DIURETICS
Part 1

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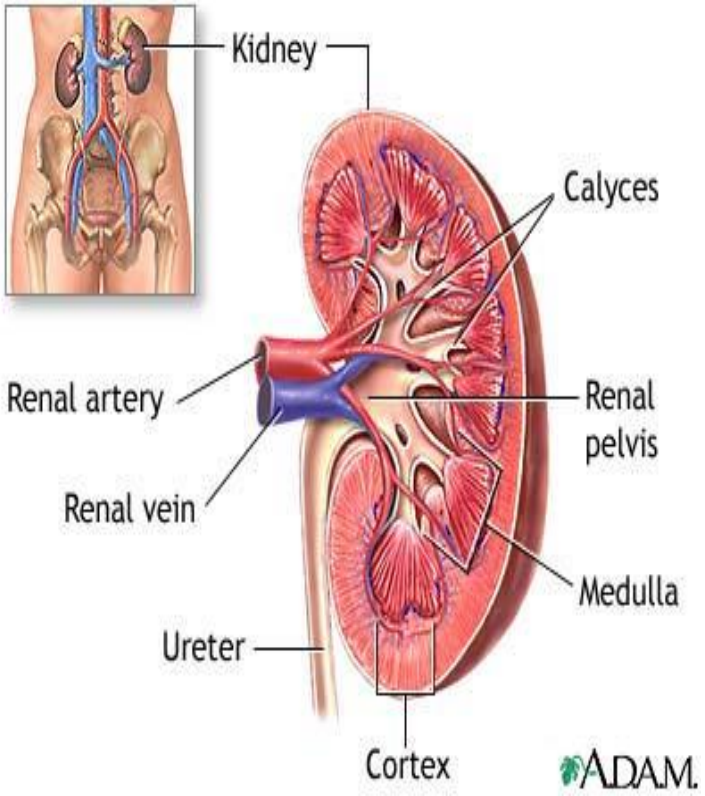
Pharmacology Unit



Diuretics

Definition

- Are drugs that increase urine volume.
- **Diuresis:** is the process of excretion of water in the urine.
- All diuretics have **naturetic** effect.

Natriuresis:

- is the process of **sodium excretion** in the urine.

INDICATIONS of DIURETICS

- Edema of any origin
- Congestive heart failure
- Hypertension
- Elimination of toxins

Mechanism of actions of diuretics

How diuretics produce their effects?

- Most diuretics act by interfering with the **normal sodium reabsorption** by the renal tubules resulting into sodium and water excretion.

- Target molecules for diuretics are carriers or transporters in luminal membrane of renal tubular cells required for tubular reabsorption of sodium from filtrate back into blood.

Normal Sodium Re-absorption

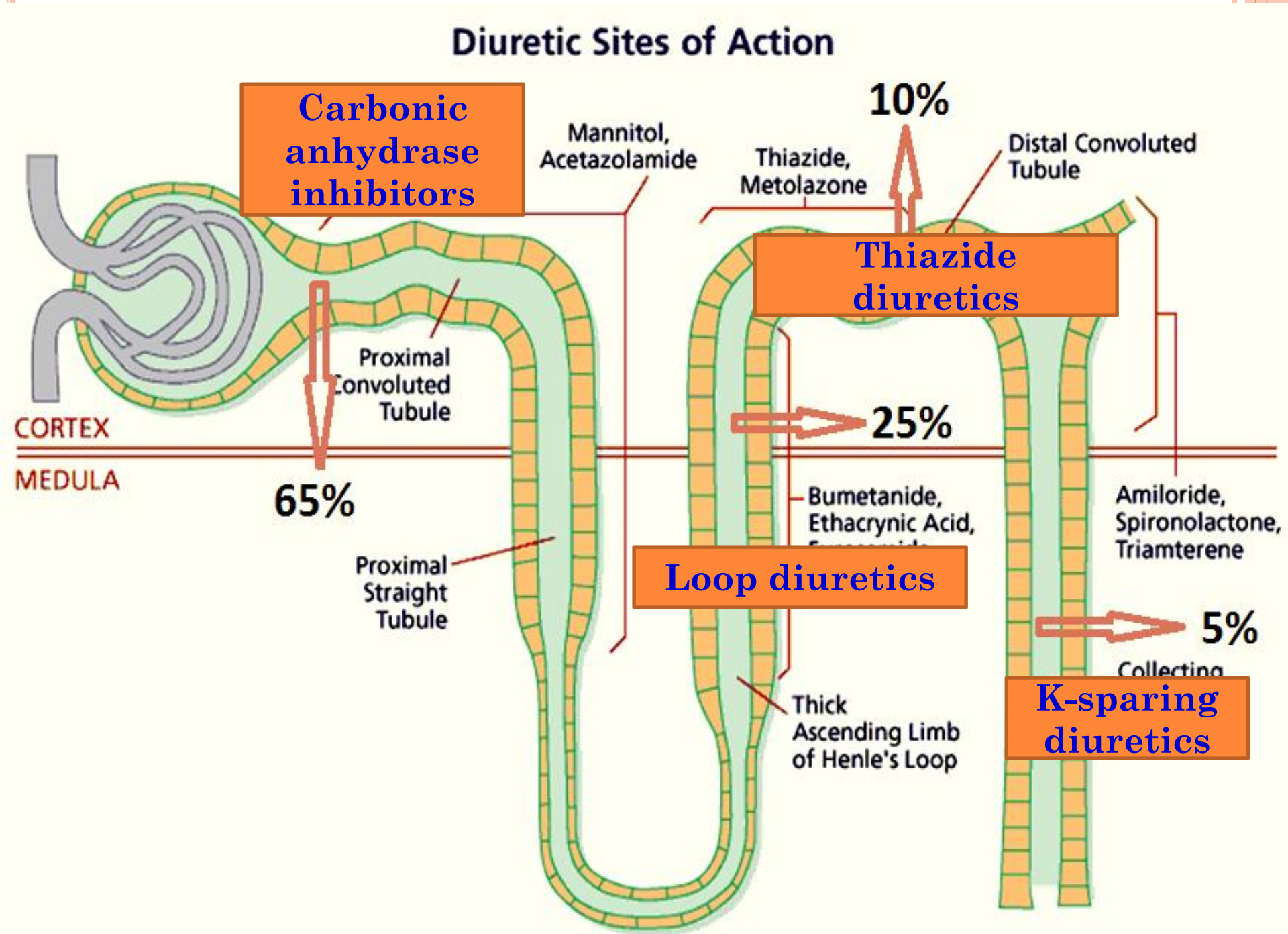
Nephron Segment	Na^+ Transporter	Filtered Na^+ re-absorbed
Proximal convoluted tubules	Na^+/H^+ transporter Carbonic anhydrase enzyme	65 % As $NaHCO_3$
Ascending Loop of Henle	$Na^+/K^+/2Cl^-$ cotransporter	20-30% Active reabsorption Na, K, Cl
Distal convoluted tubules	Na^+/Cl^- transporter	5-10% Active reabsorption Na, Cl
Cortical Collecting Tubules	Na^+ channel Aldosterone Antidiuretic hormone	5% Na reabsorption K & H secretion

Types of diuretics

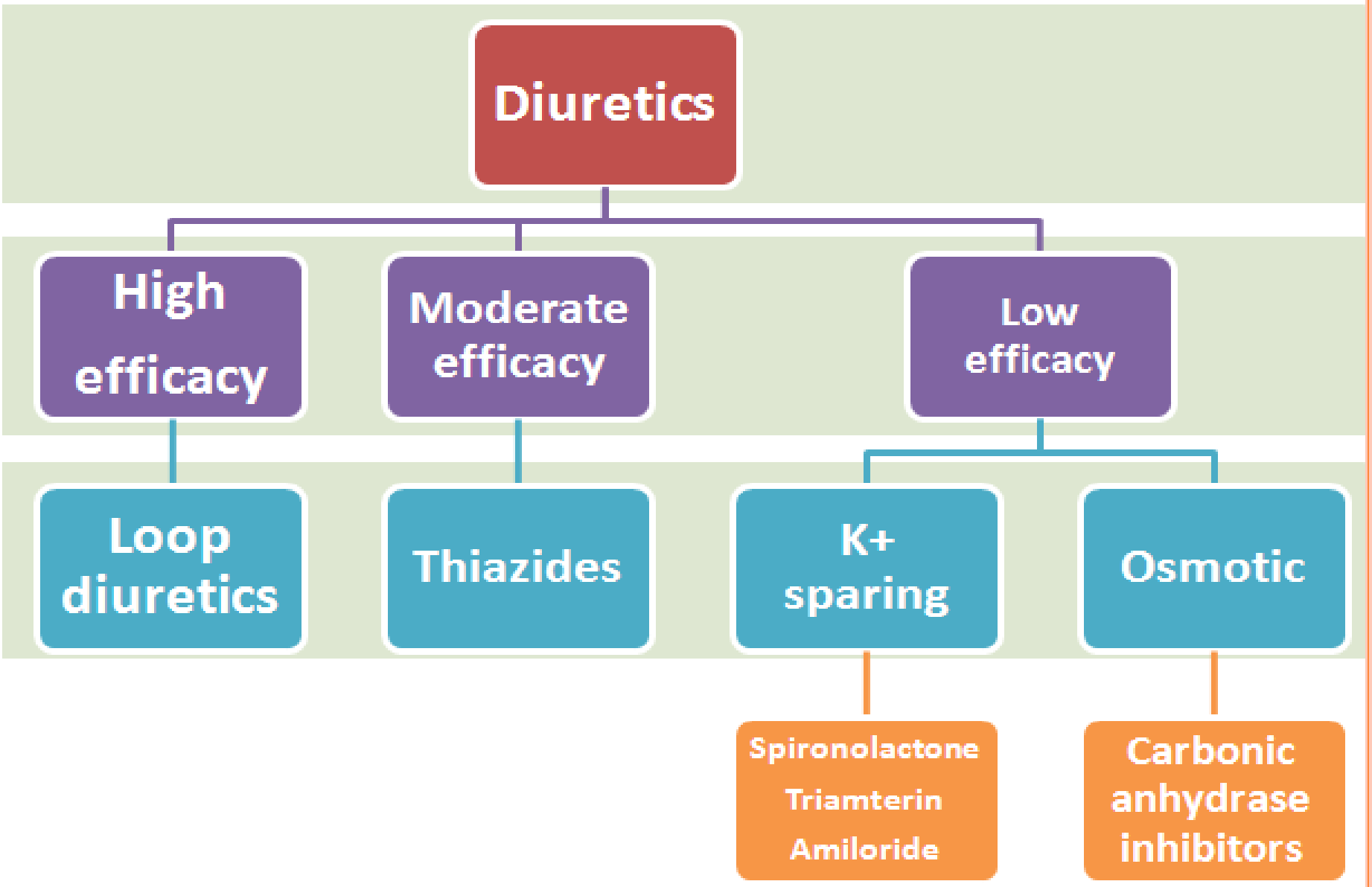
Nephron Segment	Na^+ Transporter	Diuretics
Proximal convoluted tubules	Na^+/H^+ transporter Carbonic anhydrase enzyme	Carbonic anhydrase inhibitors
Ascending Loop of Henle	$Na^+/K^+/2Cl^-$ cotransporter	Loop diuretics
Distal convoluted tubules	Na^+/Cl^- transporter	Thiazide diuretics
Cortical Collecting Tubules	Na^+ channel Aldosterone	K-sparing diuretics

Classification of diuretics

- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazide diuretics
- Potassium-sparing diuretics
- Osmotic diuretics


Diuretic Sites of Action
Carbonic anhydrase inhibitors
Mannitol, Acetazolamide
10%
Thiazide, Metolazone
Distal Convoluted Tubule
Thiazide diuretics
Proximal Convoluted Tubule
CORTEX
MEDULA
25%
65%
Bumetanide, Ethacrynic Acid,
Amiloride, Spironolactone, Triamterene
Proximal Straight Tubule
Loop diuretics
5%
Collecting
K-sparing diuretics
Thick Ascending Limb of Henle's Loop

Classification of diuretics



Carbonic Anhydrase Inhibitors

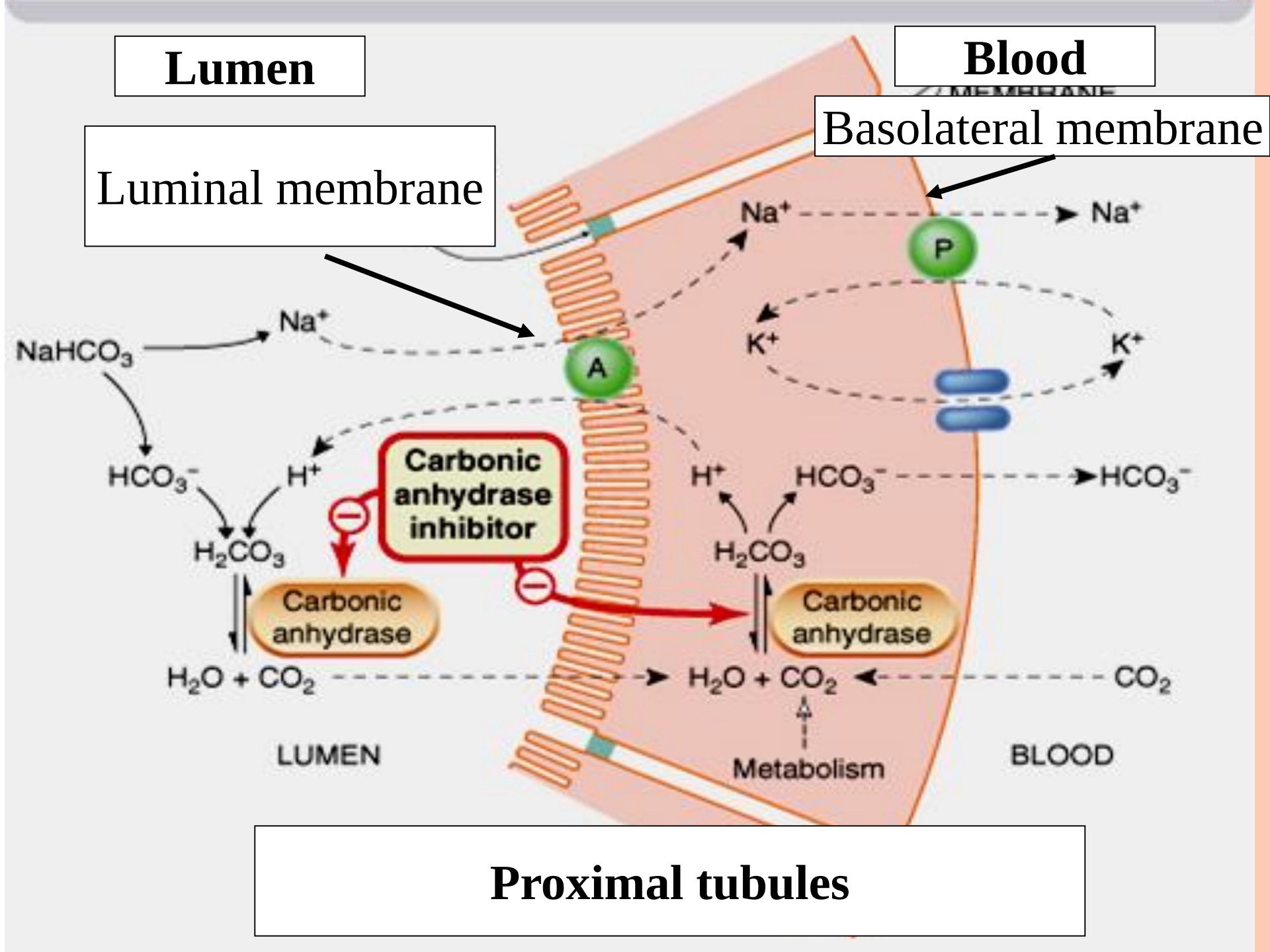
Drugs: Acetazolamide – dorzolamide

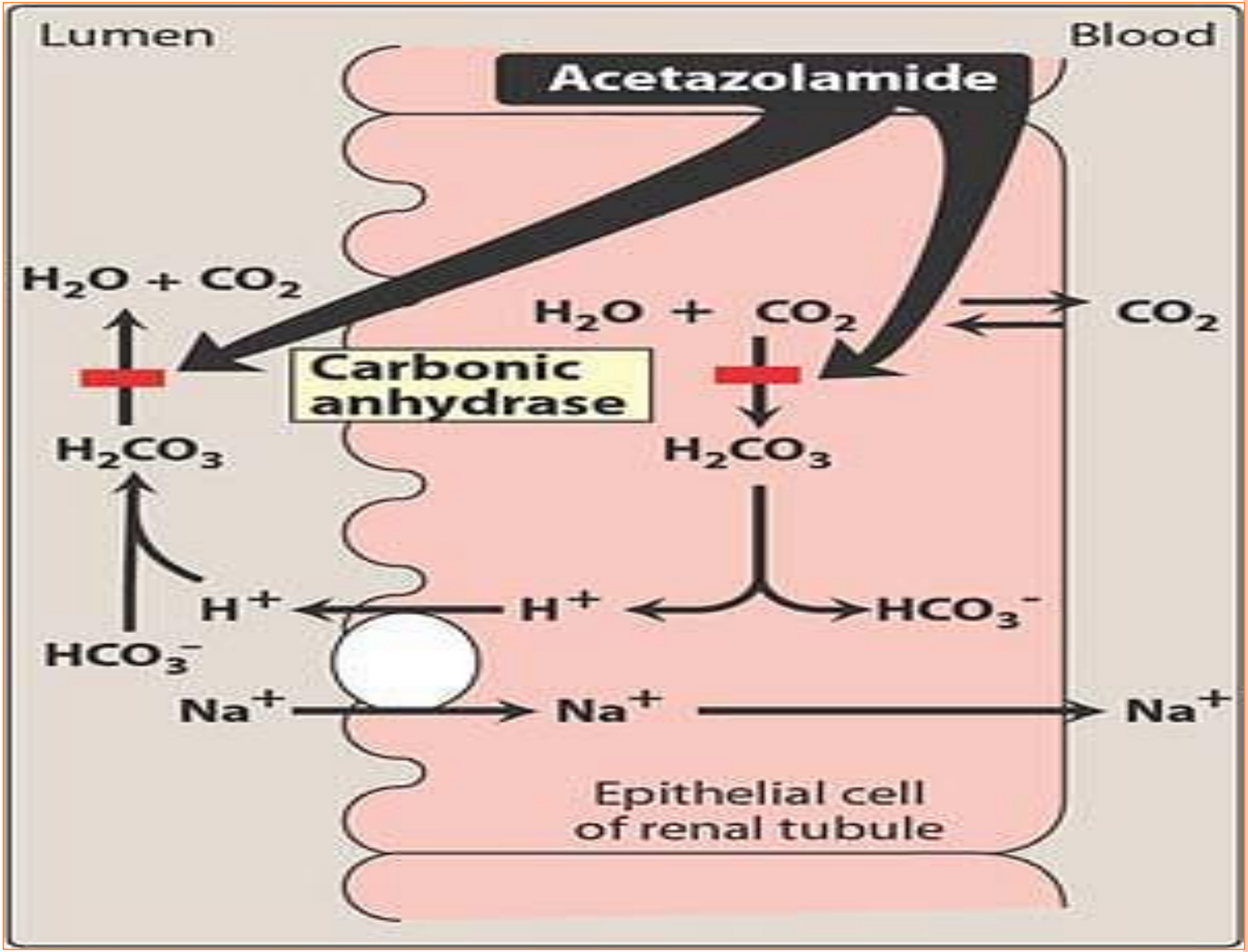
Mechanism of action:

Inhibits **carbonic anhydrase (CA) enzyme** in proximal convoluted tubules thus interferes with **NaHCO3 re-absorption** and causes diuresis.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is required for reversible reaction in which


Lumen
Blood
Luminal membrane
Basolateral membrane
Na+
Na+
P
K+
K+
NaHCO3
Na+
A
HCO3−
H+
Carbonic anhydrase inhibitor
H+
HCO3−
HCO3−
H2CO3
H2CO3
Carbonic anhydrase
Carbonic anhydrase
H2O + CO2
H2O + CO2
CO2
LUMEN
Metabolism
BLOOD
Proximal tubules


Lumen
Blood
Acetazolamide
$H_2O + CO_2$
$H_2O + CO_2$
CO_2
Carbonic anhydrase
H_2CO_3
H_2CO_3
H^+
H^+
HCO_3^-
HCO_3^-
Na^+
Na^+
Na^+
Epithelial cell of renal tubule

Pharmacokinetics of acetazolamide:

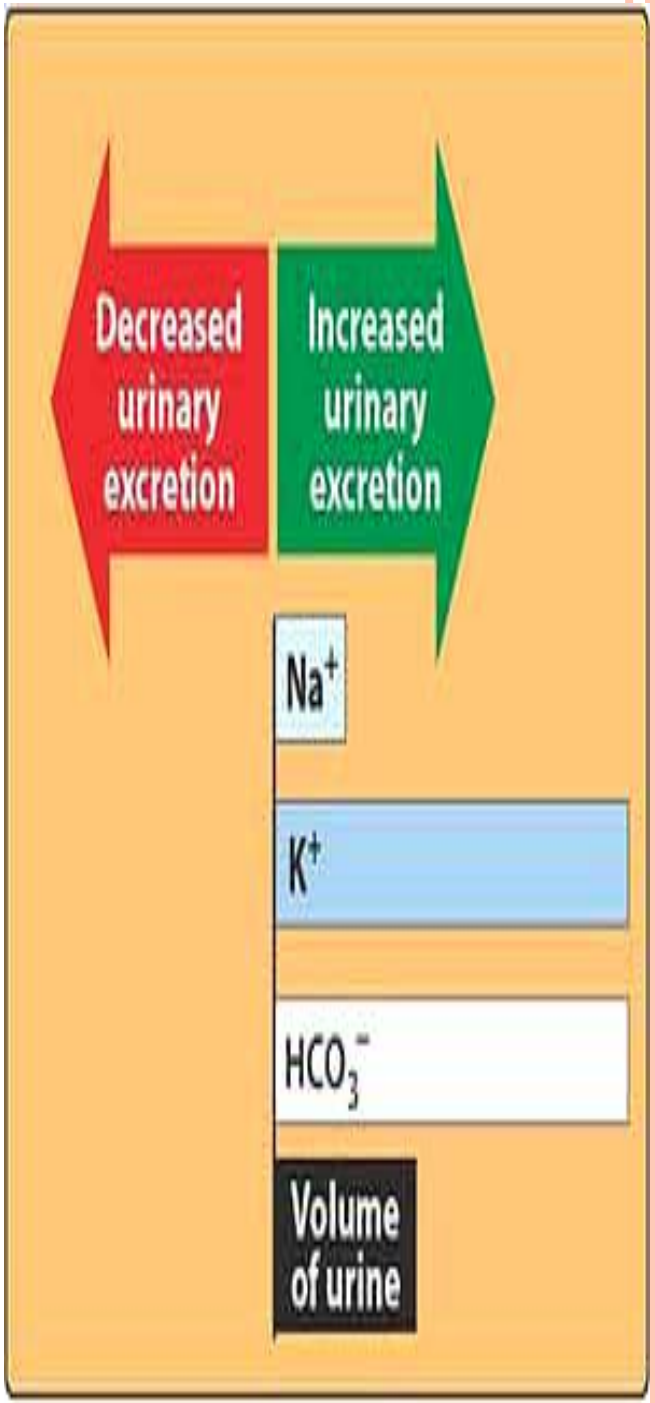
- given orally once a day.
- Onset of action is rapid (30 min).
- Duration of action (9-12 h).
- Excreted by active secretion in proximal convoluted tubules.
- Produces alkaline urine

Pharmacological actions:

- ↑ Mild increase in urine volume
- ↑ urinary excretion of sodium, potassium , bicarbonate (alkaline urine).
- Metabolic acidosis.
- ↑ Urinary phosphate excretion.
- Promotes K+ excretion by ↑the load of Na+ delivered to the distal tubules.

Why do CA inhibitors have weak diuretic properties?

Diuretic properties decreases after several days as the blood bicarbonate falls.



Dorzolamide

- **Is a carbonic anhydrase inhibitor**
- **Used topically for treatment of open-angle glaucoma.**
- **no diuretic or systemic side effects (Why?)**

Therapeutic uses:

- **Open angle glaucoma**

  carbonic anhydrase inhibitors decrease aqueous humour formation and ↓ IOP by reducing aqueous humor formation in ciliary body of eye.

- **As prophylactic therapy, in acute mountain sickness ↓ CSF of brain**

  given nightly 5 days before the ascent ↓ weakness, breathlessness , dizziness, nausea, cerebral & pulmonary oedema.

  IOP: Intraocular pressure; **CSF:** Cerebrospinal fluid

Therapeutic uses:

- **Formation of CSF:**

  (↓ of carbonic anhydrase in the choroid plexus→↓formation of CSF. Useful in treating benign intracranial hypertension).

- **Urinary alkalinization to enhance renal excretion of acidic substances (uric acid, methotrexate and cysteine in cystinuria).**

- **Hyperphosphatemia**

Therapeutic uses:

Adjunct for treatment of epilepsy:

Glial cells contain carbonic anhydrase. Nerves are highly responsive to rise in pH 7.4→ 7.8 causes convulsions. ↓ neuronal carbonic anhydrase →↓ pH in the vicinity of neurons→↓ convulsions.

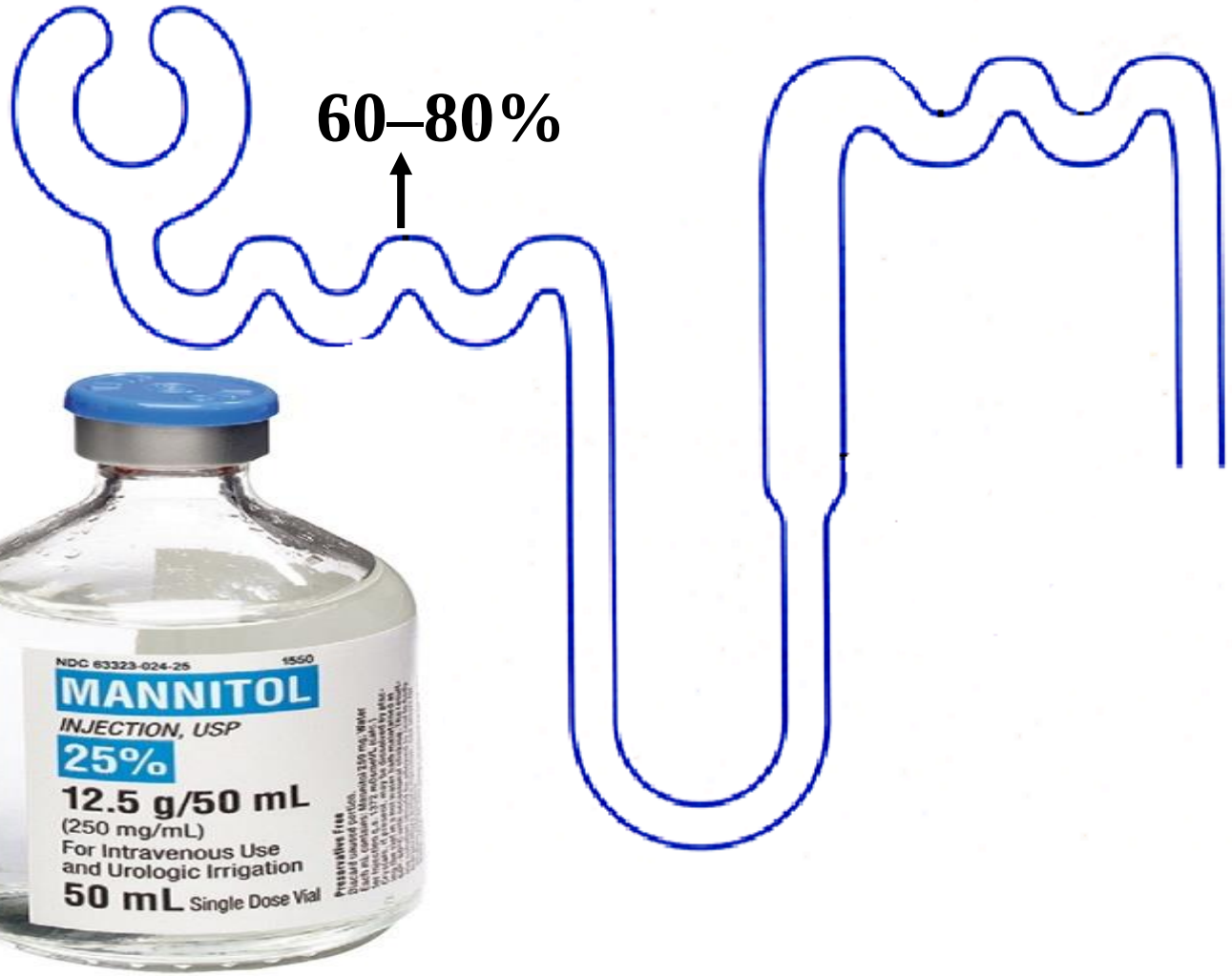
Metabolic alkalosis

Useful for correcting a metabolic alkalosis, especially an alkalosis caused by diuretic-induced increases in H^+ excretion & metabolic alkalosis of heart failure.

Adverse effects:

- **Hypokalemia (potassium loss).**
- **Metabolic acidosis.**
- **Renal stone formation (calcium phosphate stones).**
- **Hypersensitivity reaction.**

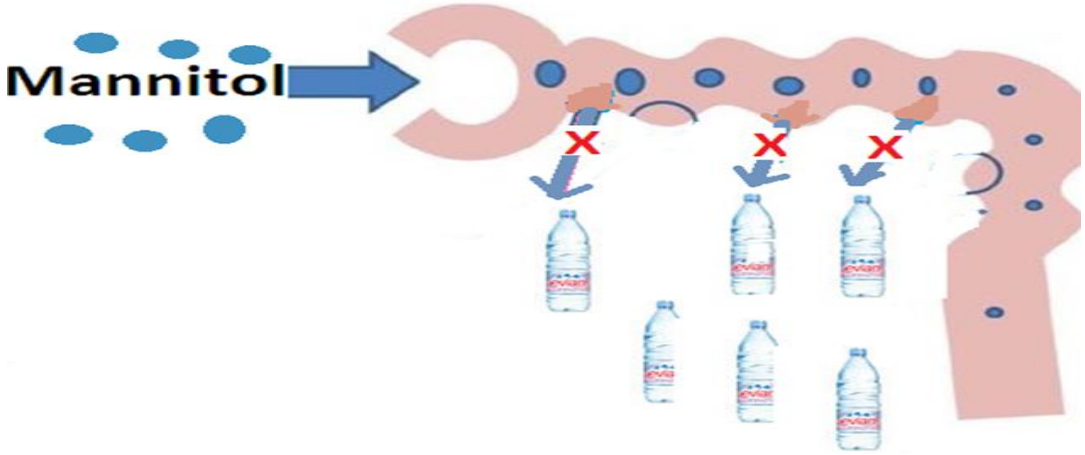
Osmotic diuretics



Osmotic diuretics

Mannitol:

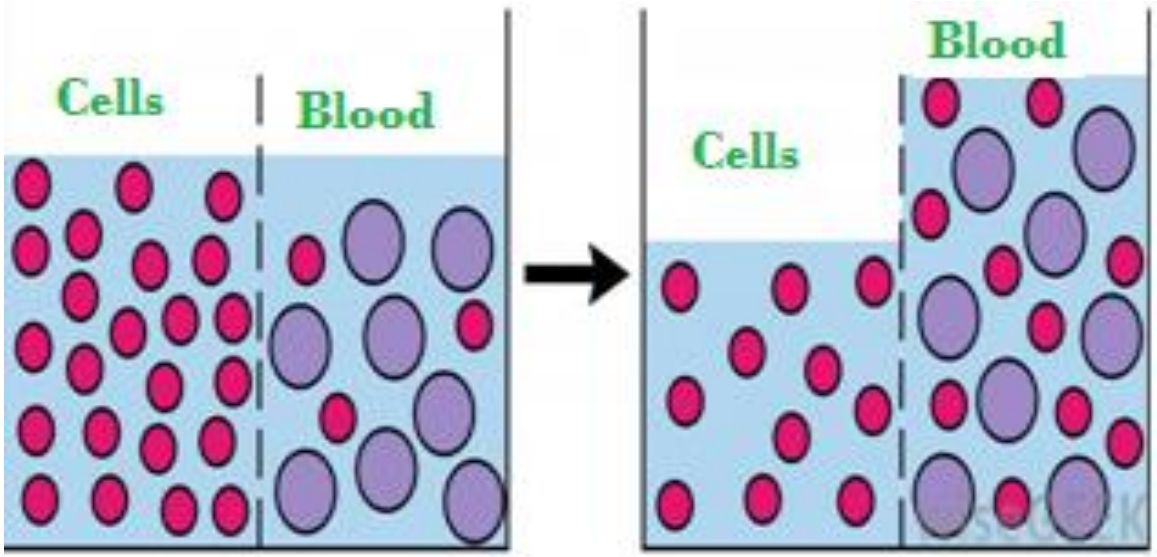
- Poorly absorbed
- If given orally ⟶ osmotic diarrhea
- Given intravenously
- Not metabolized
- Excreted by glomerular filtration **without being re-absorbed or secreted within 30-60 min**



Mannitol

- **Acts in proximal tubules & descending loop of Henle by osmotic effect.**

- **Mannitol increases urine output by osmosis, drawing water out of cells and into the blood stream.**



- IV administration of mannitol exert an osmotic pressure →↓**water & Na+ reabsorption**.
- ↑water excretion with relatively less effect on Na+.
- Expand the extracellular fluid volume, decrease blood viscosity, and inhibit renin release, ↑renal blood flow.

Therapeutic Uses:

- **Acute renal failure due to shock or trauma** (maintain urine flow- preserve kidney function).

- To maintain urine volume & prevent anuria resulting from large pigmentation load to the kidney **e.g. hemolysis, rhabdomyolysis**

- **In acute drug poisoning:** To eliminate drugs that are reabsorbed from the renal tubules e.g. salicylates, barbiturates.

- To ↓ intracranial & intraocular pressure before ophthalmic or brain procedures (**cerebral edema**).

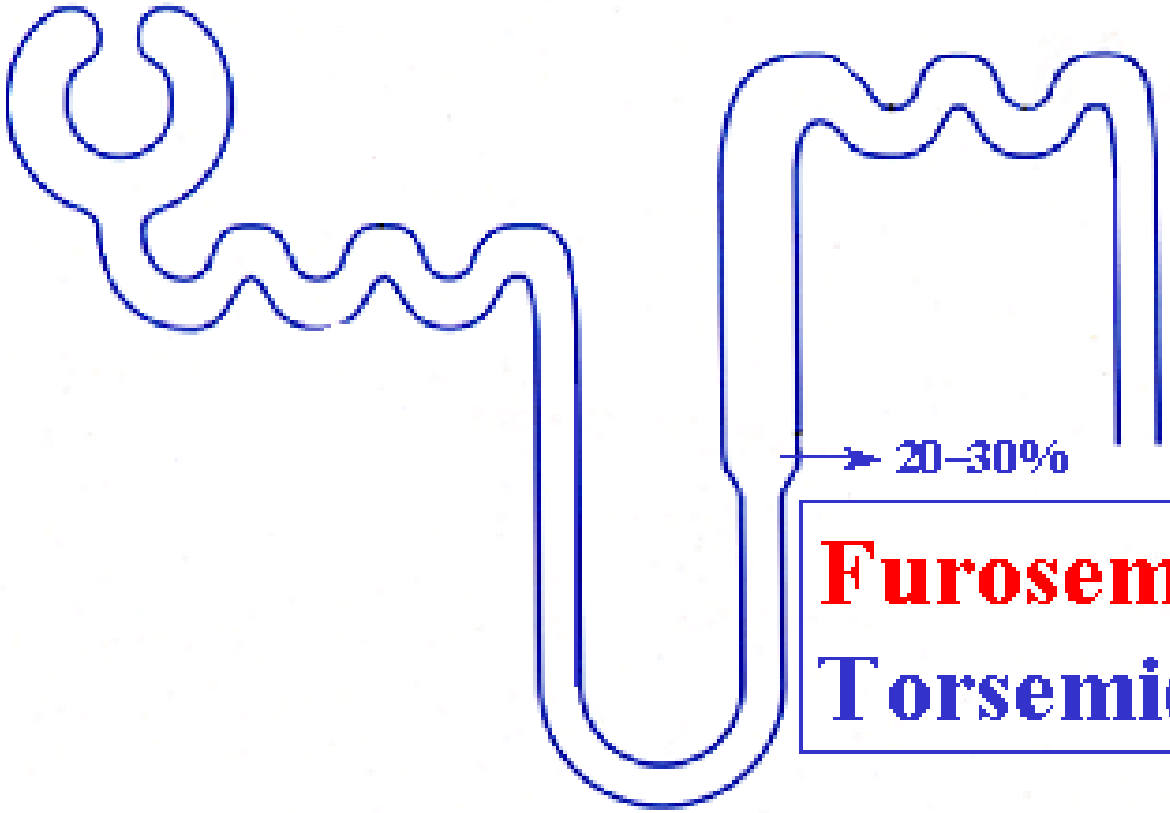
Adverse Effects:

- **Headache, nausea, vomiting**
- **Extracellular volume expansion,** complicates heart failure & pulmonary oedema
- **Excessive use→ dehydration & hypernatraemia** (Adequate water replacement is required).

Contraindication:

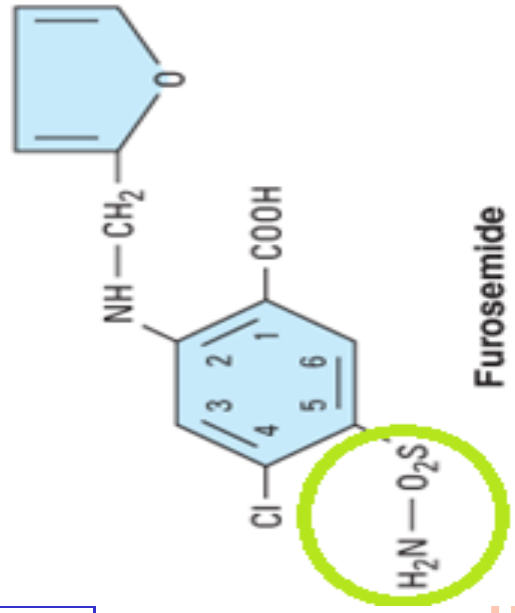
- Chronic heart failure

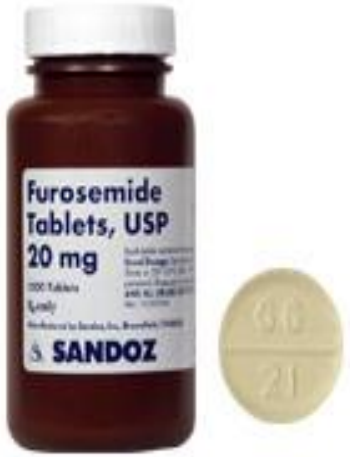
Loop Diuretics



Furosemide

Torsemide





LOOP DIURETICS
High Ceiling diuretics

- The most potent diuretic, termed **"high ceiling diuretic"**

Efficacy:

High natriuresis as 25-30% Na^+ is reabsorbed.

- **Drugs as:**
  - Furosemide - Torsemide
  - Bumetanide – Ethacrynic acid

Loop Diuretics
High Ceiling Diuretics

Bumetanide
Potency40 ,t½ 0.8 h

Ethacrynic Acid
Potency 0.7, t½ 1h

Furosemide
Potency 1, t½ 1.5h

Torsemide
Potency 3, t½ 3.5h

LOOP DIURETICS

Mechanism:

- **inhibit Na^+ / K^+ / 2 Cl^- co-transporter in the luminal membrane of the thick ascending loop of Henle (TAL).**
- **inhibit Ca^{++} and Mg^{++} re-absorption.**

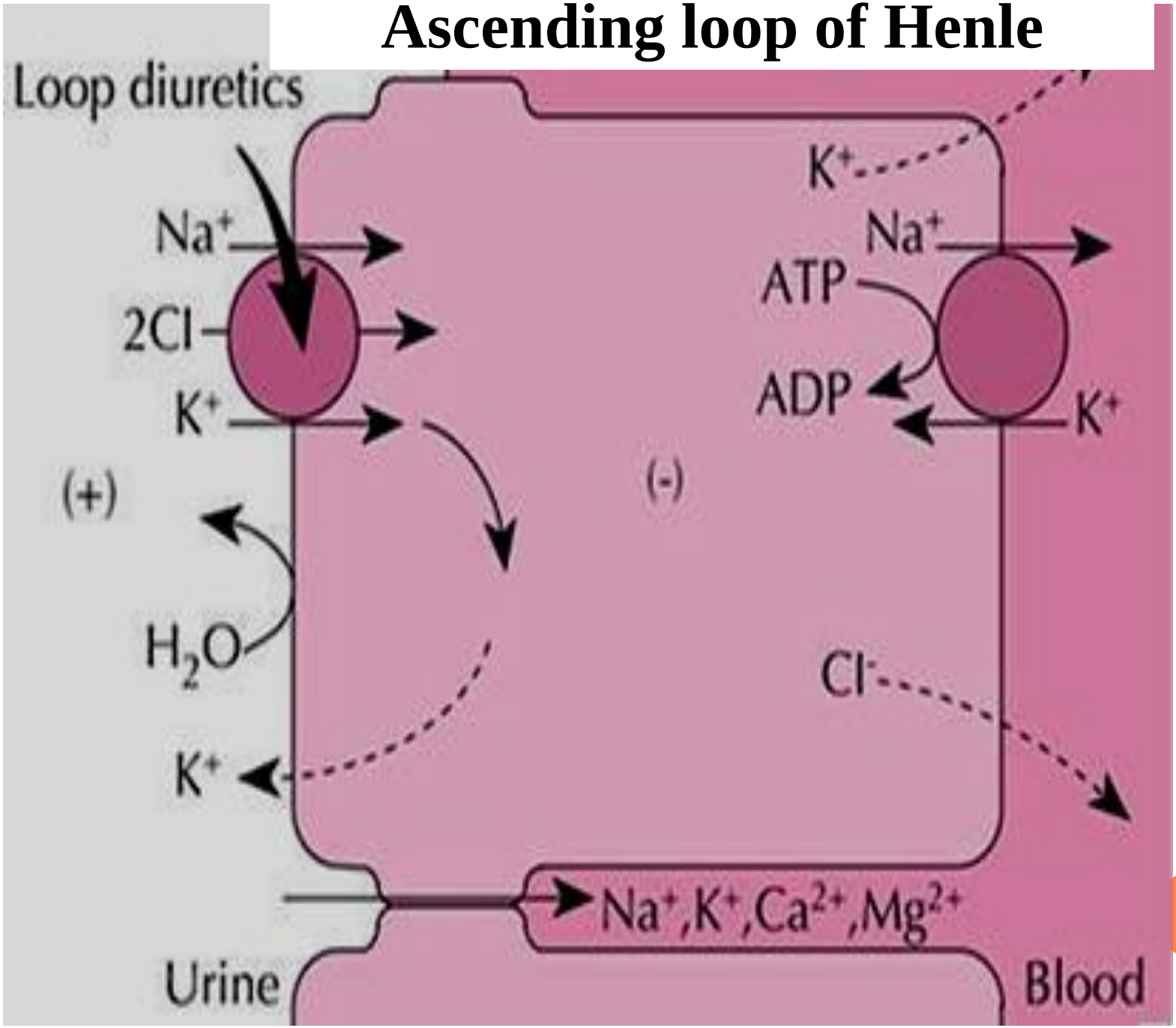
Ascending loop of Henle

- Is impermeable to water

Thick ascending loop of Henle (TAL)

- is responsible for active re-absorption of Na, K and Cl **(25-30% Na^+ is reabsorbed)** via transport system in luminal membrane called **Na^+/ K^+ / $2Cl^-$ co-transporter**
- Ca and Mg are reabsorbed and enter the interstitial fluid via paracellular pathway

Ascending loop of Henle

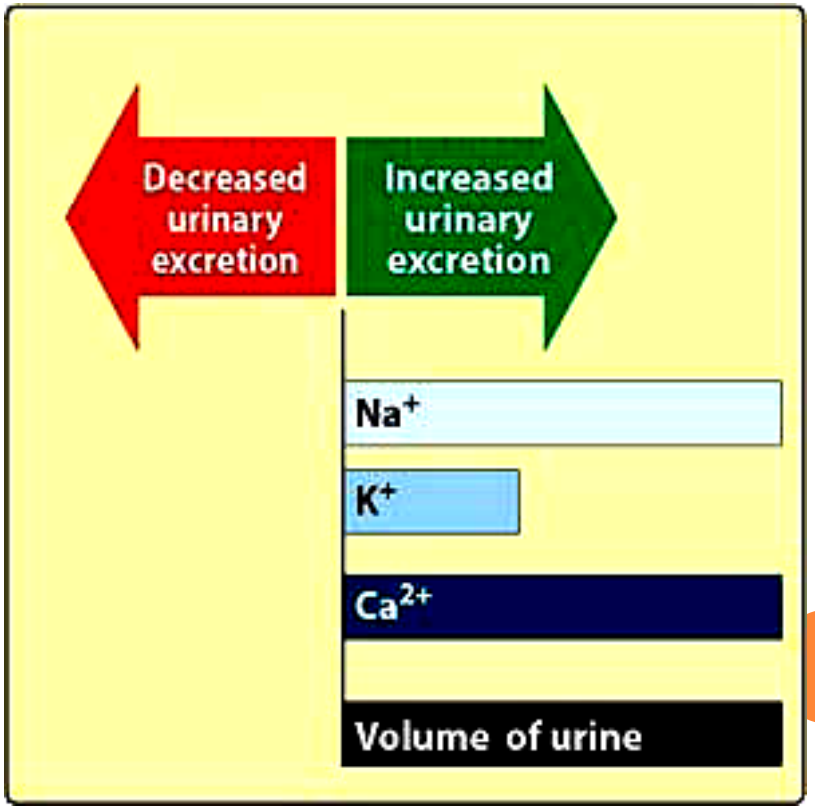


Pharmacokinetics

- Given orally or I. V.
- Have fast onset of action (suitable for emergency)
- Have short duration of action.
- Excreted by active tubular secretion of weak acids into urine
- Interfere with uric acid secretion (hyperuricemia).

Pharmacological effects:

- ↑ urinary excretion of Na^+ and K^+
- ↑ urinary excretion Ca^{++} and Mg^{++}
- ↑ urine volume
- ↑ renal blood flow.



Uses:

are drug of choice for emergency situations as:

- Edema associated with congestive heart failure, nephrotic syndrome
- **Acute** pulmonary edema
- **Acute** hyperkalaemia.
- **Acute** hypercalcemia

ADVERSE EFFECTS

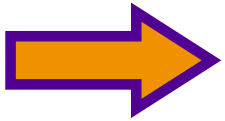
- Volume Depletion
- Hypokalemia
- Hypocalcaemia
- Hypomagnesaemia

- Metabolic Alkalosis
- Ototoxicity
- Hyperuricemia
- Hyperglycemia

LOOP DIURETICS

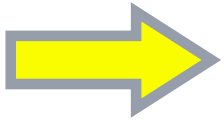
DRUG- DRUG INTERACTIONS

NSAIDS



↓Diuretic Response

Aminoglycosides



↑ Ototoxicity of Loop Diuretic

Adverse effects :

- **Hypo**volemia
- **Hypo**natremia (↓ blood Na^+).
- **Hypo**kalemia (↓ blood K^+)
- **Hypo**magnesaemia (↓ blood Mg^{2+})
- **Hypo**calcaemia (↓ blood Ca^{2+})
- Metabolic alkalosis.
- Postural hypotension
- **Hyper**uricemia *(increase blood uric acid and gouty attack).*
- **Ototoxicity** *(risk increased if combined with aminoglycosides)*
- Allergic reactions
- Dietary K supplementation or K-sparing diuretics should be used to avoid hypokalemia .

Thiazide diuretics

Drugs as:

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

THIAZIDE DIURETICS

Chlorothiazide
Potency 0.1, t½ 2h

Chlorthalidone
Potency 10, t½ 26h

Metolazone
Potency 5, t½ 5h

Hydrochlorothiazide
Potency 1 , t½ 3h

Indapamide
Potency 20, t½ 16h

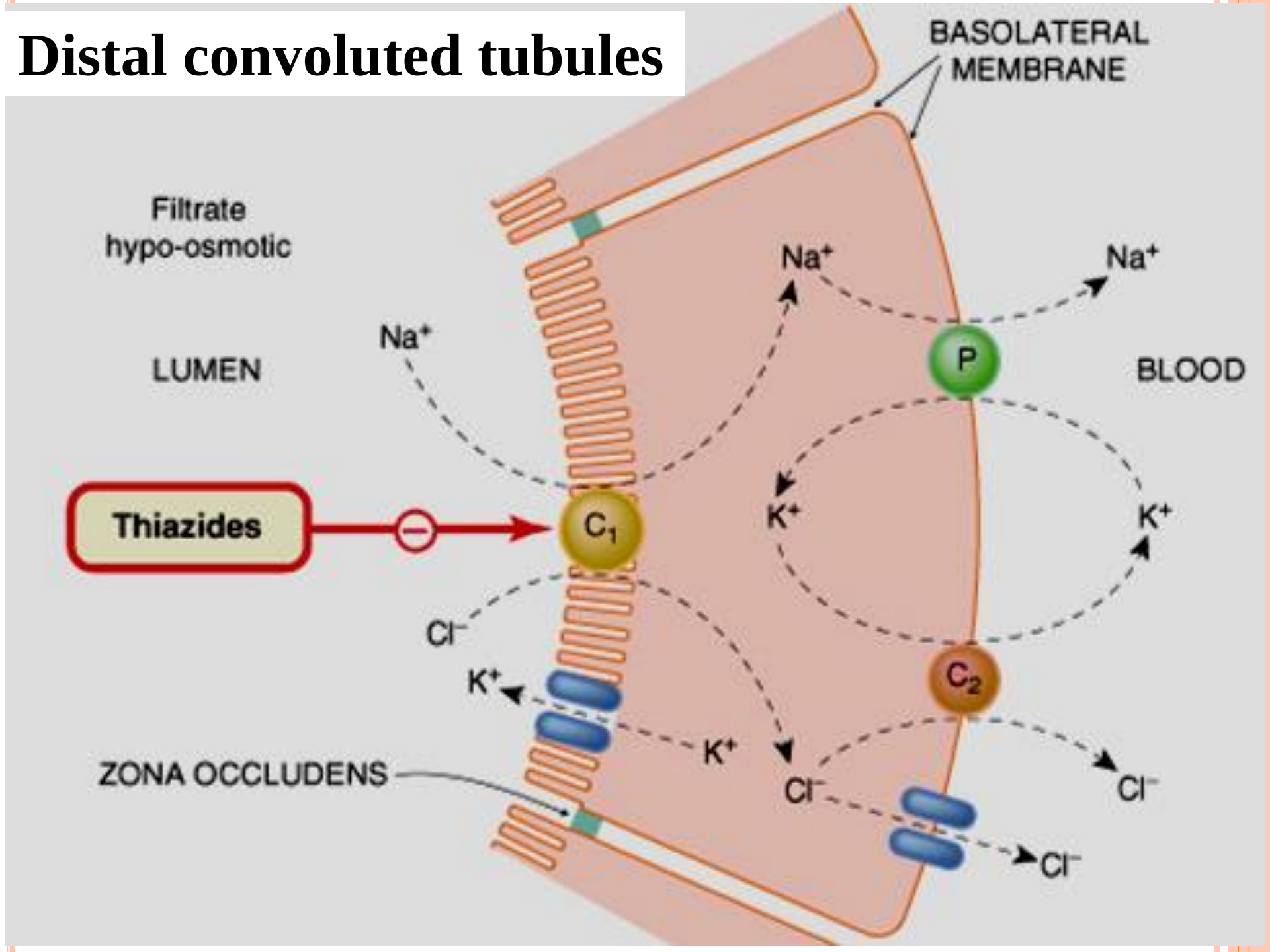
Thiazide diuretics

Mechanism of action:

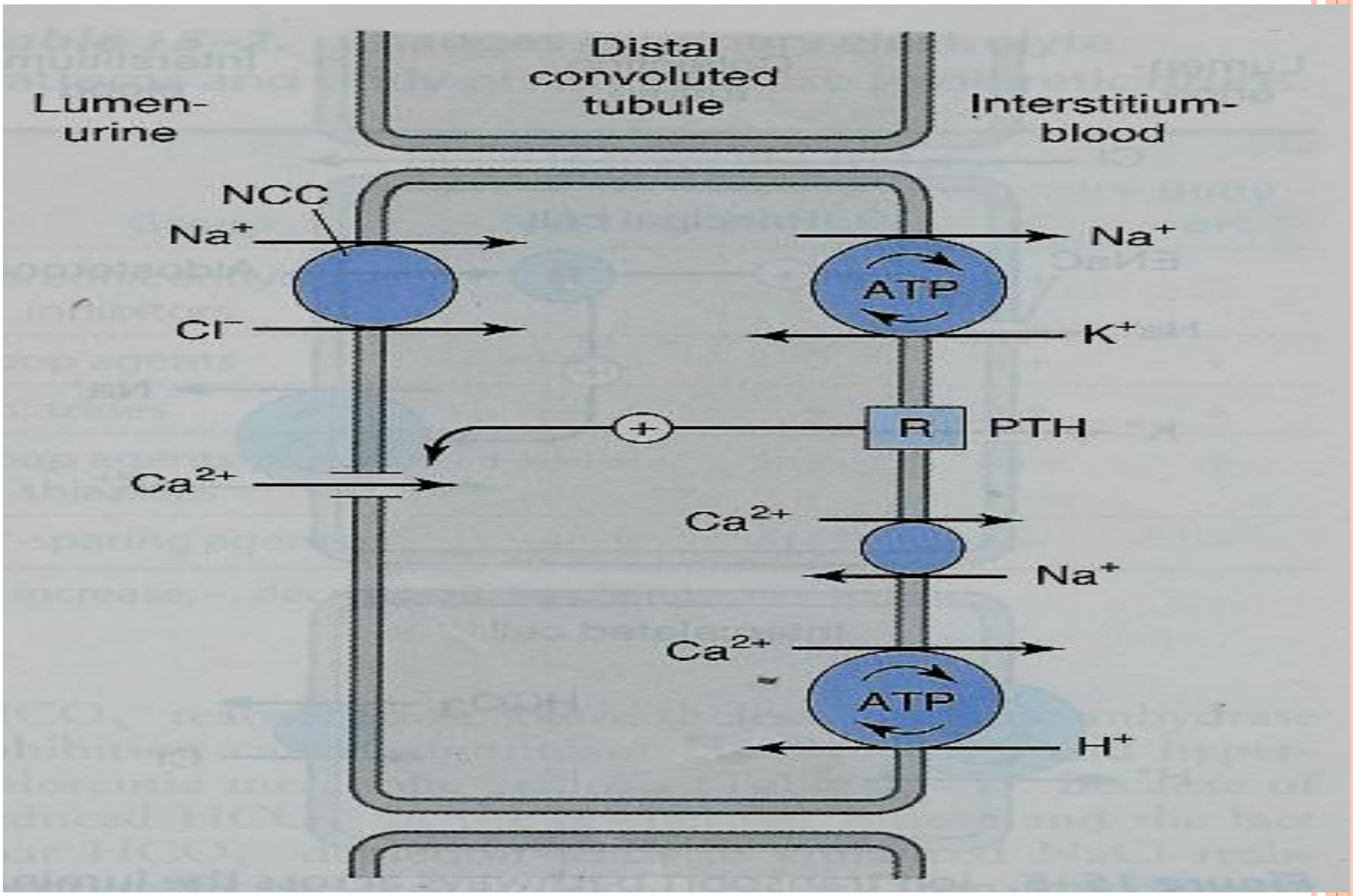
- **acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.**

- Efficacy: **Moderate natriuresis (5-10% of filtered load of sodium is reabsorbed).**

Distal convoluted tubules



Mechanism of action of thiazide diuretics

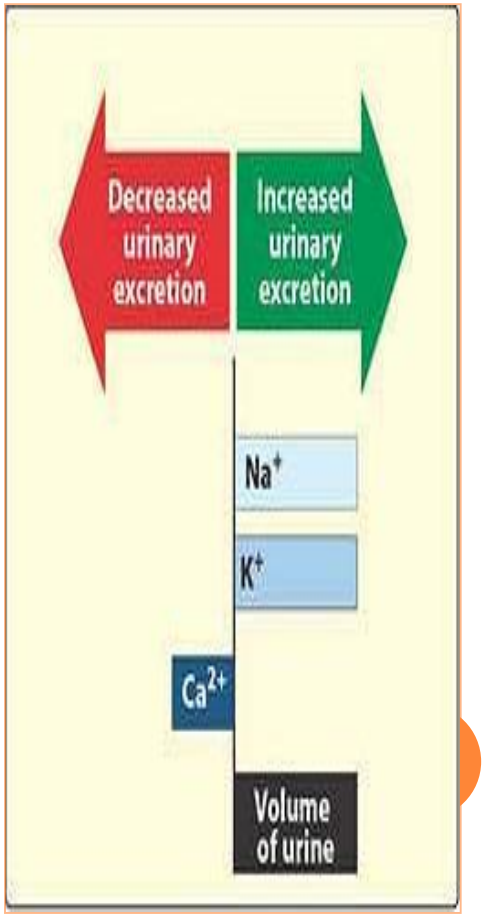


Pharmacokinetics:

- **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:

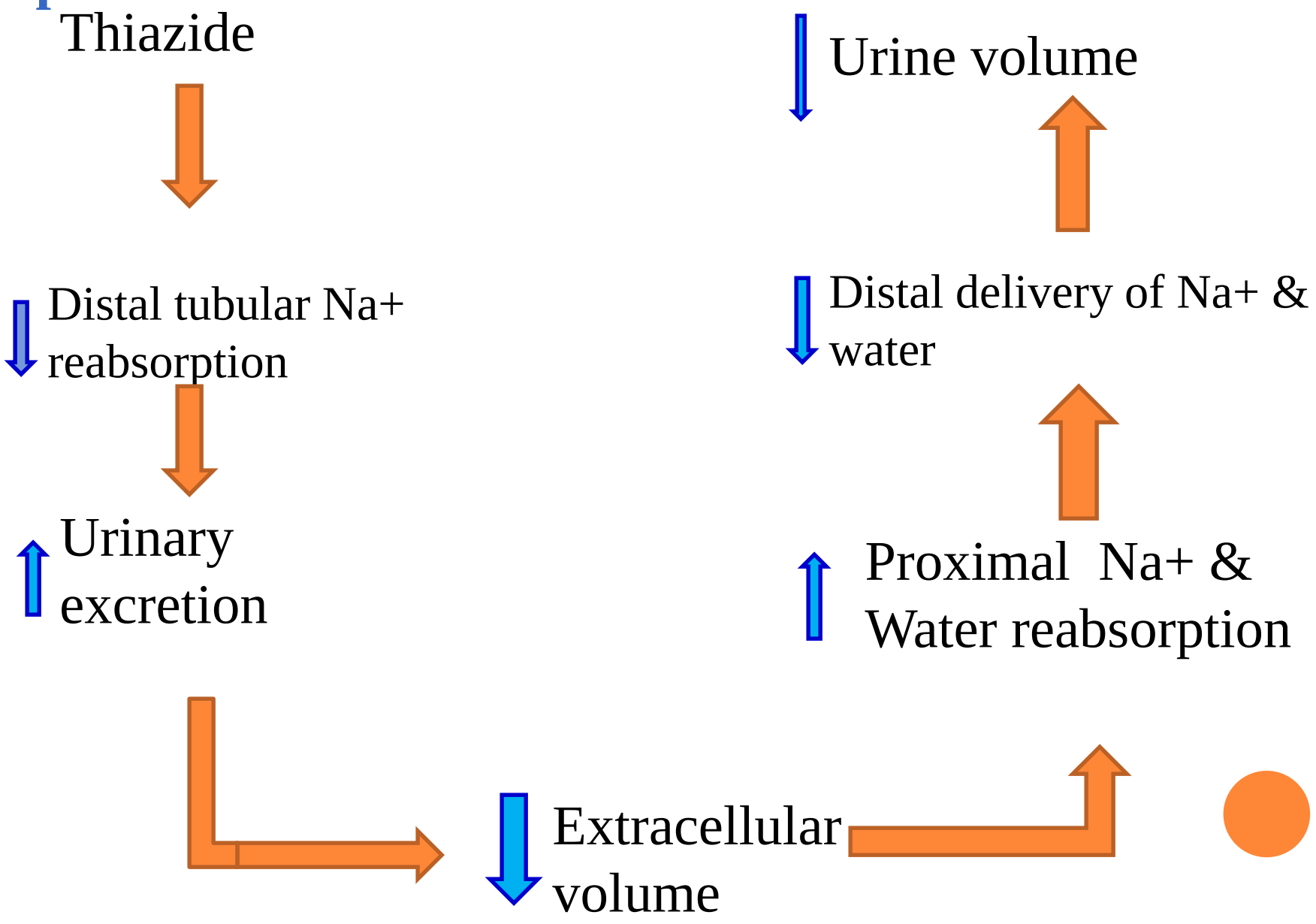
- ↑ urinary NaCl excretion
- ↑ urinary K excretion **(Hypokalemia)**
- ↑ urinary magnesium excretion
- ↓ **urinary calcium excretion**
- ↑ calcium re-absorption **hypercalcemia**



Uses:

- **Treatment of essential hypertension *(cheap-well tolerated).***
- **Treatment of mild heart failure *(to reduce extracellular volume).***
- **Treatment of osteoporosis**
- **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
- **Hypo**natremia
- **Hypo**volemia (volume depletion)
- **Hypo**kalemia
- Metabolic alkalosis.
- **Hyper**uricemia (gout)
- **Hyper**calcemia
- **Hyper**glycemia
- **Hyper**lipidemia

ADVERSE EFFECTS

Volume Depletion

Metabolic Alkalosis

Hypokalemia

Hyperuricemia

Hypercalcaemia

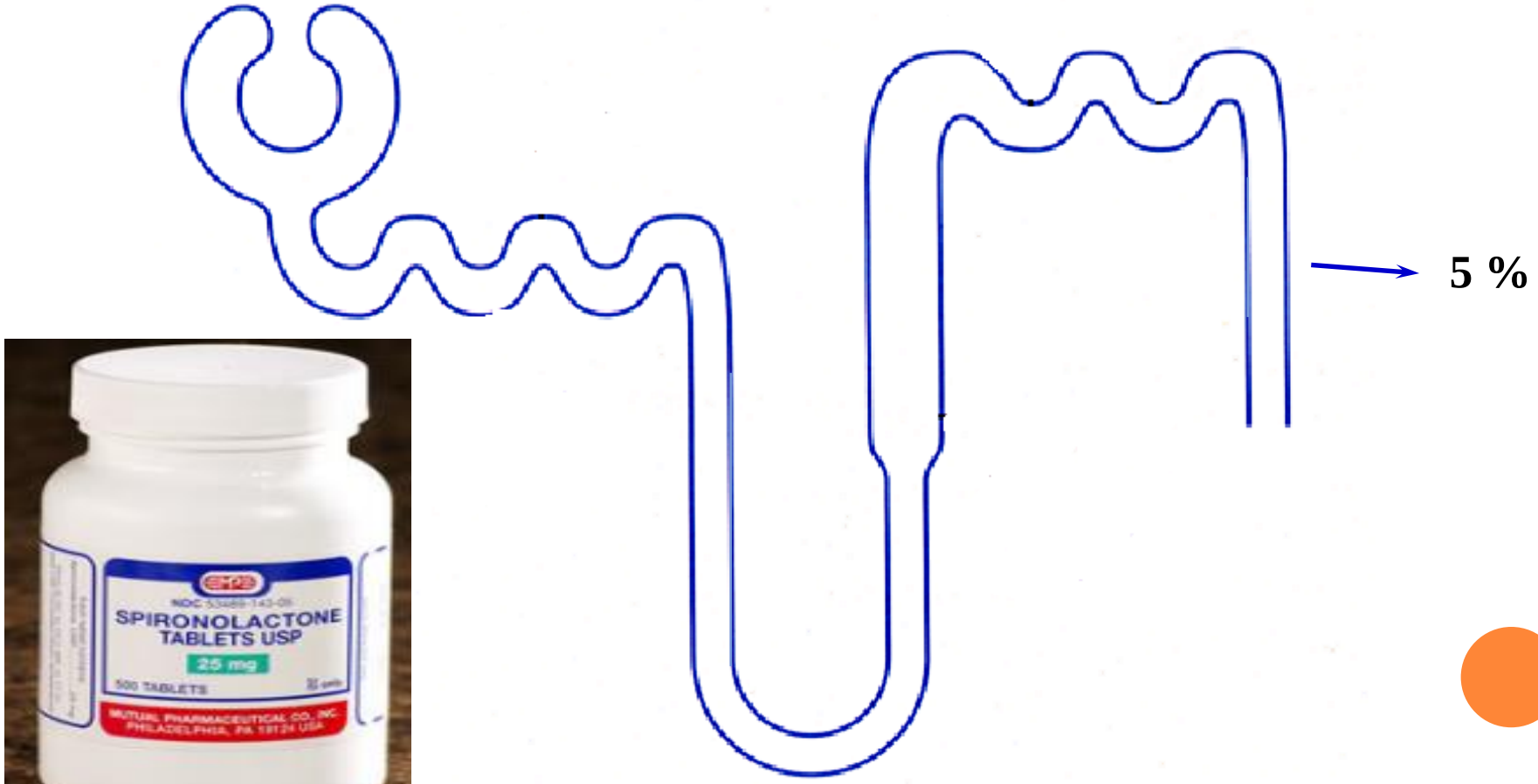
Hypomagnesaemia

Hyperglycemia

Hyperlipidemia

Potassium-sparing diuretics

Spironolactone
Amiloride
Triamterene



Potassium-sparing diuretics

Steroids

Competitive aldosterone antagonists

- Spironolactone
- Eplerenone

Nonsteroids

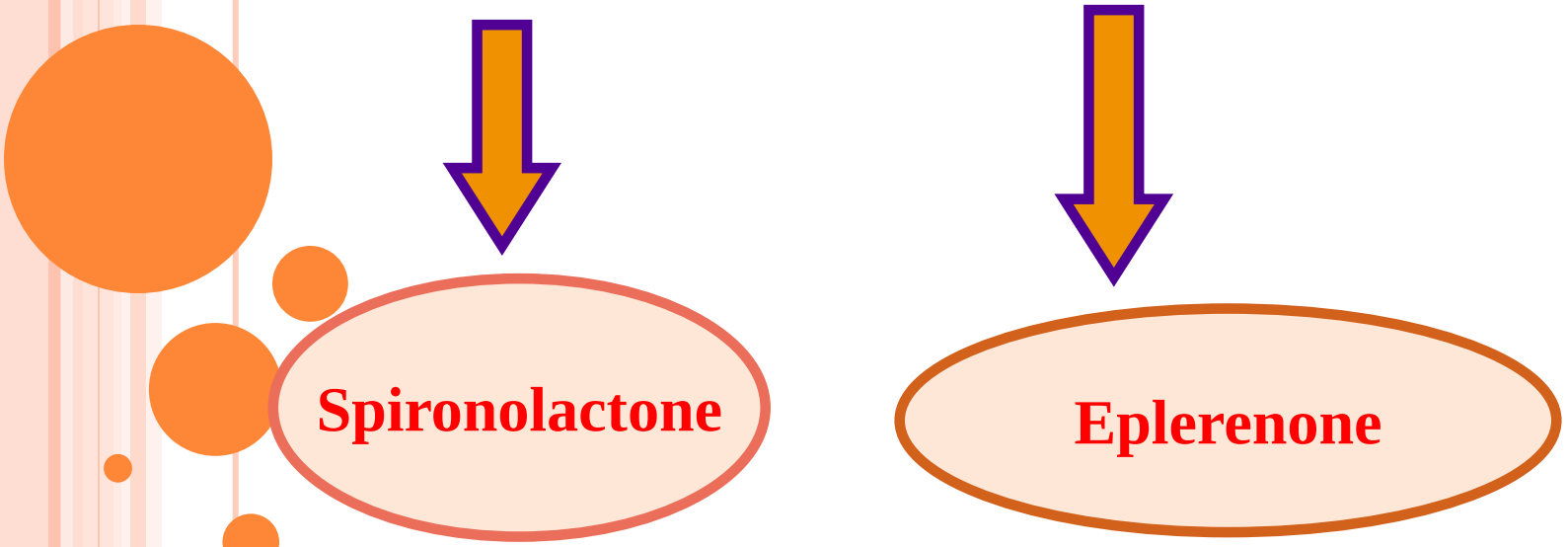
Na^+ channels inhibitors

- Amiloride
- Triamterene

Aldosterone Antagonists

Also Called:

- K-Sparing Diuretics
- Mineralocorticoid receptor antagonists

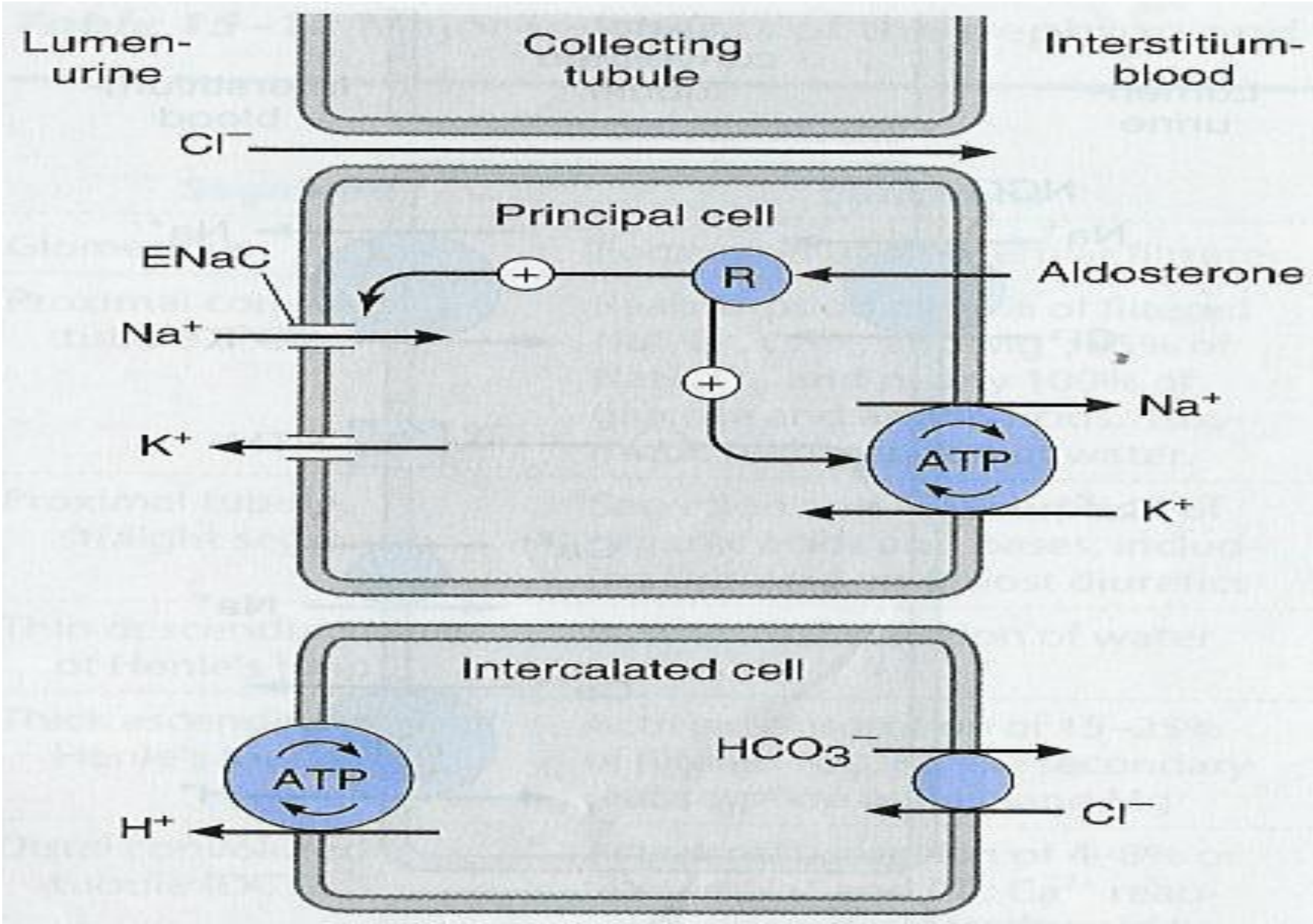


Mechanism of action

Spironolactone:

act at the collecting duct by competitive inhibition of cytoplasmic aldosterone receptors →↑ Excretion of Na+, Cl^- & ↓Excretion of K+,H+

COLLECTED TUBULES (CT)



Pharmacokinetics of spironolactone

- Well absorbed from the GIT
- Highly protein-bound
- Undergoes enterohepatic recycling
- Delayed onset of action (nuclear receptor), maximum diuretic action 4 days.
- Converted in the gut & liver to active metabolite, $t_{1/2}$=16h]

Pharmacodynamics:

- ↑ **urinary Na^+ excretion**
- ↓ **urinary K^+ excretion Hyperkalemia**
- ↓ **H^+ excretion (acidosis).**
- has antiandrogenic action.

Therapeutic uses:

- **Treatment of hypertension**

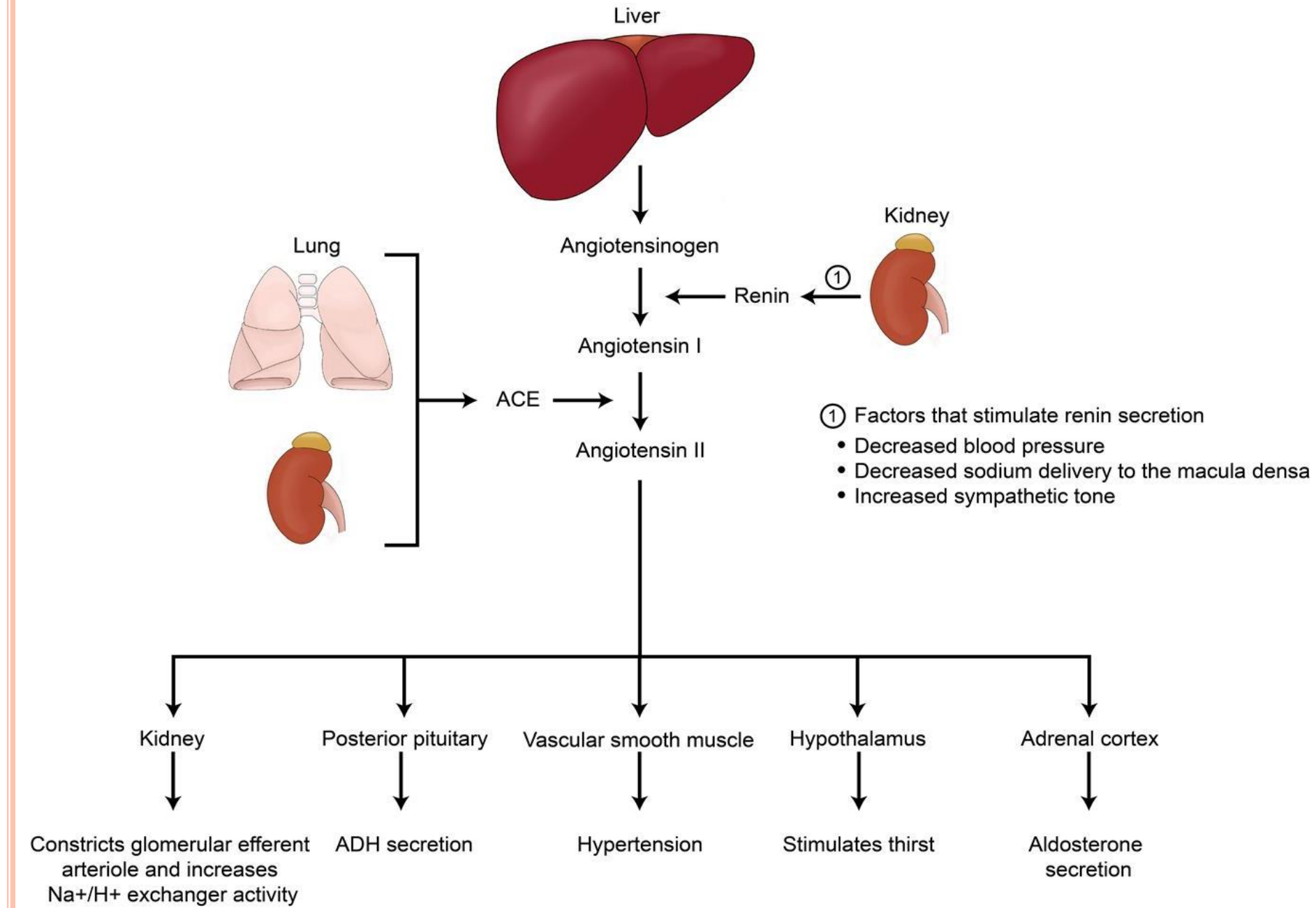
Usually used combined with thiazide or loop diuretics to:

1) **Enhances natriuresis caused by other diuretics**
2) **Correct for hypokalemia.**

Therapeutic uses of aldosterone antagonists:

- **Treatment of primary hyperaldosteronism (Conn's syndrome)**
- **Treatment of hirsutism, acne** due to the antiandrogenic effects.
- **Treatment of secondary hyperaldosteronism in diseases as**
  - **CHF**
  - **Edema of hepatic cirrhosis**
  - **Nephrotic syndrome**

Renin-Angiotensin-Aldosterone System



Adverse Effects

- Hyperkalemia.
- Metabolic acidosis.
- Gynecomastia
- Impotence
- Menstrual irregularities
- GIT upset and peptic ulcer

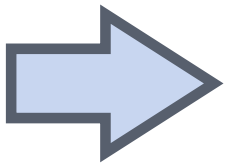
Contraindications:

- **Hyperkalemia:**
  - **chronic renal failure**
  - **K+ supplement use**
  - **β-blockers**
  - **ACE inhibitors.**

- **Liver disease (dose adjustment is needed).**

Drug -Drug Interactions

ACE Inhibitors
Beta-Blockers
K Supplements
K-Sparing Diuretics



↑ Hyperkalemia-induced by K-Sparing diuretics

Potassium-sparing diuretics

Na^+ channels inhibitors

- **Amiloride**
- **Triamterene**

SODIUM CHANNEL INHIBITORS

Triamterene
Potency 0.1,
t½ 4.2 h,

Amiloride
Potency 1,
t½ 21h,

Mechanism of action

- **Inhibition of Na influx through** direct blockade of the **epithelial sodium channel (ENaC) on the lumen side of the kidney collecting tubule (triamterene – amiloride).**

USES OF SODIUM CHANNEL INHIBITORS

- Used in Combination with Loop & Thiazide Diuretics
- Treatment for lithium-Induced Diabetes Insipidus

ADVERSE EFFECTS

Hyperkalemia

CONTRAINDICATIONS OF SODIUM CHANNEL INHIBITORS

Triamterene & amiloride

The risk of developing **hyperkalemia** is increased in patients who are also on ACE inhibitors, angiotensin II receptor antagonists, other potassium-sparing diuretics, or any potassium-containing supplements.

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.

Therapeutic applications of diuretics

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 ≥ 40-50 ml/min
- Loop diuretic are used below given values, with increasing the dose 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 the drug of choice.

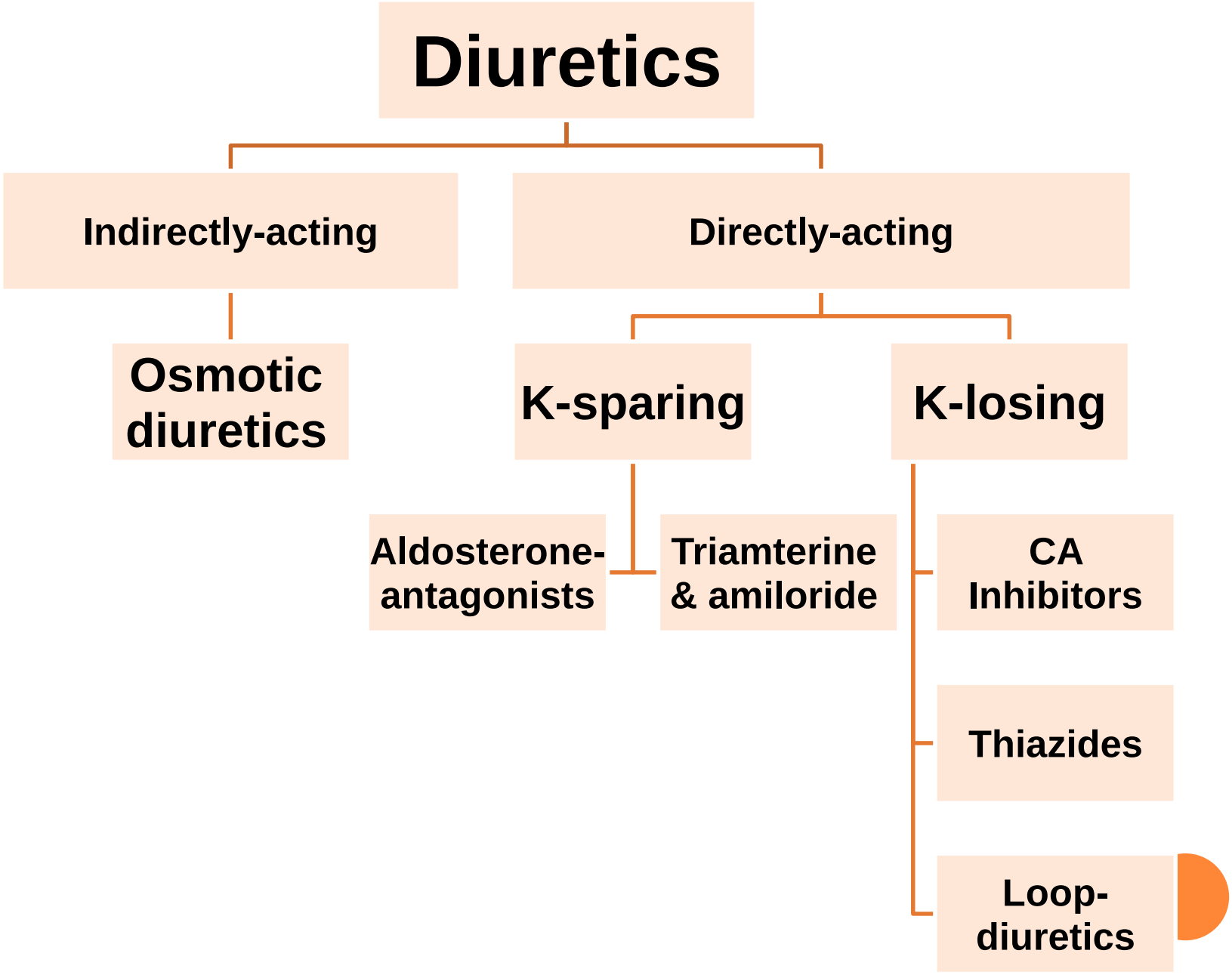
Site of action of diuretics

segment	Function	transporter	Diuretics
Proximal convoluted tubules	Re-absorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 65% $NaHCO_3$	Na/H transporter, Carbonic anhydrase enzyme	Carbonic anhydrase inhibitors
Proximal Straight Tubules	Secretion and re-absorption of organic acids and bases	Acid & base transporter	None
Thick ascending loop	Active reabsorption 25% Na, K, Cl Secondary Ca, Mg reabsorption	Na/K/2Cl transporter	Loop diuretics
Distal convoluted tubules	Active tubular reabsorption of 5%Na, Cl, Ca	Na and Cl cotransporter	Thiazide diuretics
Collecting tubules	Na reabsorption K & H secretion	Na channels K & H transporter	K-sparing diuretics

Diuretics	Mechanism of action	Effects
CA inhibitors Acetohexamide Dorzolamide	Inhibition of NaHCO3 reabsorption in PCT	↑ Urinary Na HCO3, K Urinary alkalosis Metabolic acidosis
Osmotic diuretic Mannitol	Osmotic effect in PCT	↑Urine excretion ↑ Little Na
Loop diuretics Furosemide	Na/K/2Cl transporter in TAL the most effective	↑Urinary Na, K, Ca, Mg
Thiazide diuretics hydrochlorothiazide	Na and Cl cotransporter in DCT	↑Urinary Na, K, Mg BUT↓ urinary Ca (hypercalcemia) Metabolic alkalosis
K-sparing diuretic Spironolactone.	competitive antagonist of aldosterone in CCT	↑ Urinary Na ↓ 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


Diuretics
Indirectly-acting
Directly-acting
Osmotic diuretics
K-sparing
K-losing
Aldosterone-antagonists
Triamterine & amiloride
CA Inhibitors
Thiazides
Loop-diuretics