DIURETICS
Part 1

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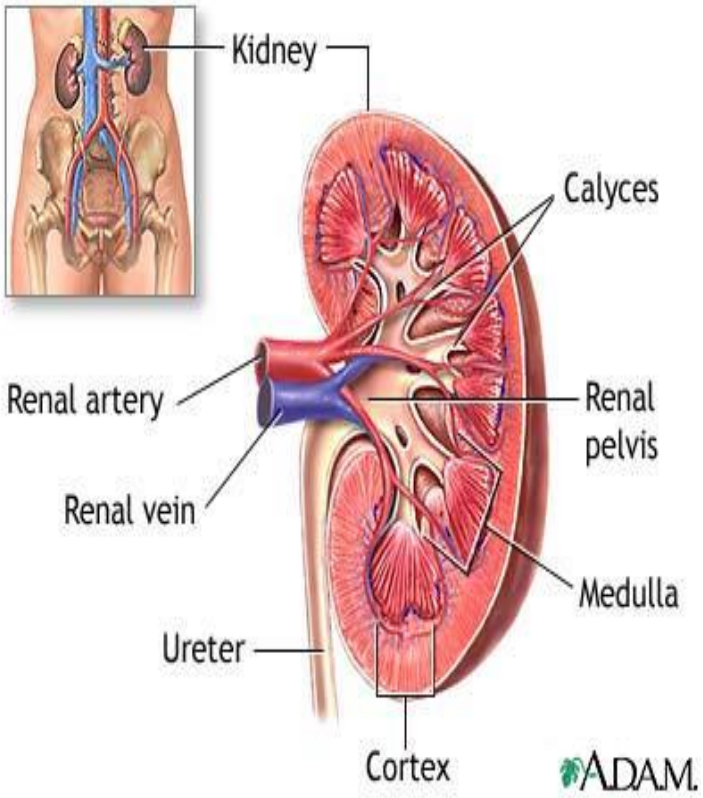
Pharmacology Unit



Diuretics

- Are drugs that increase renal excretion of sodium and water resulting in increase in urine volume.
- **Diuresis:** is the process of excretion of water in the urine.
- **Natriuresis:** is the process of excretion of sodium in the urine .

Mechanism of actions of diuretics

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

Normal Sodium Re-absorption

Nephron Segment	Filtered Na^+ re-absorbed
Proximal convoluted tubules	65 % Na , HCO3
Ascending Loop of Henle	20-30% Active reabsorption Na, K, Cl Ca and Mg
Distal convoluted tubules	5-10% Active reabsorption Na, Cl
Cortical Collecting Tubules	5% Na reabsorption K & H secretion

Normal Sodium Re-absorption

Nephron Segment	Na^+ Transporter	Filtered Na^+ re-absorbed
Proximal convoluted tubules	Na^+/H^+ transporter Carbonic anhydrase enzyme	**65 %** **As Na, HCO3**
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**

Site of action of diuretics

segment	Function	transporter
Proximal convoluted tubules	Re-absorption of 100% glucose and amino acids, 66% Na, K, Ca, Mg; 85% $NaHCO_3$	Na/H transporter Carbonic anhydrase enzyme
Proximal Straight Tubules	Secretion and re-absorption of organic acids and bases	Acid & base transporter
Thick ascending loop	Active reabsorption 25% Na, K, Cl, Secondary re-absorption of Ca, Mg	Na/K/2Cl transporter
Distal convoluted tubules	Active tubular reabsorption of 5%Na, Cl, Ca	Na and Cl cotransporter
Collecting tubules	Na reabsorption K & H secretion	Na channels K & H transporter

Sites of action for diuretics

How diuretics produce their effects?

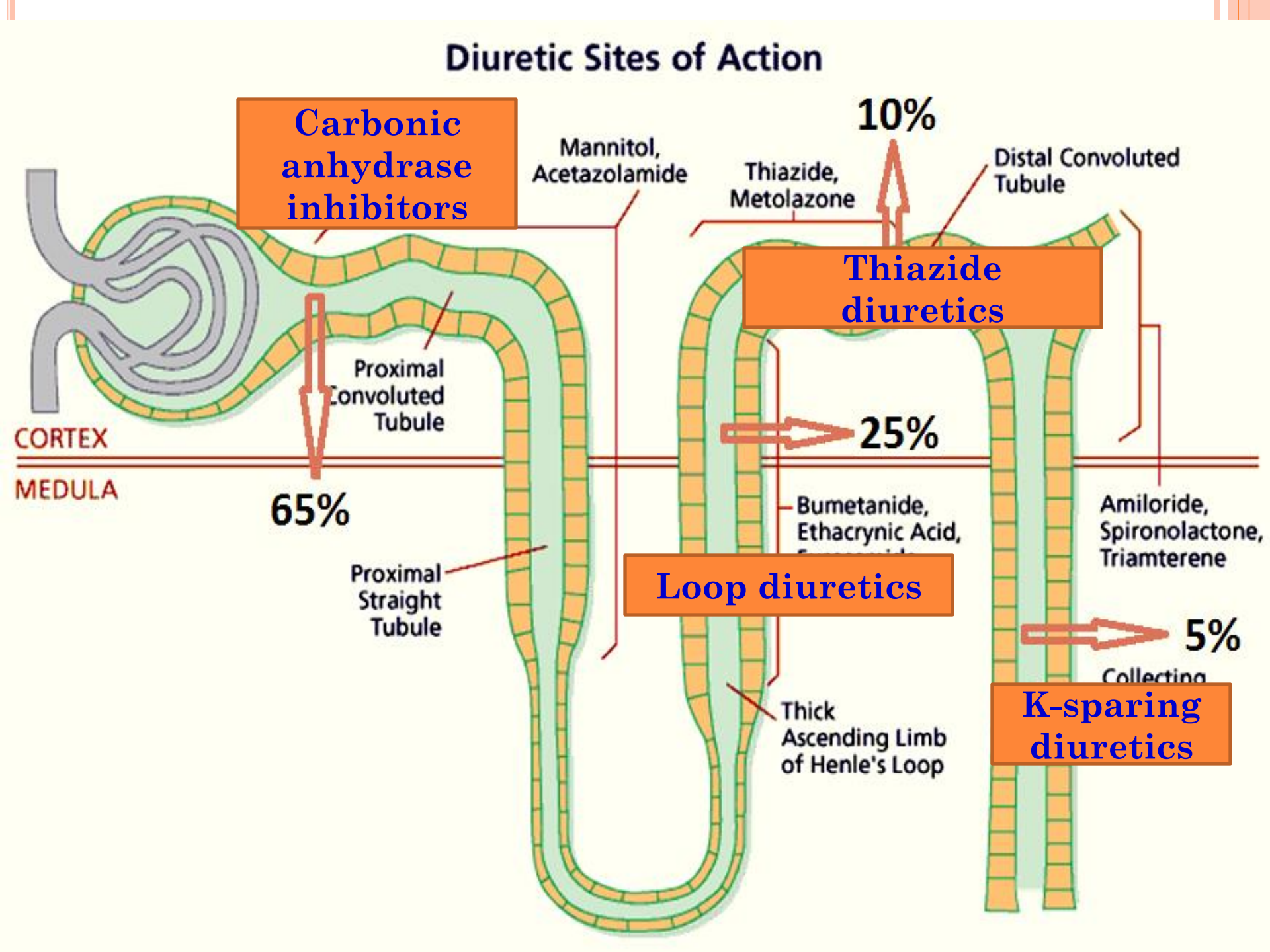
- Diuretics affect carriers or transporters in luminal membrane of renal tubular cells required for tubular reabsorption of sodium from filtrate back into blood.

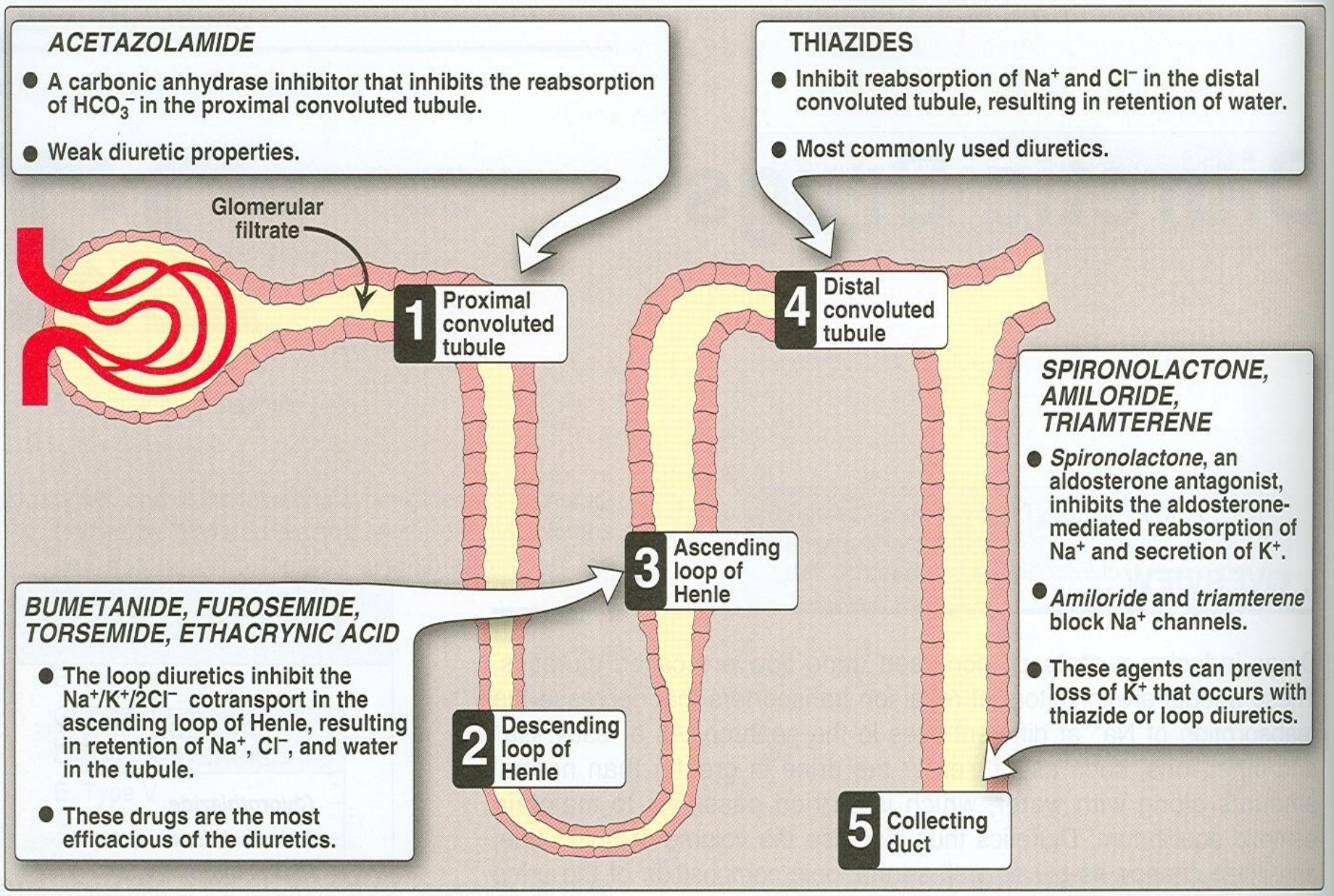
Types of diuretics

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



Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

Carbonic Anhydrase Inhibitors

Carbonic Anhydrase Inhibitors

Acetazolamide – dorzolamide

Mechanism of action:

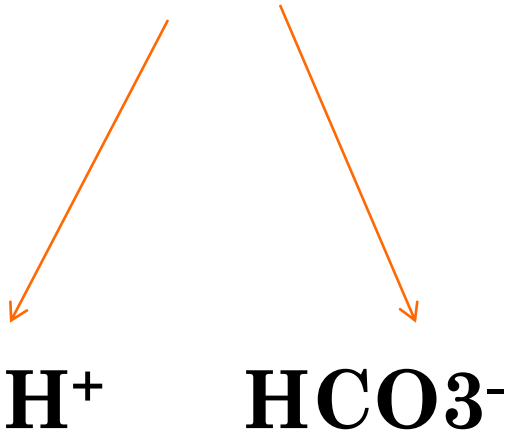
Site of action: proximal convoluted tubules

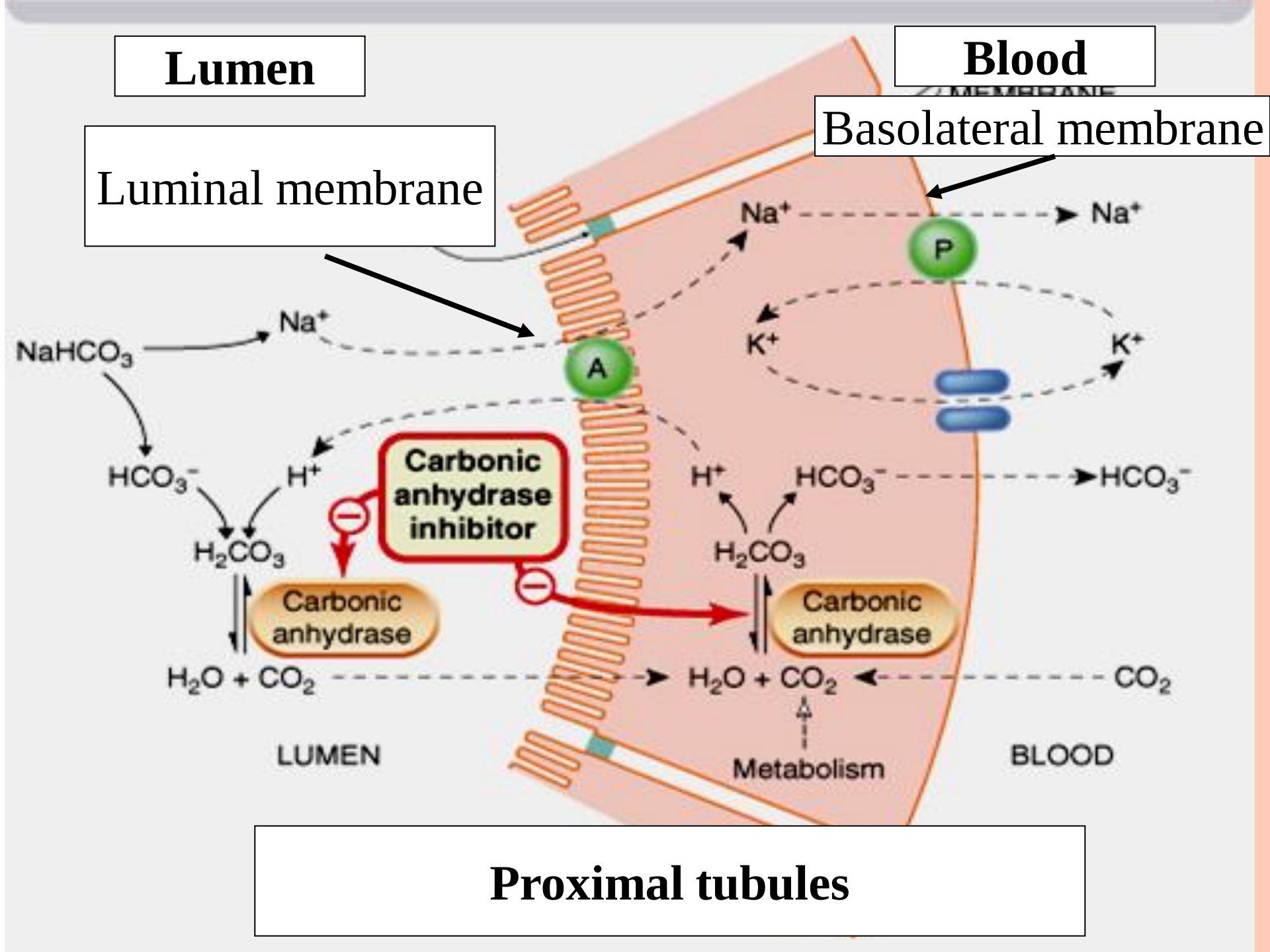
Inhibits **carbonic anhydrase (CA) enzyme** in proximal convoluted tubules thus interferes with **NaHCO3 re-absorption** and causes diuresis.

Carbonic Anhydrase Inhibitors

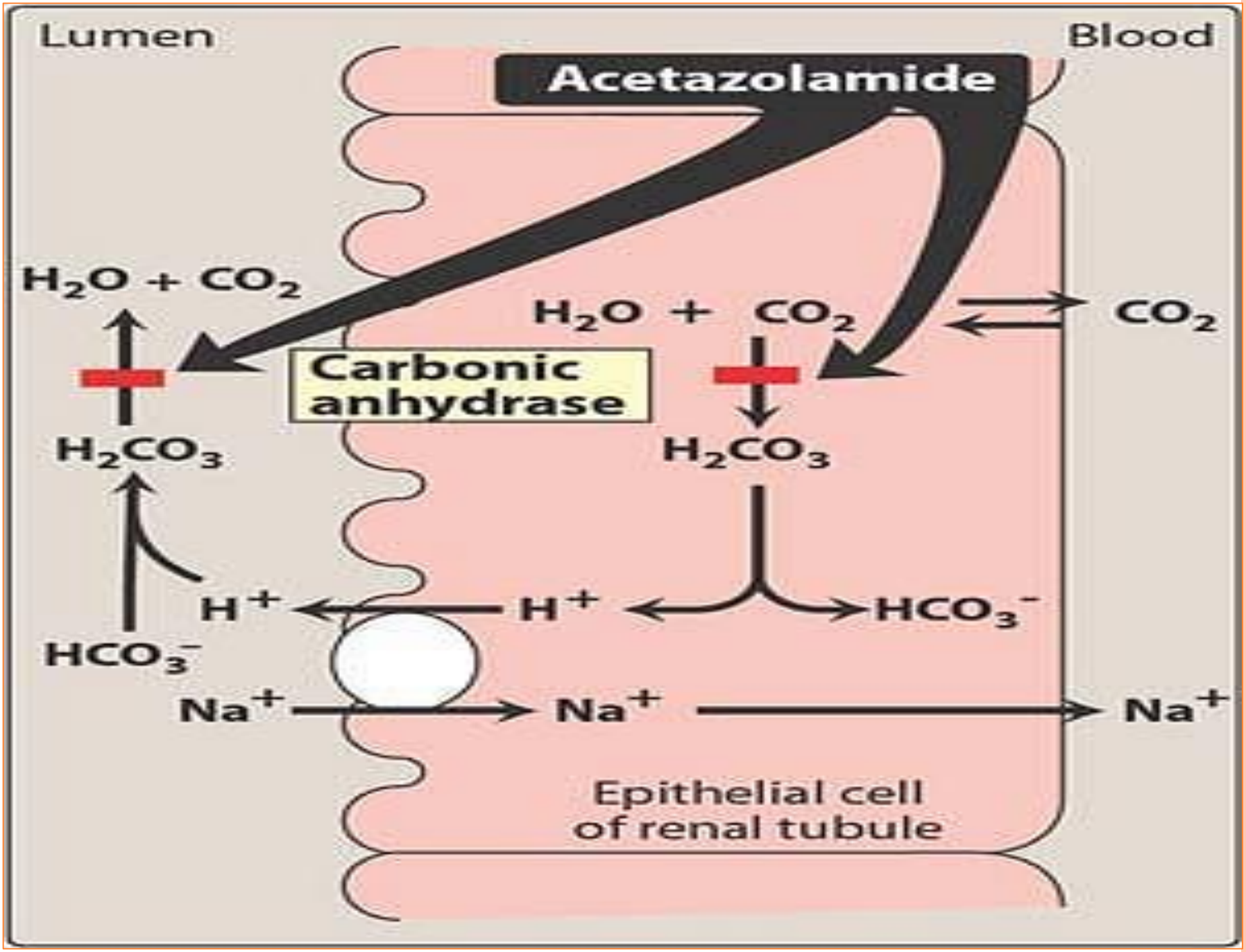
CA is required for reversible reaction,

in which $CO_2 + H_2O \rightleftharpoons H_2CO_3$





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:

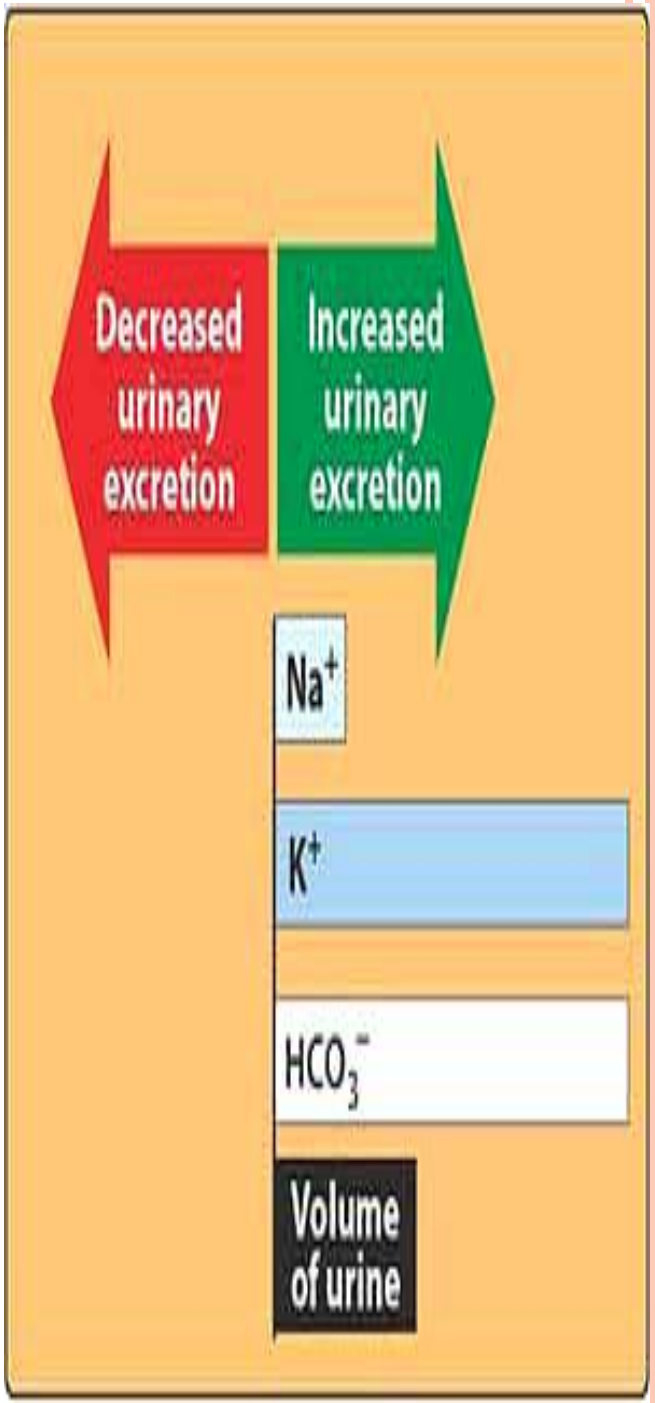
- given orally once a day.
- Onset of action is rapid (30 min).
- Duration of action (12 h).
- Excreted by active secretion in proximal convoluted tubules.
- Produces alkaline urine

Pharmacological actions:

- ↑ urine volume mildly
- ↑ 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.



Therapeutic uses:

- **Open angle glaucoma**

  carbonic anhydrase inhibitors cause ↓ 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:

- **Epilepsy (decrease cerebrospinal fluid, CSF).**
- **Metabolic alkalosis**
- **Urinary alkalinization to enhance renal excretion of acidic substances (cysteine in cystinuria).**
- **Hyperphosphatemia**

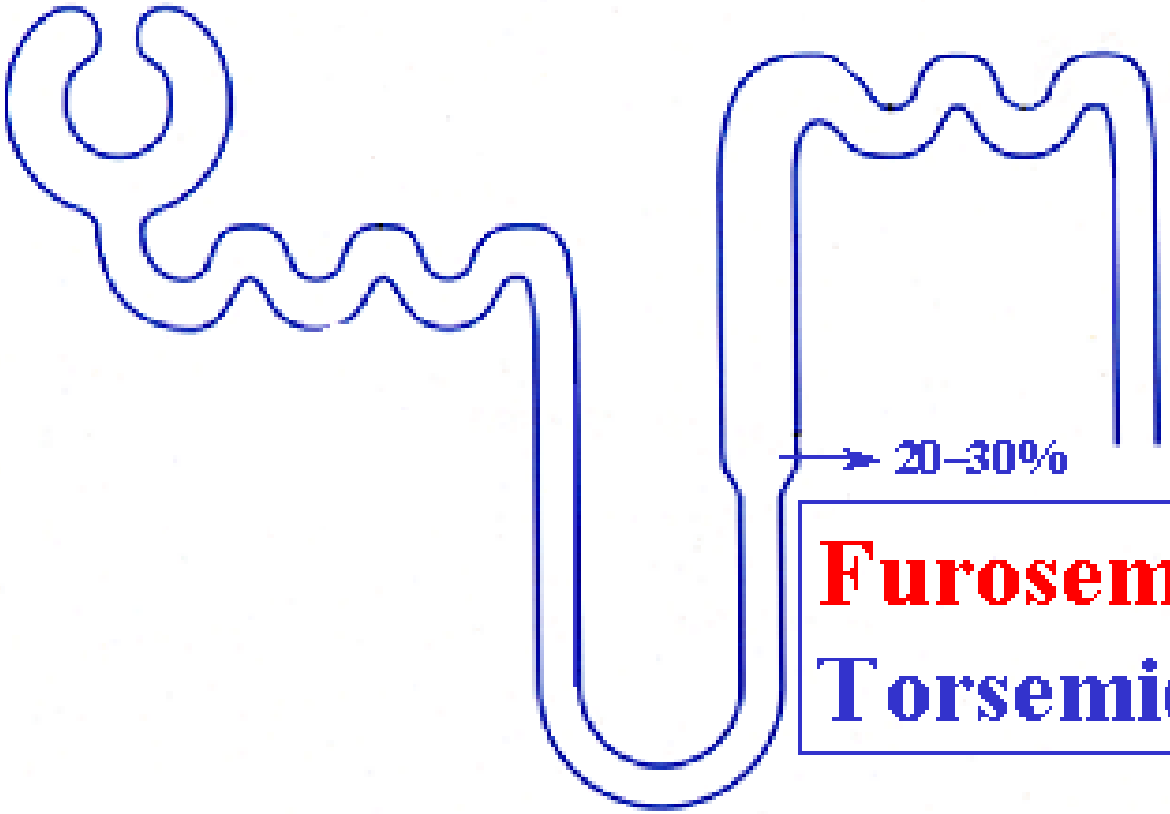
Adverse effects:

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

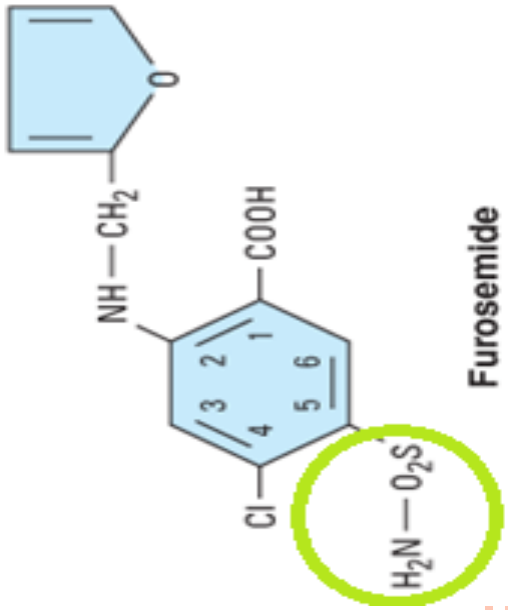
Dorzolamide

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

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 - Ethcrynic 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

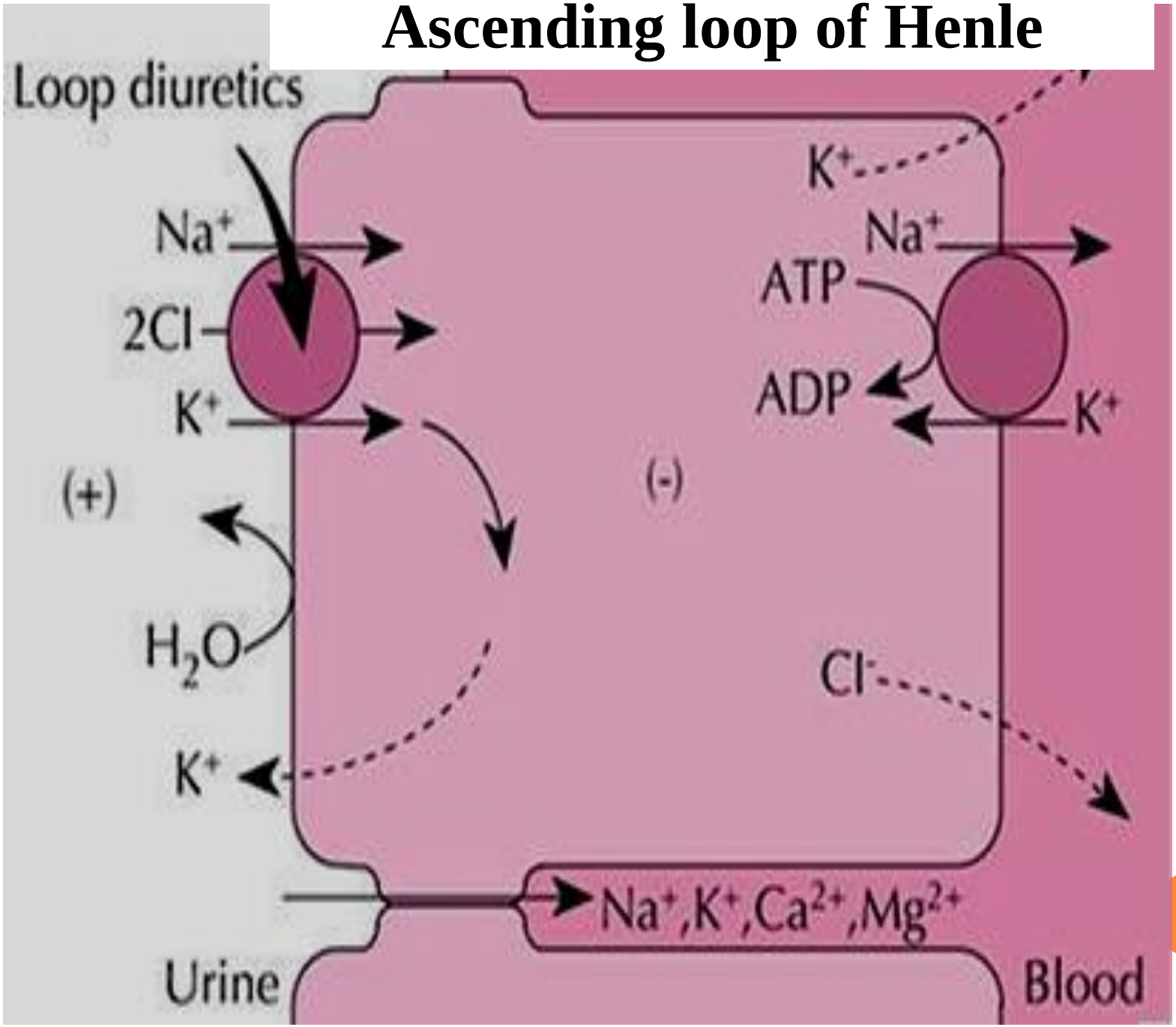
Mechanism:

- 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
- **In 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

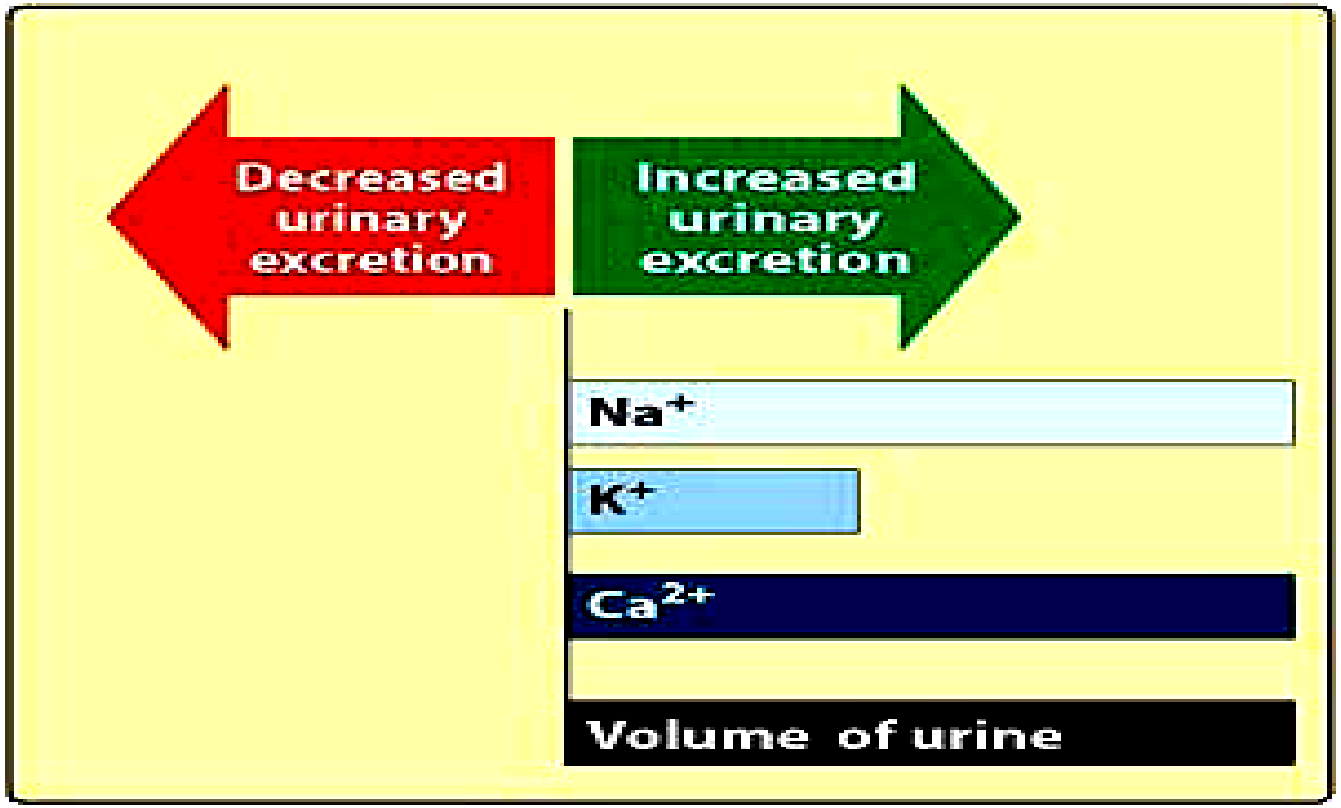


Pharmacokinetics

- 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

Adverse effects :

- **Hypovolemia**
- **Hyponatraemia (↓ blood Na^+).**
- **Hypokalemia (↓ blood K^+)**
- **Hypomagnesaemia (↓ blood Mg^{2+})**
- **Hypocalcaemia (↓ blood Ca^{2+})**
- **Metabolic alkalosis.**
- **Postural hypotension**
- **Dietary K supplementation or K-sparing diuretics should be used to avoid hypokalemia .**

Adverse effects :

- **Hyperuricemia *(increase blood uric acid and gouty attack).***
- **Ototoxicity *(risk increased if combined with aminoglycosides)***
- **Allergic reactions**

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

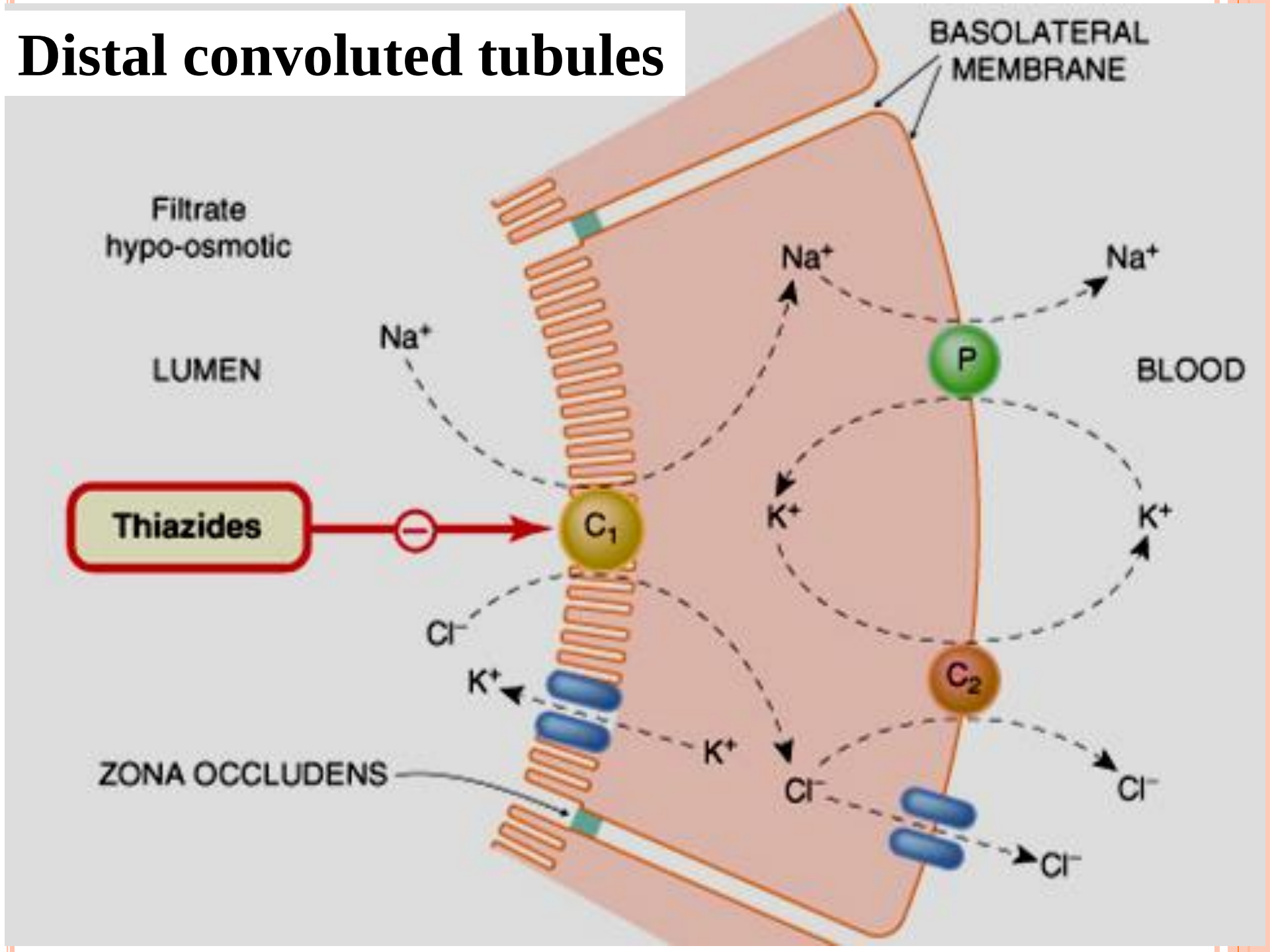
Thiazide diuretics

Mechanism of action:

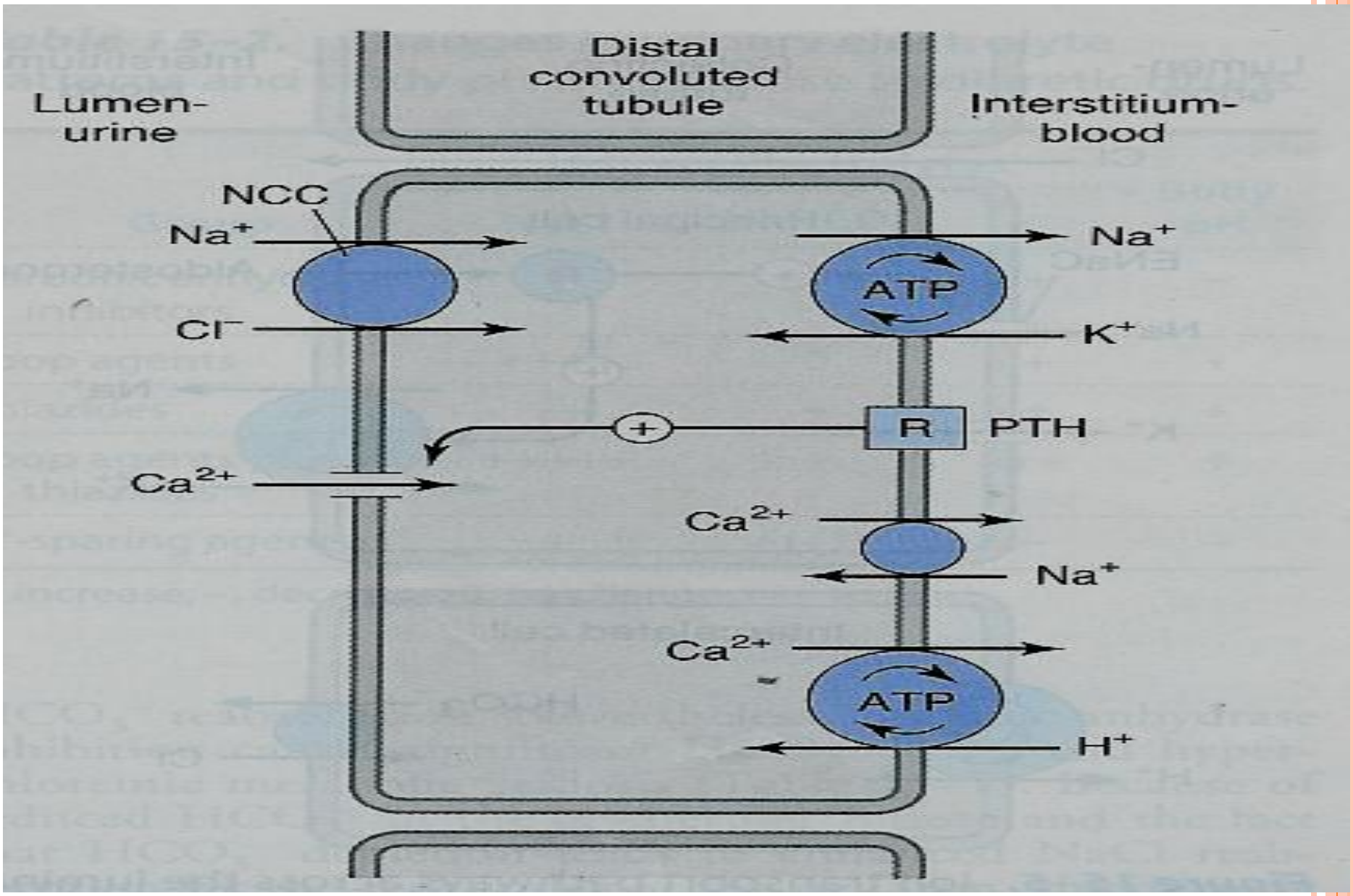
- **acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.**

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

Distal convoluted tubules



Mechanism of action of thiazide diuretics



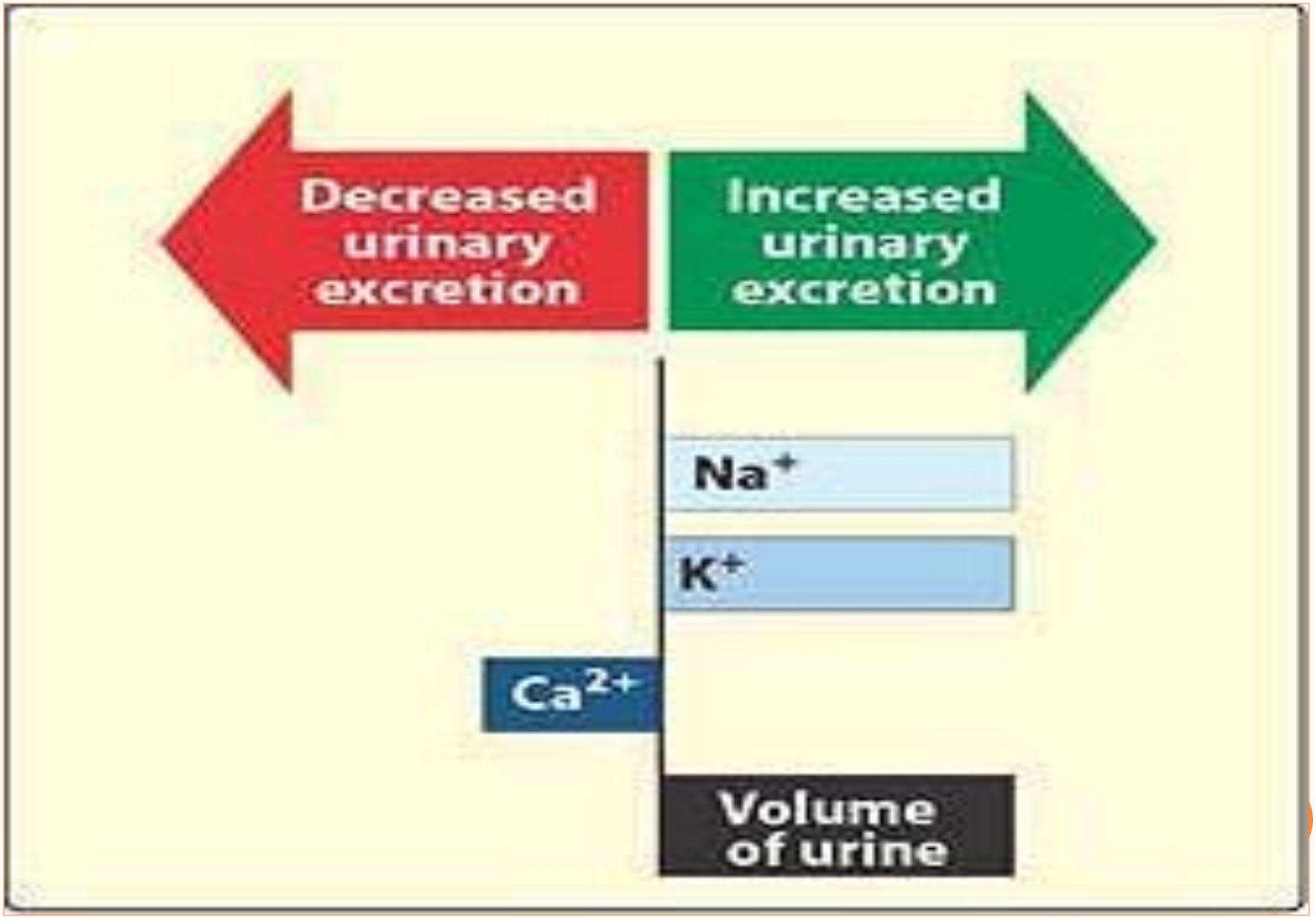
Pharmacokinetics:

- 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**

Thiazide diuretics



Uses:

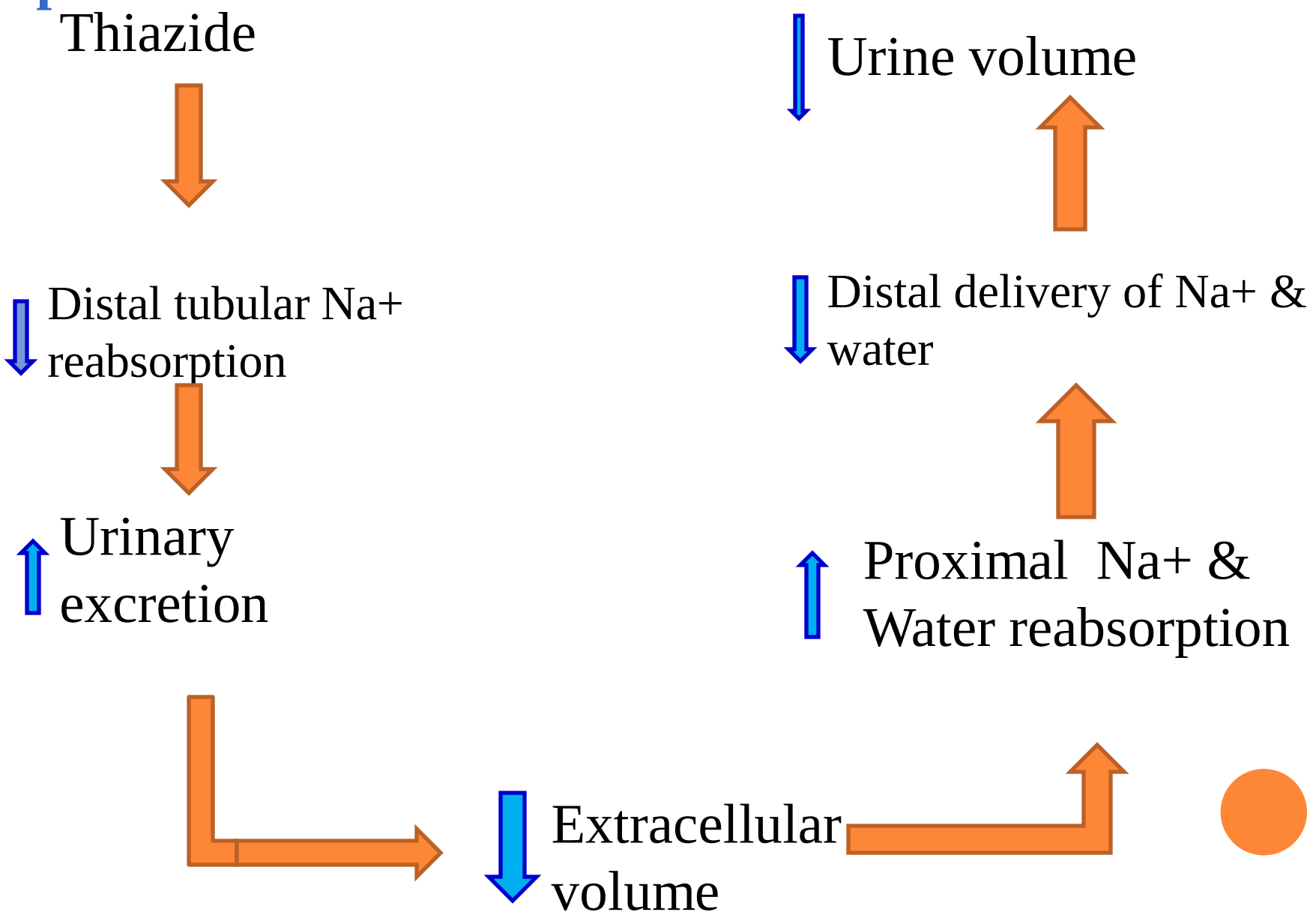
- **Treatment of essential hypertension *(cheap-well tolerated).***
- **Treatment of mild heart failure *(to reduce extracellular volume).***

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

Hypomagnesaemia

Metabolic Alkalosis

Hyperlipidemia

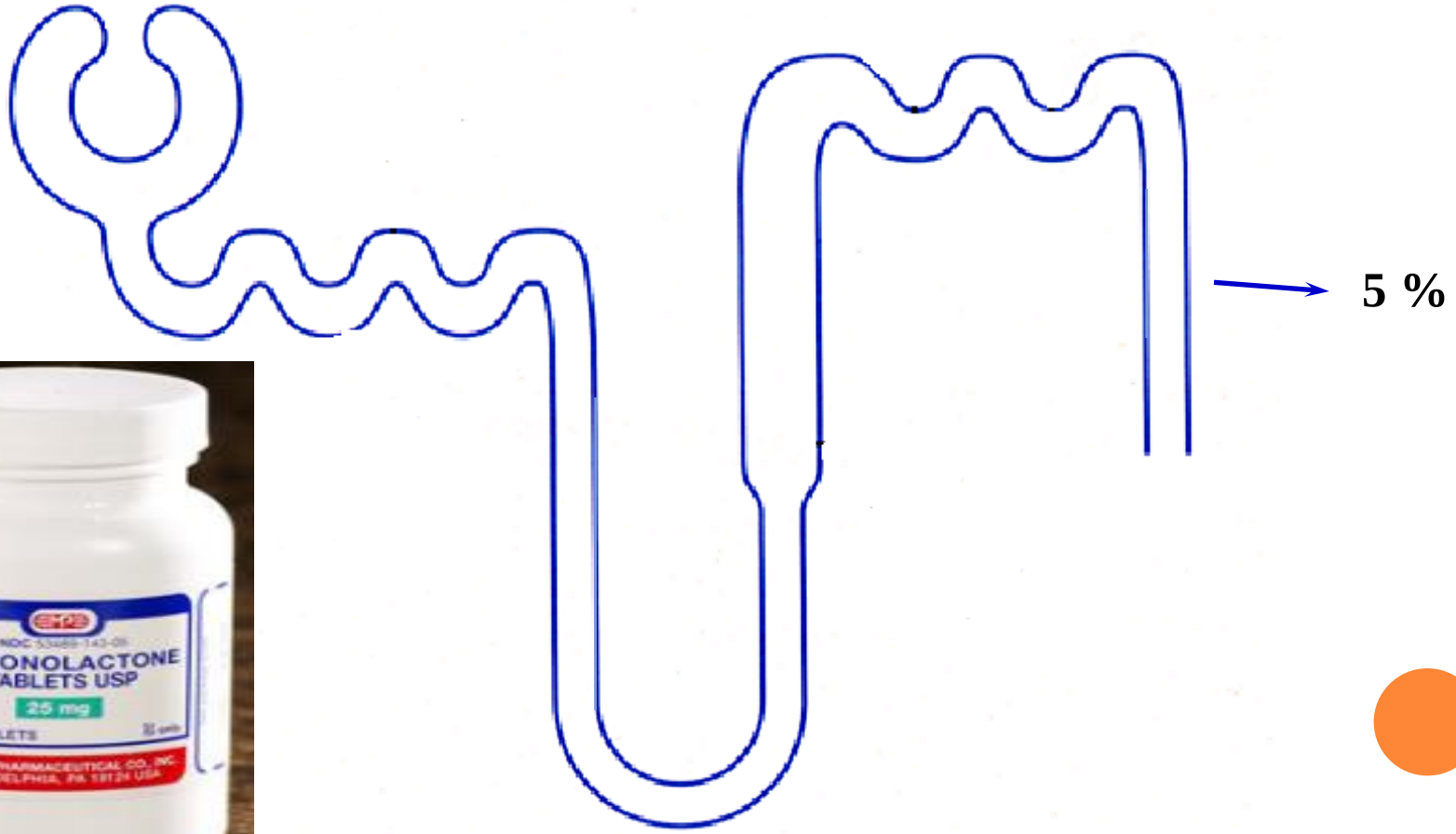
Hyperuricemia

Hyperglycemia

Hypercalcaemia

Potassium-sparing diuretics

Amiloride
Triamterene
Spironolactone



Potassium-sparing diuretics

Steroids

Nonsreroids

Aldosterone antagonists

- Spironolactone

Na^+ channels inhibitors

- Amiloride
- Triamterene

Mechanism of action

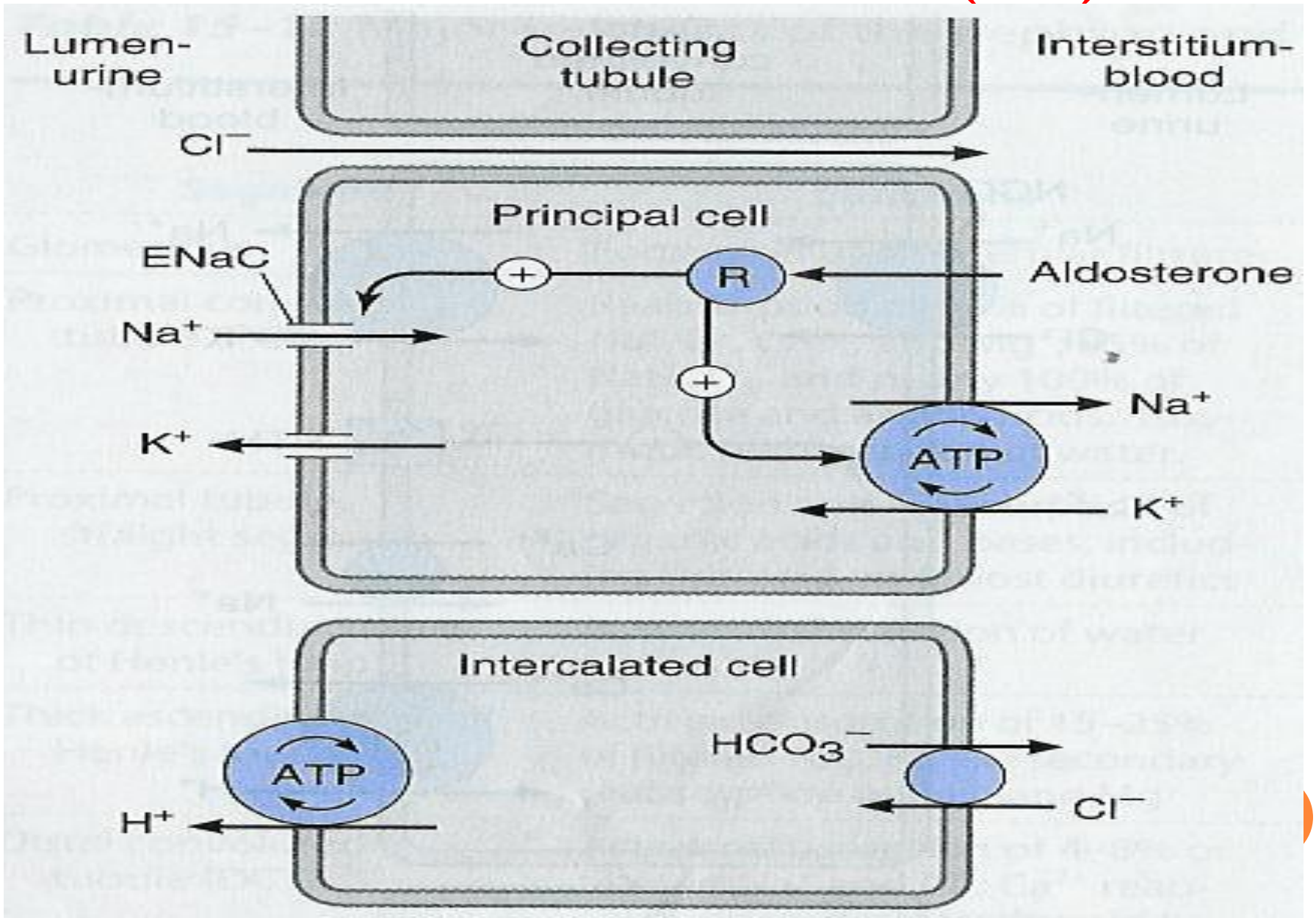
- **Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion (K-sparing effect) by either:**

- **Inhibition of Na influx through Na channels in the luminal membrane (triamterene – amiloride).**

Mechanism of action

- **or by antagonizing cytoplasmic aldosterone receptors (spironolactone).**

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

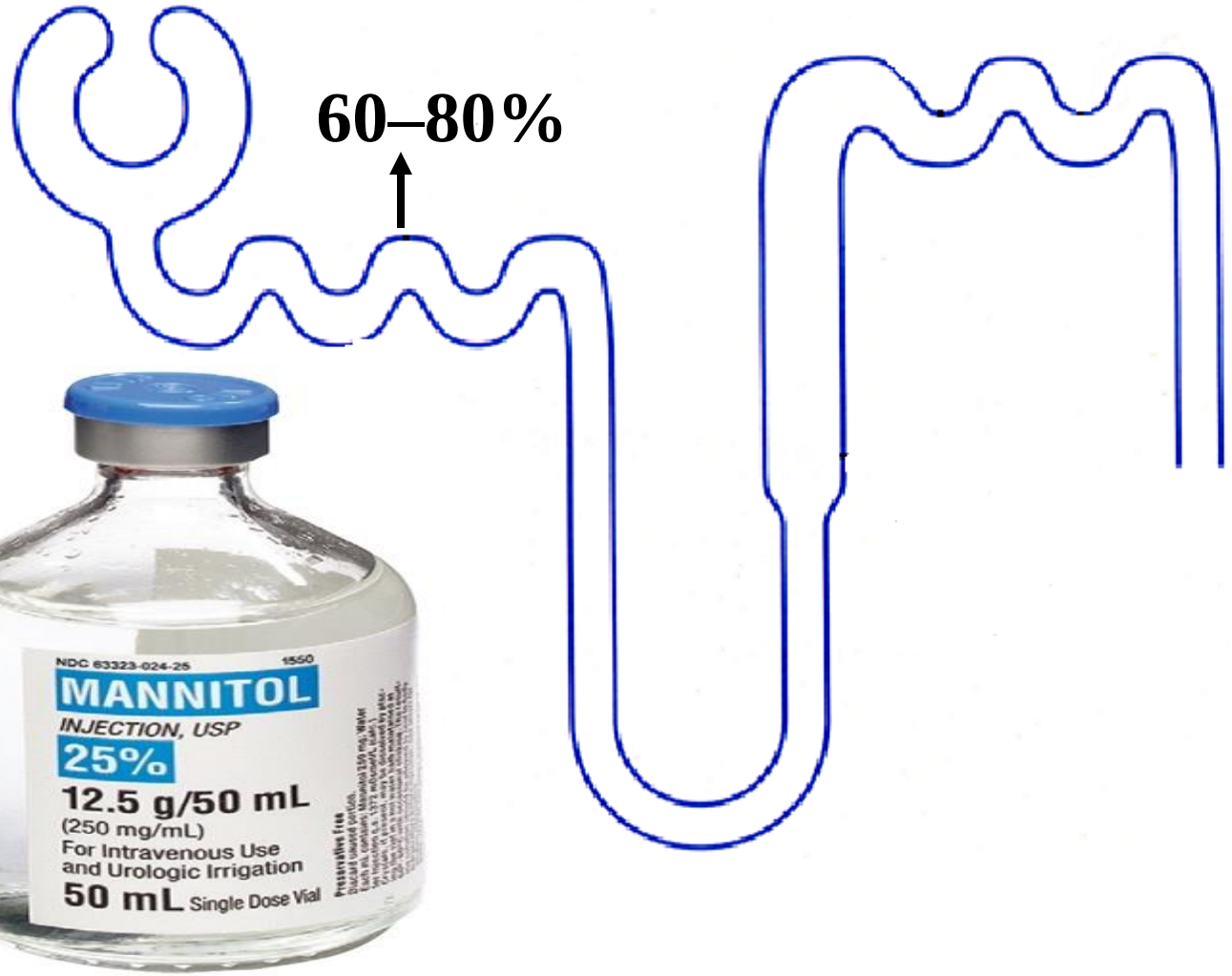
- Hyperkalaemia.
- Metabolic acidosis.
- Gynaecomastia
- GIT upset and peptic ulcer

Contraindications:

- **Hyperkalaemia: as in chronic renal failure, K+ supplementation, β-blockers or ACE inhibitors.**

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

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, IV, ↑water excretion with relatively less effect on Na+ (water diuresis).**
- **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).

- **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 & hypernatremia** (adequate water replacement is required).

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.

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.**

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

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

Renal failure

- Thiazides are used till GFR ≥ 40-50 ml/min
- Loop diuretic are used below given values.

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 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