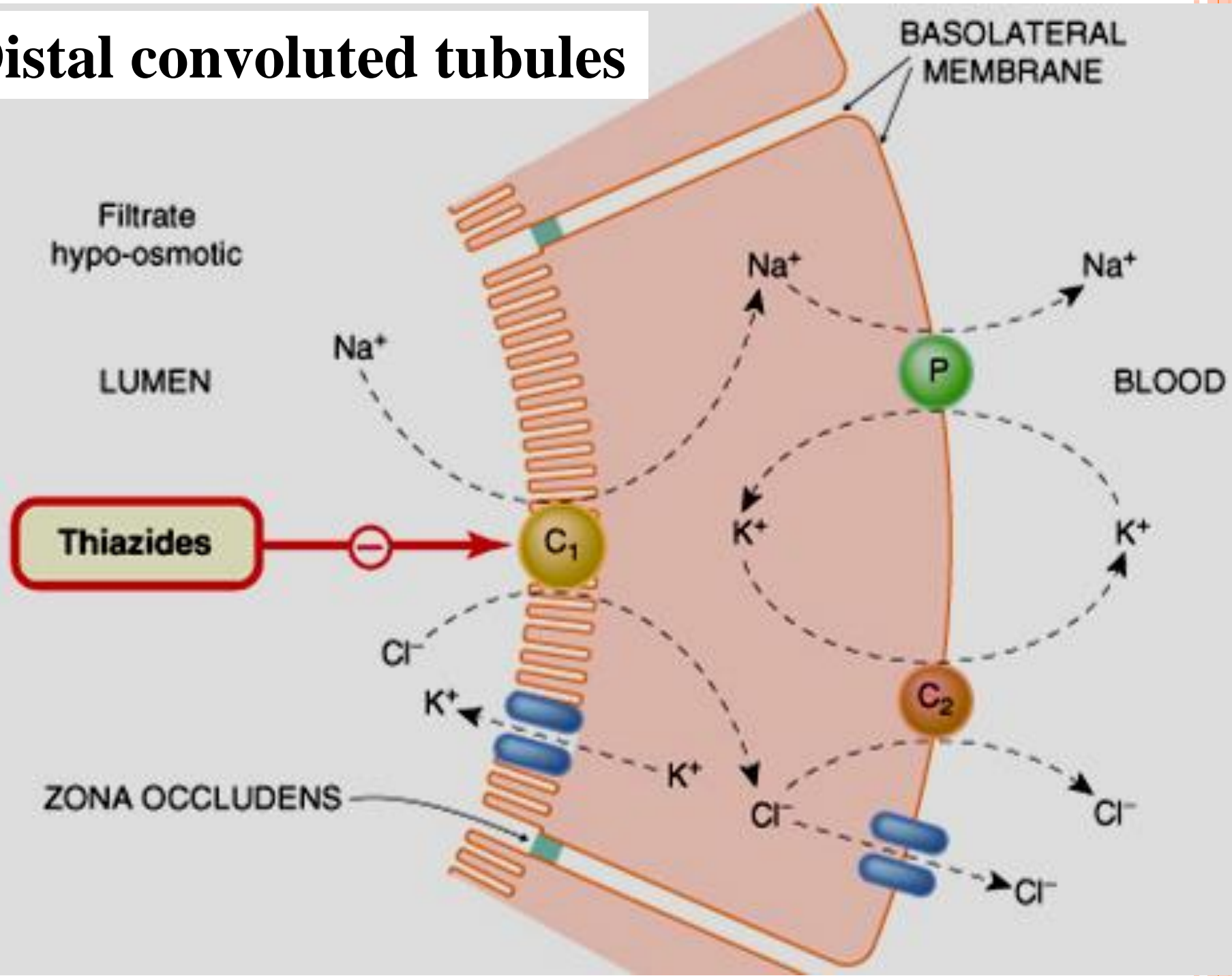
Thiazide diuretics

Mechanism of action:

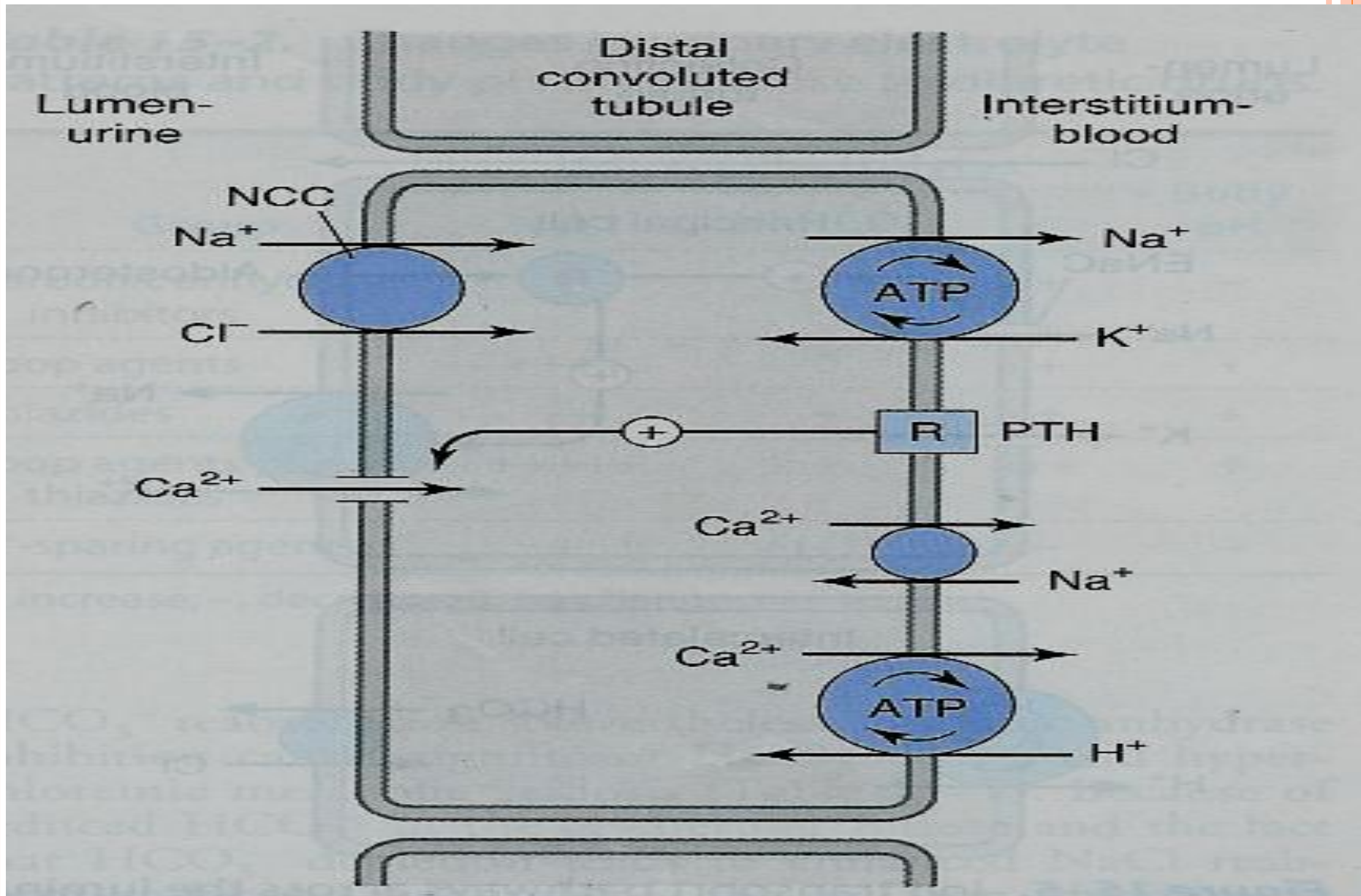
- acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.
- **Efficacy:** Moderate natriuresis (5-10% of filtered load of sodium is reabsorbed).



Distal convoluted tubules



Mechanism of action of thiazide diuretics



Pharmacokinetics:

- Given orally, slow of onset
- long duration of action (40 h)
- are secreted by active tubular secretory system of the kidney
- may interfere with uric acid secretion and cause *hyperuricemia*



Pharmacological effects:

↑ urinary NaCl excretion

↑ urinary K excretion (**Hypokalemia**)

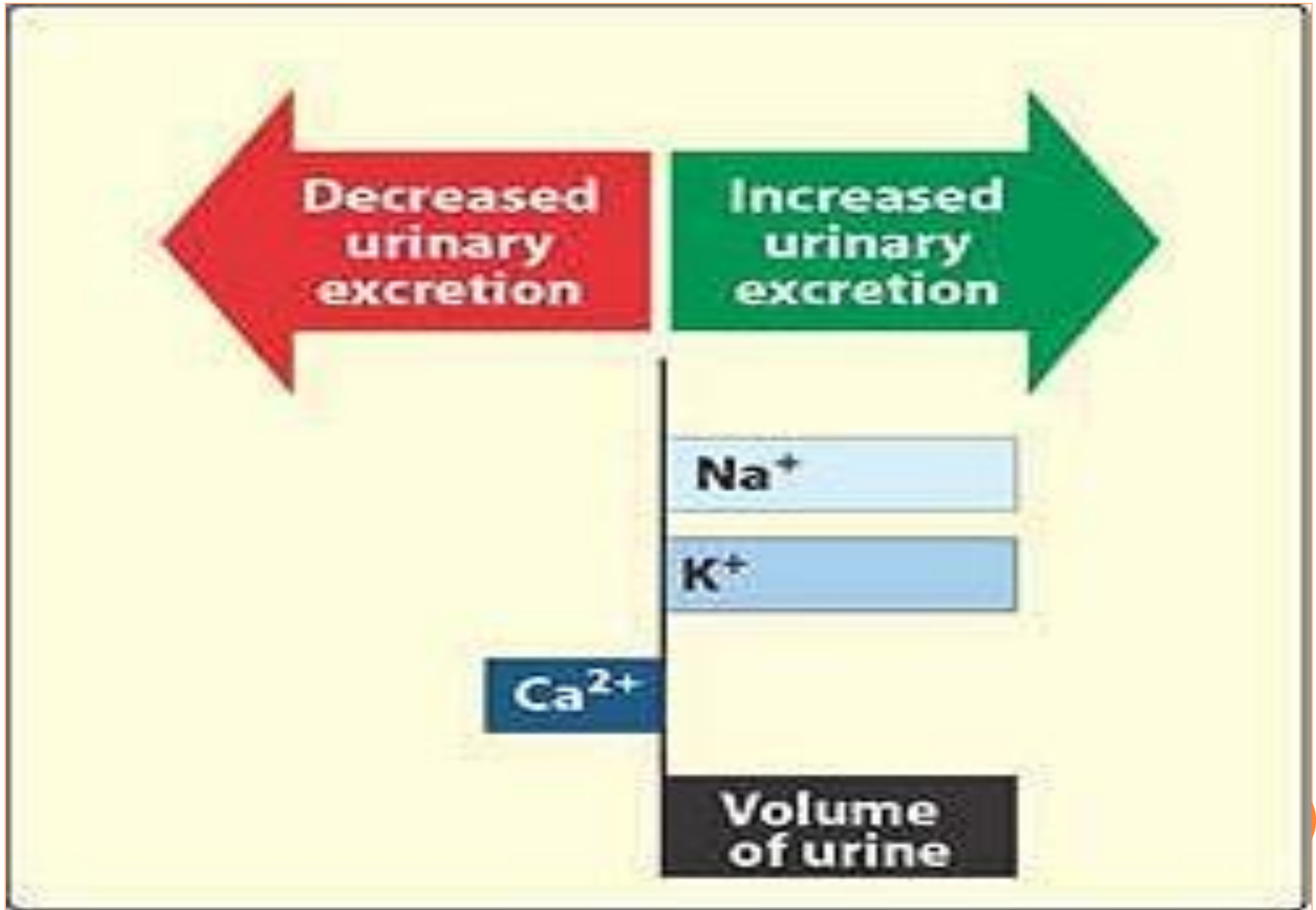
↑ urinary magnesium excretion

↓ urinary calcium excretion

↑ calcium re-absorption **hypercalcemia**



Thiazide diuretics



Uses:

- Treatment of essential hypertension (*cheap-well tolerated*).
- Treatment of mild heart failure (*to reduce extracellular volume*).

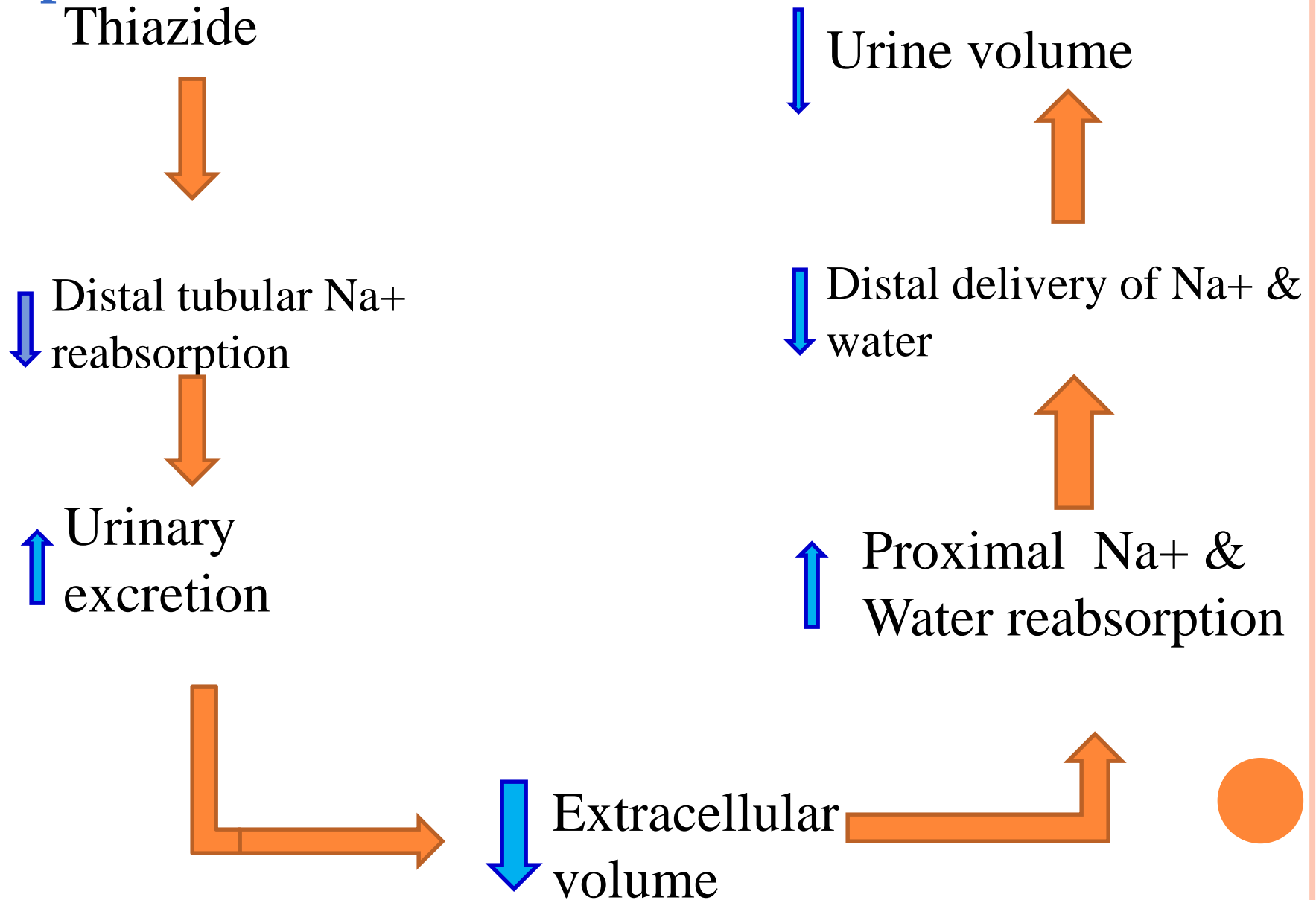


Uses:

- Calcium nephrolithiasis due to hypercalciuria (*to increase calcium re-absorption and decrease renal calcium stones*)
- Nephrogenic diabetes insipidus (*decrease blood volume and GFR*)



Mechanism of antidiuretic effect of thiazide in diabetes insipidus



Adverse effects:

- **Fluid and electrolyte imbalance**
- **Hyponatremia**
- **Hypovolemia (volume depletion)**
- **Hypokalemia**
- **Metabolic alkalosis.**
- **Hyperuricaemia (gout)**
- **Hypercalcemia**
- **Hyperglycaemia**
- **Hyperlipidemia**



ADVERSE EFFECTS

**Volume
Depletion**

Hypokalemia

Hypocalcaemia

Hypomagnesaemia

**Metabolic
Alkalosis**

Hyperuricemia

Hyperglycemia

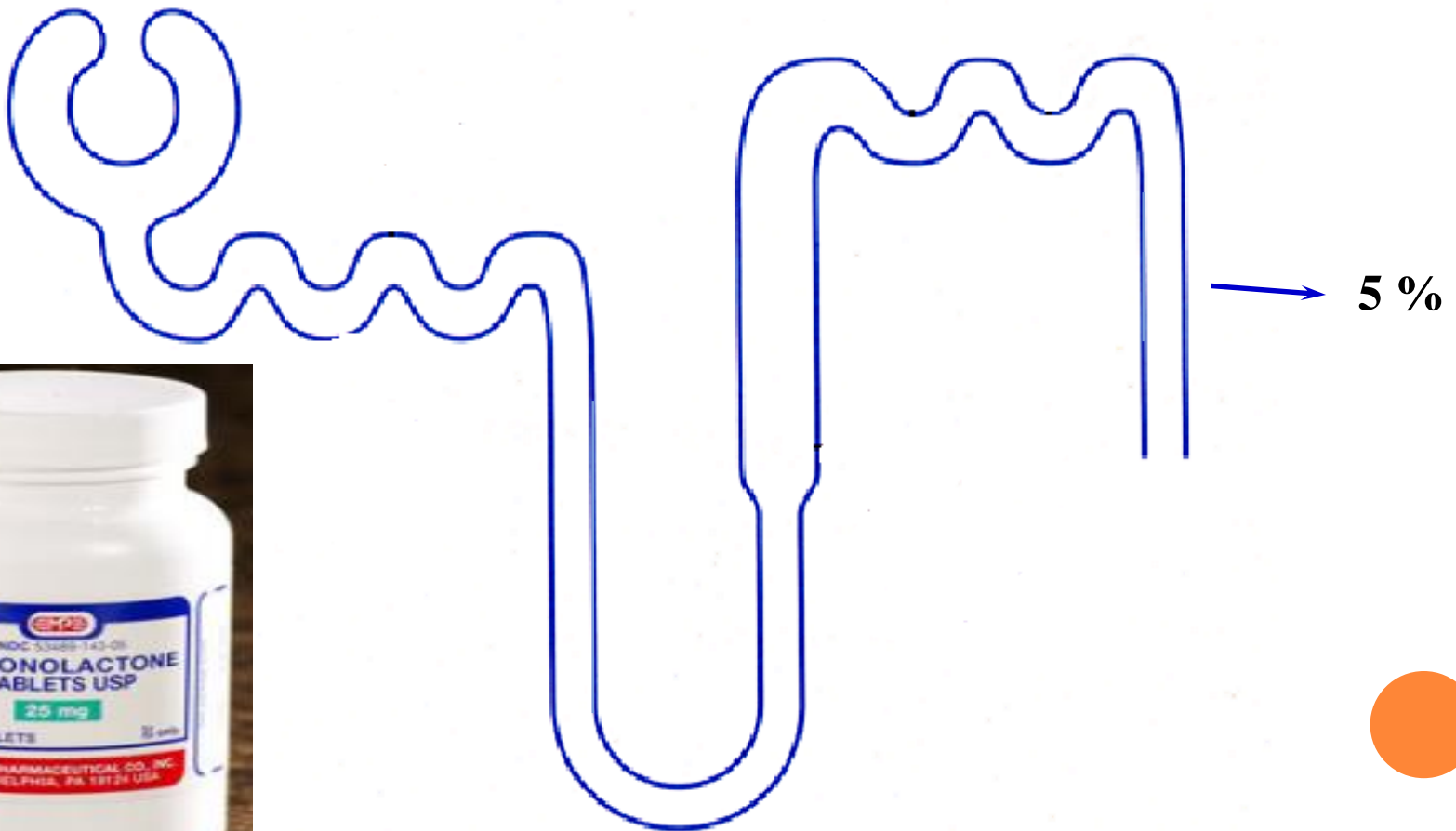


Hyperlipidemia



Potassium-sparing diuretics

Amiloride
Triamterene
Spironolactone



Potassium-sparing diuretics

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graph TD; A[Potassium-sparing diuretics] --> B[Steroids]; A --> C[Nonsrerooids]; B --> D["Aldosterone antagonists<br/>• Spironolactone"]; C --> E["Na+ channels inhibitors<br/>• Amiloride<br/>• Triamterene"];
```

Steroids

Aldosterone antagonists

- Spironolactone

Nonsrerooids

Na⁺ channels inhibitors

- Amiloride
- Triamterene

Mechanism of action

- Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion (**K-sparing effect**) by **either**:
 - Inhibition of Na influx through Na channels in the luminal membrane (**triamterene – amiloride**).

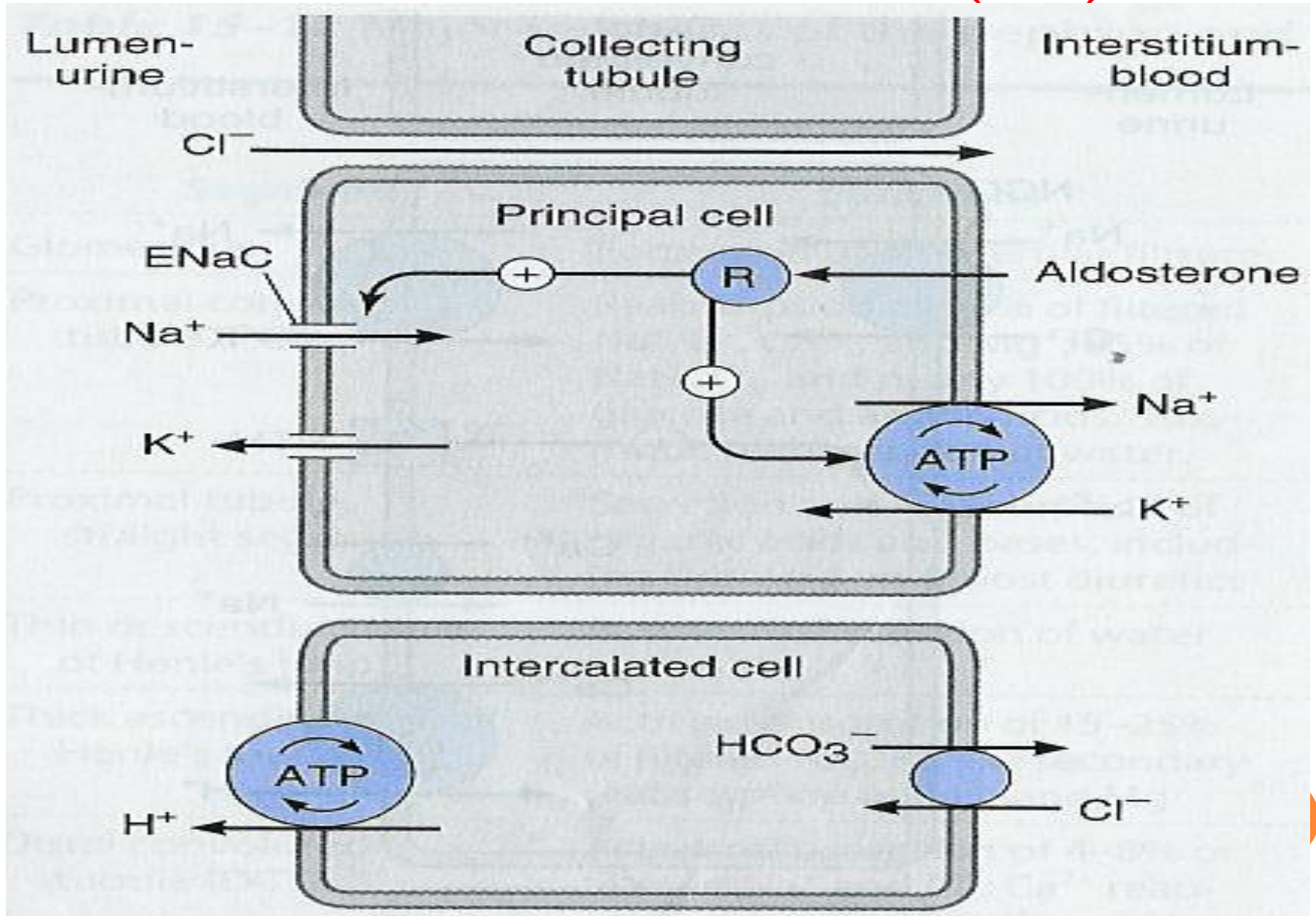


Mechanism of action

- **Spirolactone:** by antagonizing cytoplasmic aldosterone receptors



COLLECTED TUBULES (CT)




Pharmacodynamics:

- **↑**urinary Na^+ excretion
- **↓**urinary K^+ excretion **Hyperkalemia**
- **↓** H^+ excretion (**acidosis**)



Therapeutic uses:

- **Drug of choice for patients with hepatic cirrhosis**
 - **Secondary hyperaldosteronism (CHF, hepatic cirrhosis, nephrotic syndrome).**
 - **Treatment of hypertension (combined with thiazide or loop diuretics to correct for hypokalemia).**
- 

Adverse Effects

- **Hyperkalaemia.**
- **Metabolic acidosis.**
- **Gynaecomastia**
- **GIT upset and peptic ulcer**



Contraindications:

- **Hyperkalaemia:** as in chronic renal failure, K⁺ supplementation, β -blockers or ACE inhibitors.
- **liver disease** (dose adjustment is needed).



Therapeutic applications of diuretics

Treatment of hypertension:

- Thiazide diuretics
- used alone or in combination with beta-blockers at low-dose (fewer side effects)
- In presence of renal failure, loop diuretic is used.

Edema States Thiazide diuretic is used in mild edema with normal renal function

- Loop diuretics are used in cases with impaired renal function.



Congestive Heart failure

- Thiazides may be used in only mild cases with well-preserved renal function
- Loop diuretics are much preferred in severe cases especially when GF is lowered
- In life-threatening acute pulmonary edema, furosemide is given IV.



Renal failure

- Thiazides are used till $GFR \geq 40-50$ ml/min
- Loop diuretic are used below given values, with increasing the dose with as GFR goes down.

Diabetes inspidus

Large volume(>10 L/day) of dilute urine
thiazide diuretics reduces urine volume

Hepatic cirrhosis with ascites

- Spironolactone is of choice.



Diuretics	Mechanism of action	Effects
CA inhibitors Acetohexamide Dorzolamide	Inhibition of NaHCO_3 reabsorption in PCT	\uparrow Urinary Na HCO_3 , K Urinary alkalosis Metabolic acidosis
Osmotic diuretic Mannitol	Osmotic effect in PCT	\uparrow Urine excretion \uparrow Little Na
Loop diuretics Furosemide	Na/K/2Cl transporter in TAL the most effective	\uparrow Urinary Na, K, Ca, Mg
Thiazide diuretics hydrochlorothiazide	Na and Cl cotransporter in DCT	\uparrow Urinary Na, K, Mg BUT \downarrow urinary Ca (hypercalcemia) Metabolic alkalosis
K-sparing diuretic Spironolactone.	competitive antagonist of aldosterone in CCT	\uparrow Urinary Na \downarrow K, H secretion Metabolic acidosis

Diuretics

Uses

CA inhibitors

Acetohexamide

Dorzolamide (topically) for
glaucoma

Glaucoma, epilepsy

Mountain sickness

Alkalosis

Phosphatemia

Osmotic diuretic

Mannitol

• Cerebral edema, glaucoma

• Acute renal failure, drug toxicities

Loop diuretics

Furosemide

Acute pulmonary edema (**Drug of
choice**)

Heart failure

Hyperkalemia, Hypercalcemia

Thiazide diuretics

hydrochlorothiazide

Commonly used

Hypertension, mild heart failure,
nephrolithiasis, diabetes inspidus

K-sparing diuretic

Spironolactone.

Hepatic cirrhosis

(**Drug of choice**)

Diuretics	Side effects
CA inhibitors Acetohexamide Dorzolamide	Metabolic acidosis , Urinary alkalosis Hypokalemia
Osmotic diuretic Mannitol	Extracellular water expansion Dehydration Hypernatremia
Loop diuretics Furosemide	Hypokalemia, hypovolemia, hyponatremia, hypomagnesemia, hypocalcemia Precipitate gout, alkalosis
Thiazide diuretics hydrochlorothiazide	Hypokalemia, hyponatremia, hypovolemia, hypomagnesemia, hypercalcemia Alkalosis, precipitate gout Hyperlipidemia, hyperglycemia
K-sparing diuretic Spironolactone.	Gynaecomastia Hyperkalaemia , Metabolic acidosis. GIT upset and peptic ulcer

