DIURETICS
Part 1

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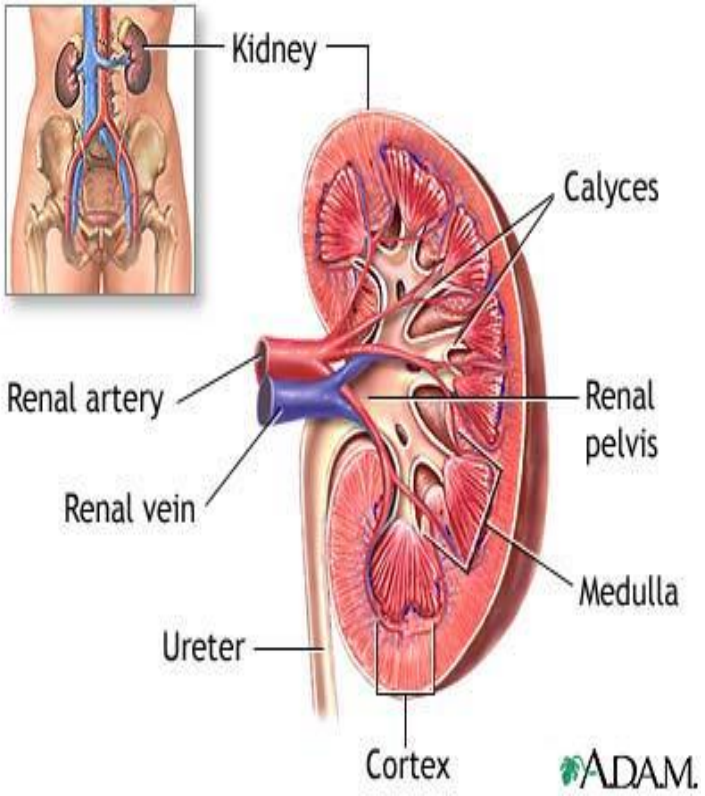
Pharmacology Unit



Diuretics

Definition

- Are drugs that increase urine volume.
- **Diuresis:** is the process of excretion of water in the urine.
- **Can we use water as a diuretic?**

Diuretics

- All diuretics have **naturetic** effect.

Natriuresis:

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

INDICATIONS of DIURETICS

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

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.

Sites of action for diuretics

How diuretics produce their effects?

- 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 NaHCO3**
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

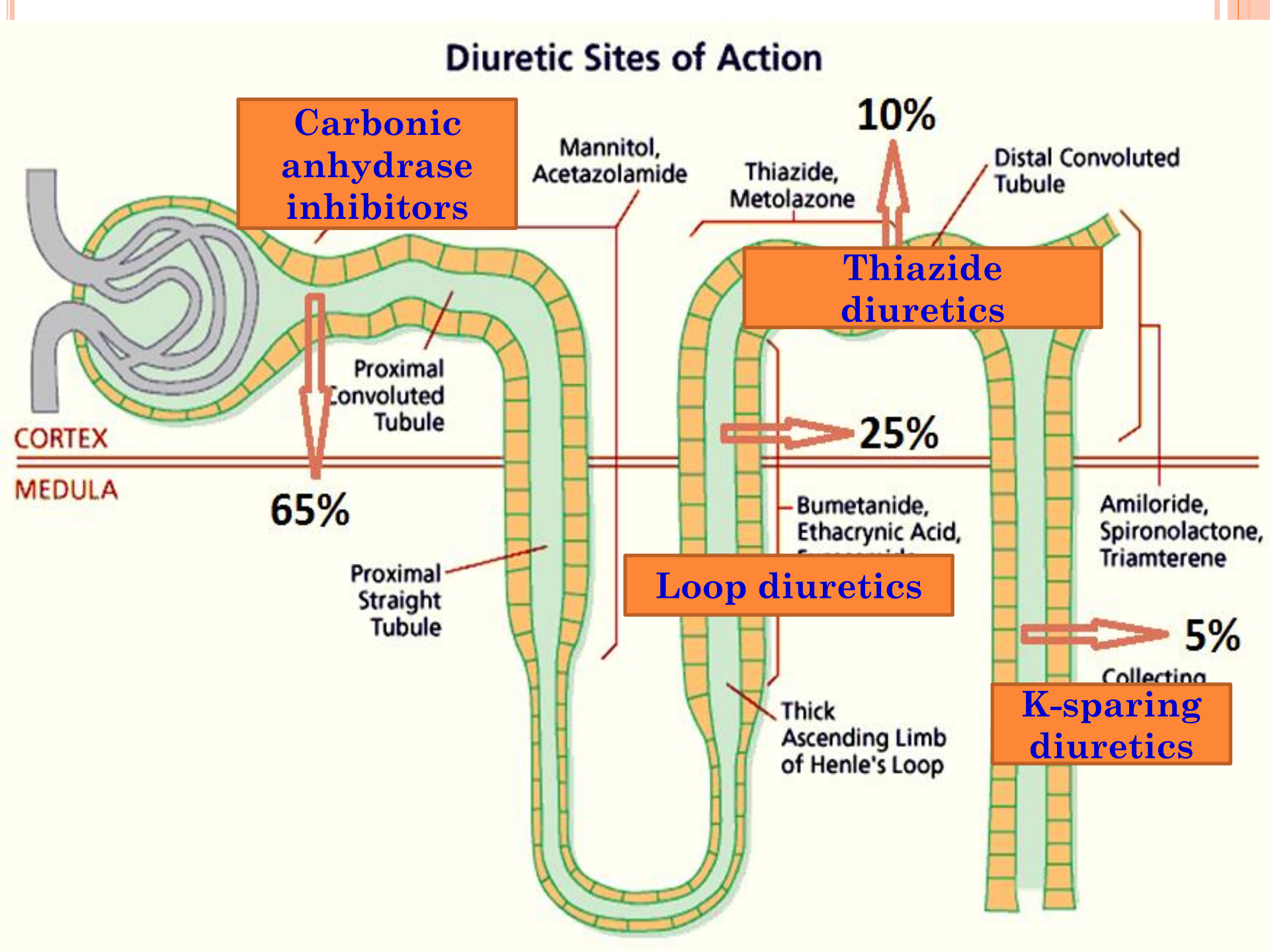
segment	Function	transporter	Diuretics
Proximal convoluted tubules	Re-absorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% $NaHCO_3$	Na/H transporter, Carbonic anhydrase enzyme	Carbonic anhydrase inhibitors
Proximal Straight Tubules	Secretion and re-absorption of organic acids and bases	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

Types of diuretics

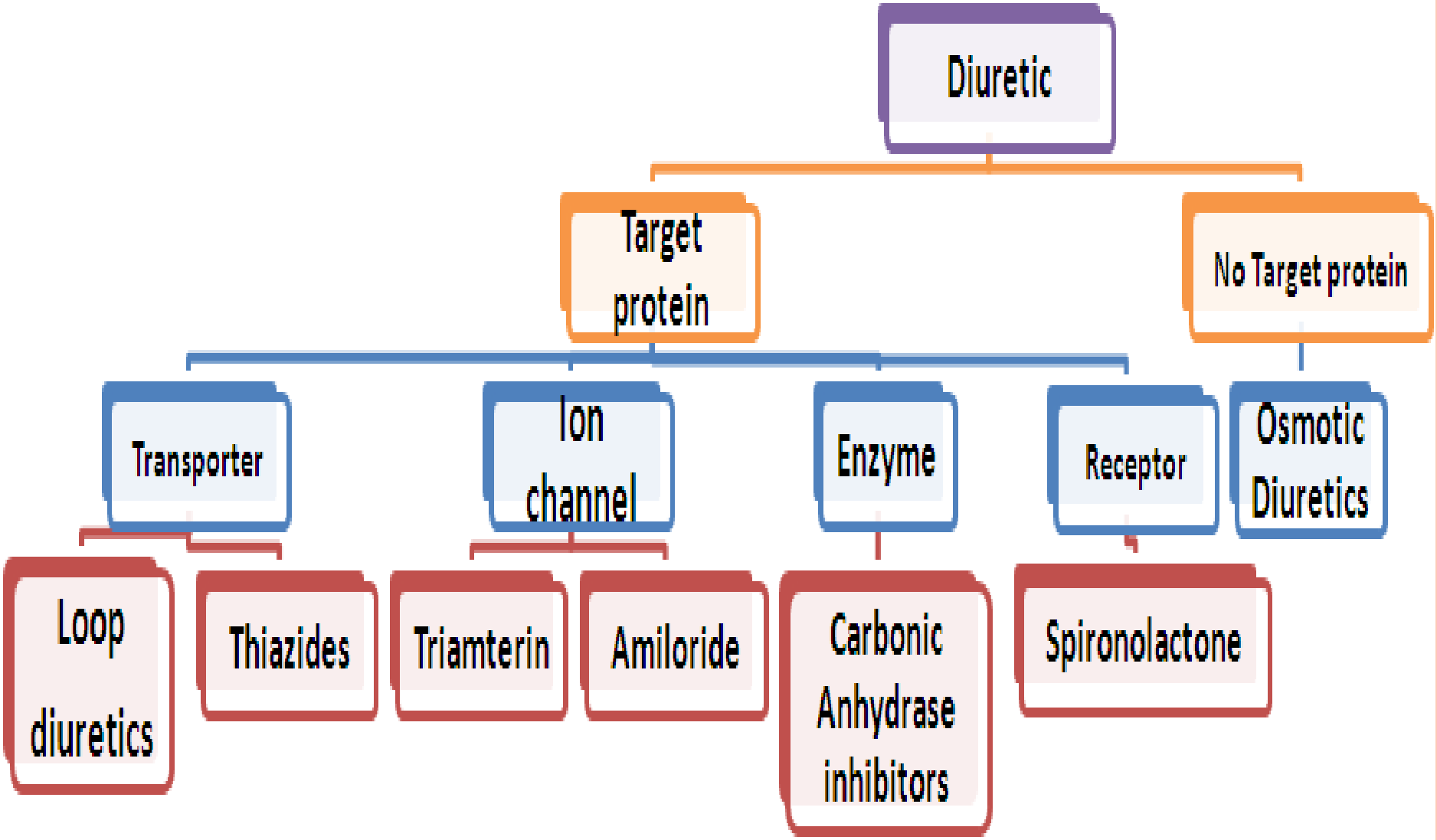
Nephron Segment	Na^+ Transporter	Diuretics
Proximal convoluted tubules	Na^+/H^+ transporter Carbonic anhydrase enzyme	**Carbonic anhydrase inhibitors**
Ascending Loop of Henle	$Na^+/K^+/2Cl^-$ cotransporter	**Loop diuretics**
Distal convoluted tubules	Na^+/Cl^- transporter	**Thiazide diuretics**
Cortical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

Classification of diuretics

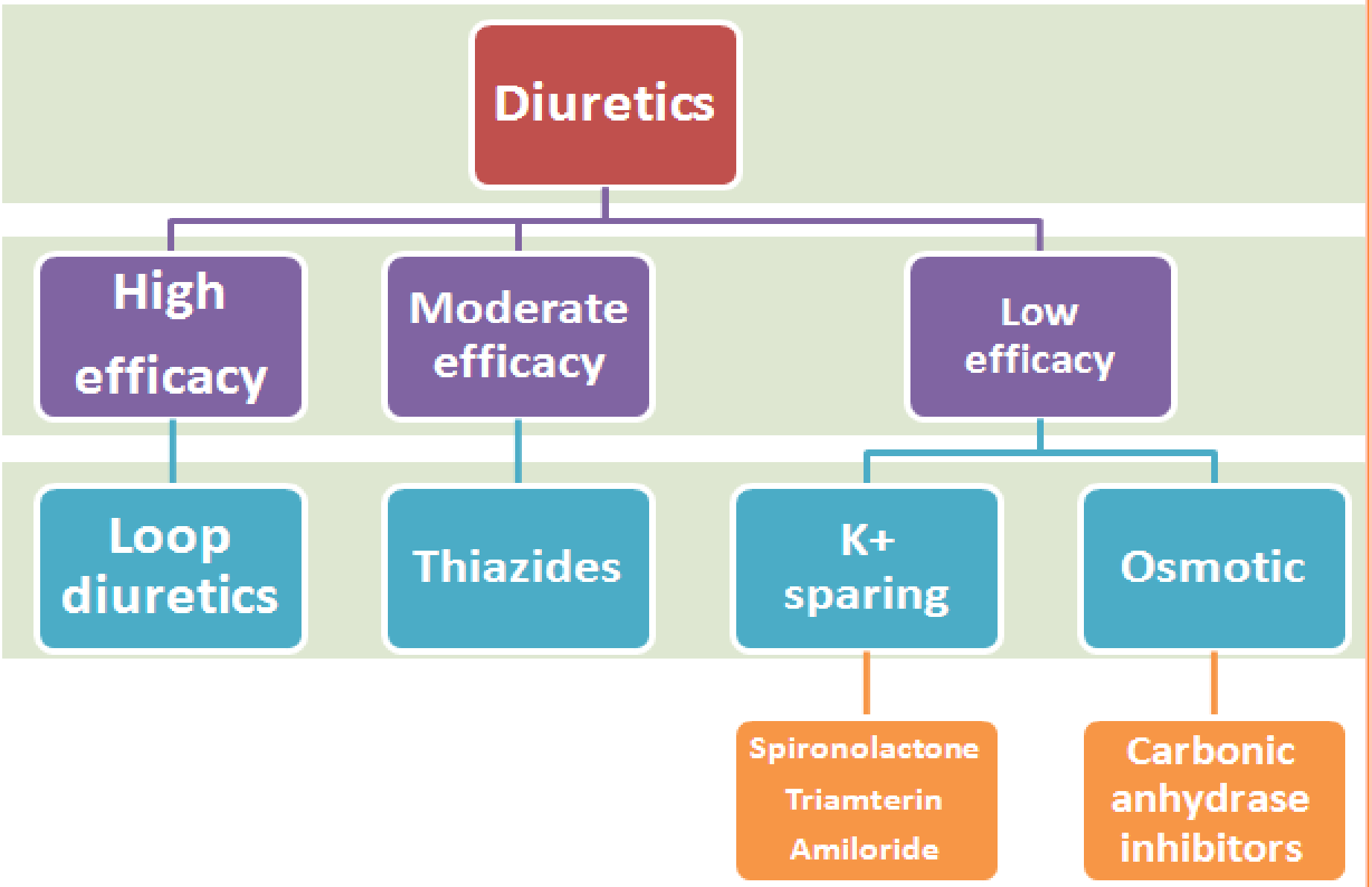
- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazide diuretics
- Potassium-sparing diuretics
- Osmotic diuretics

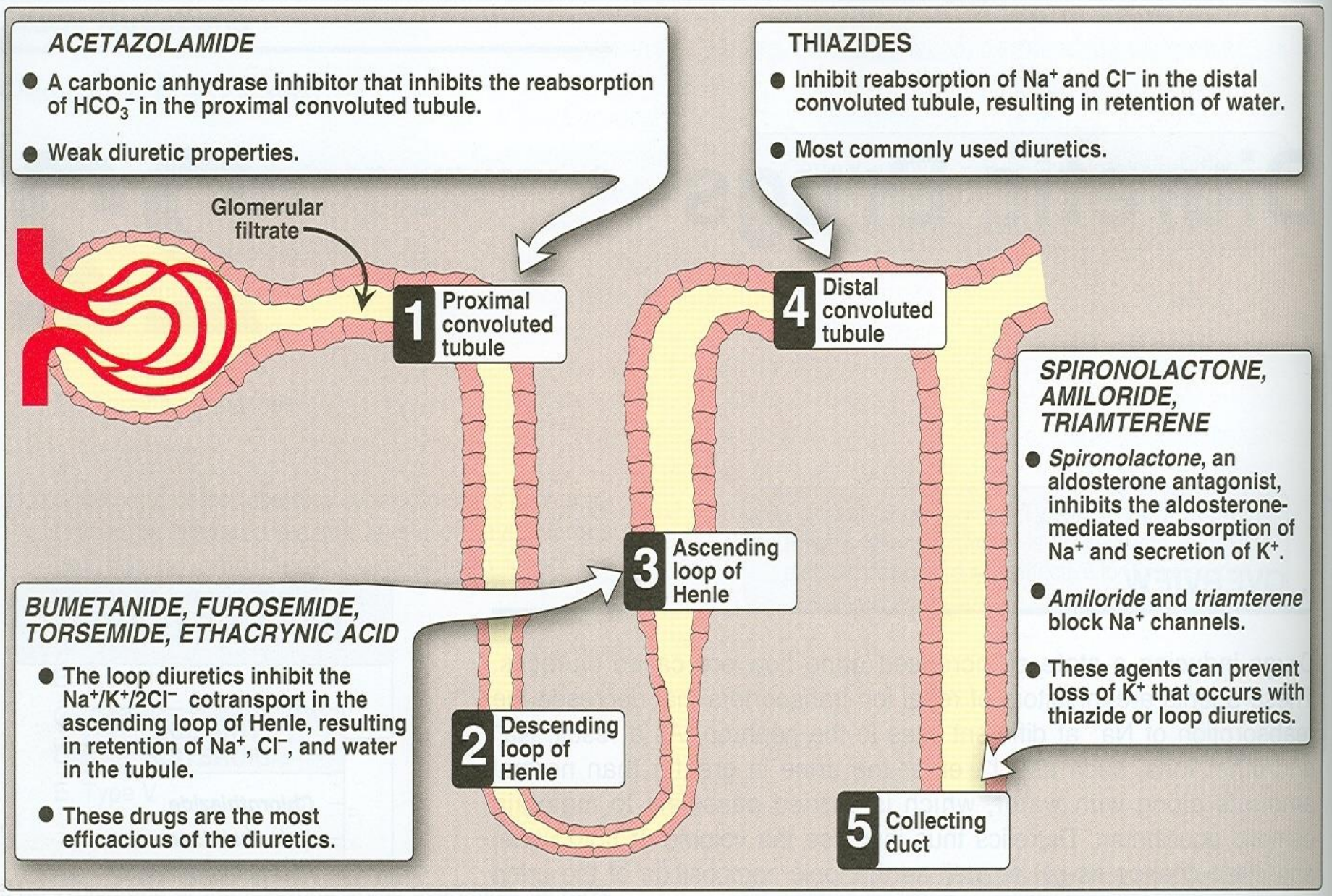

Diuretic Sites of Action
Carbonic anhydrase inhibitors
Mannitol, Acetazolamide
10%
Thiazide, Metolazone
Distal Convoluted Tubule
Thiazide diuretics
Proximal Convoluted Tubule
CORTEX
MEDULA
25%
65%
Bumetanide, Ethacrynic Acid,
Amiloride, Spironolactone, Triamterene
Proximal Straight Tubule
Loop diuretics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

Classification of diuretics



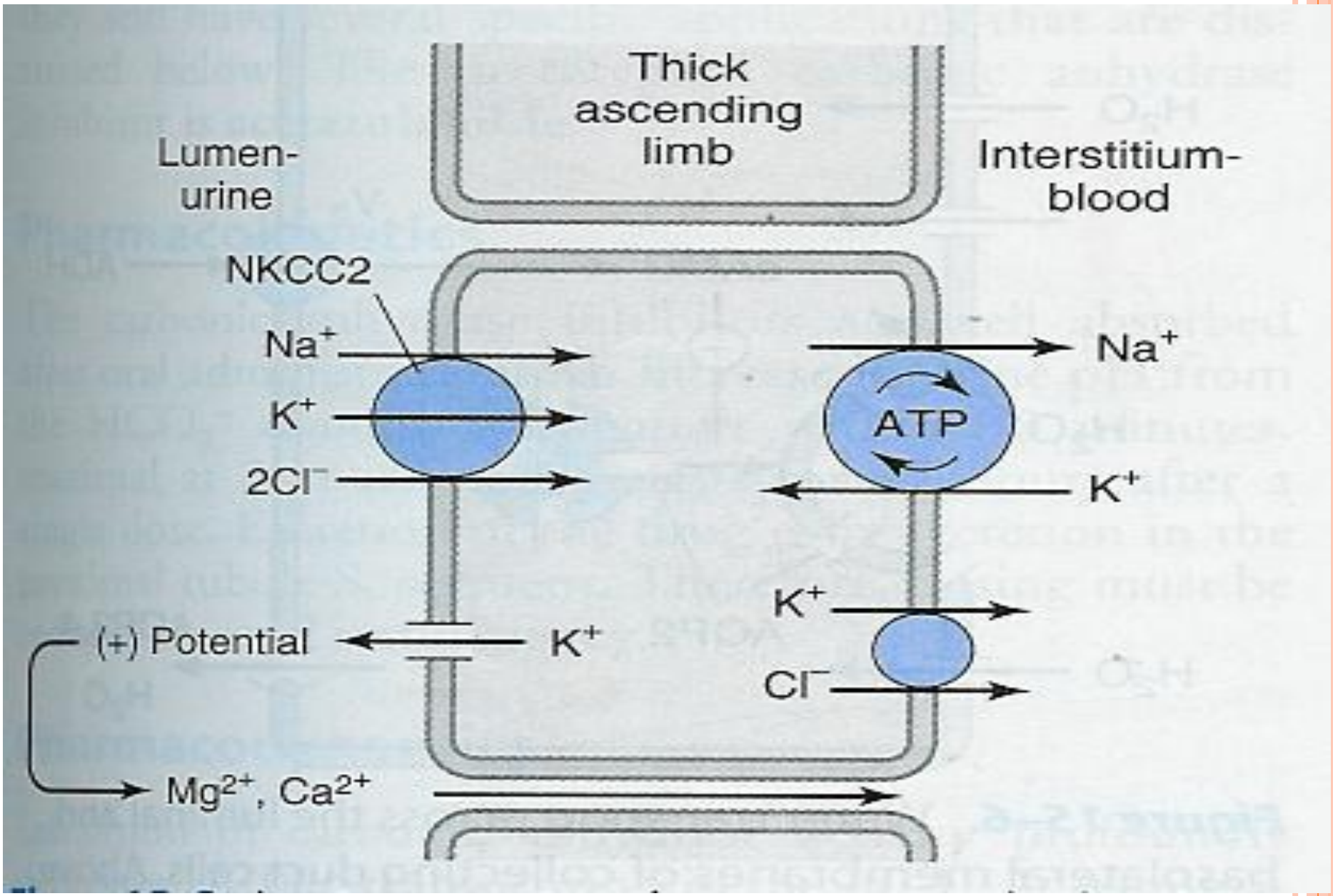
Classification of diuretics



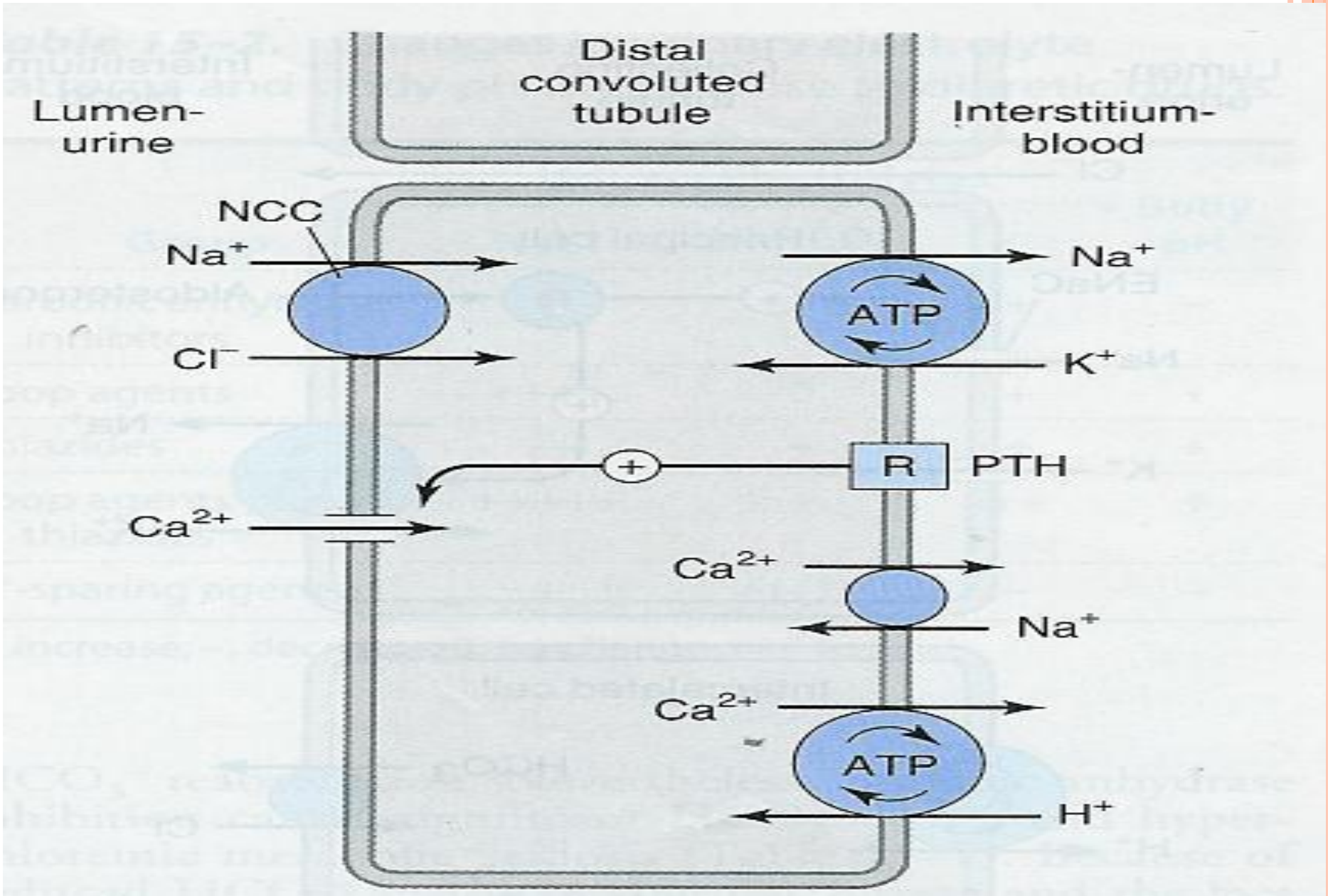


Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

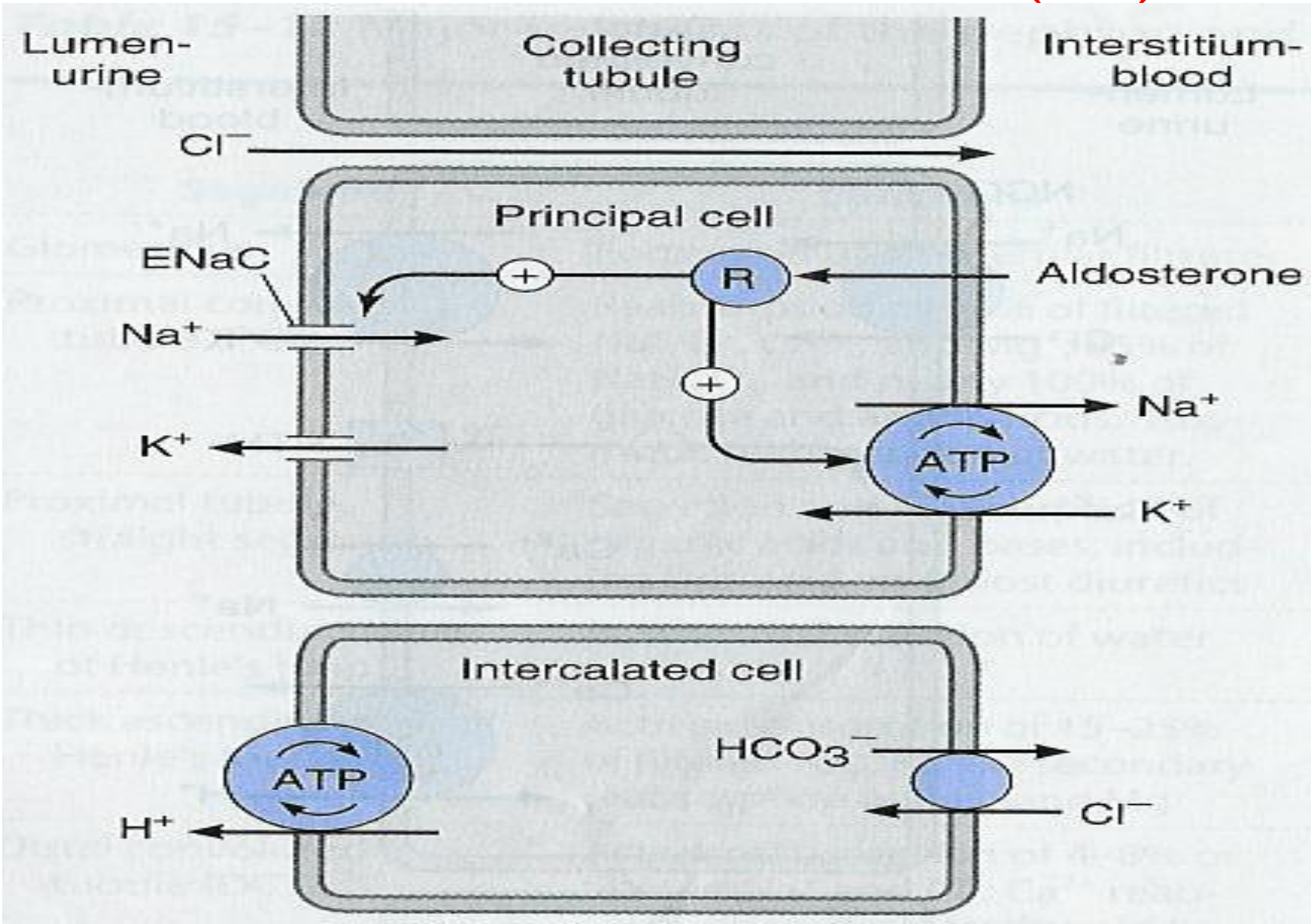
Ascending loop of Henle



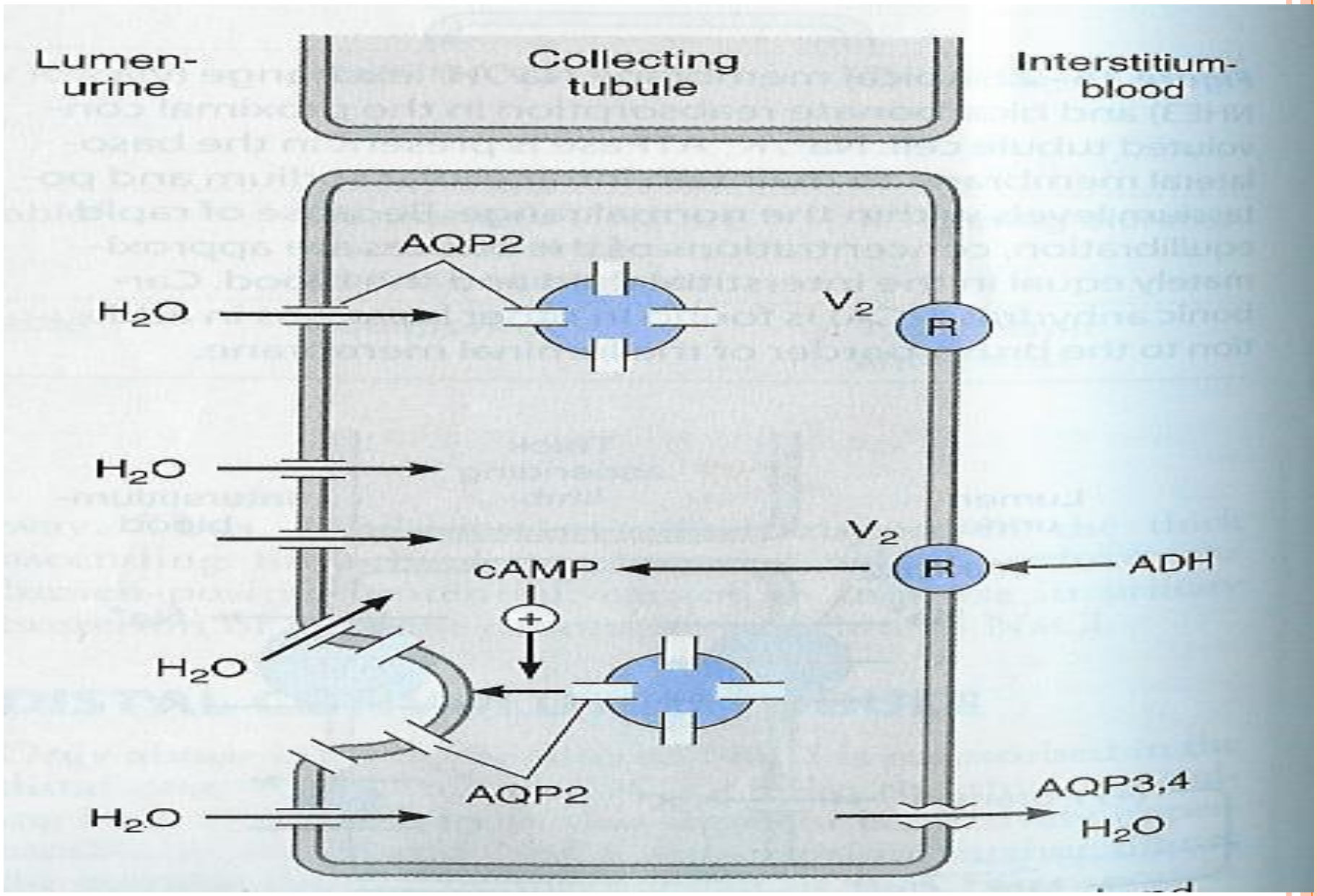
Distal convoluted tubules (DCT)



COLLECTING TUBULES (CT)



COLLECTING TUBULES (CT)



Carbonic Anhydrase Inhibitors

Carbonic Anhydrase Inhibitors

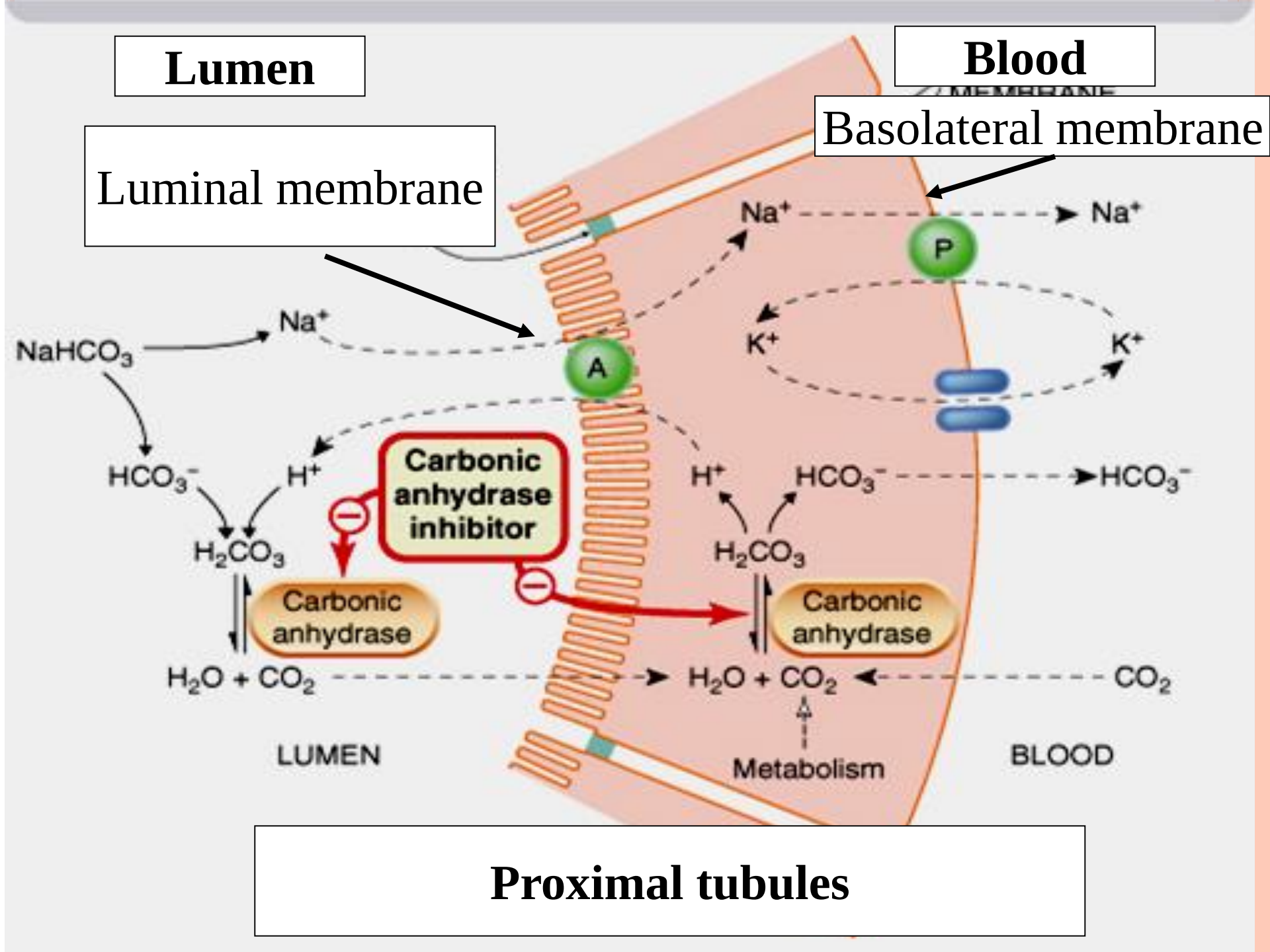
Drugs: Acetazolamide – dorzolamide

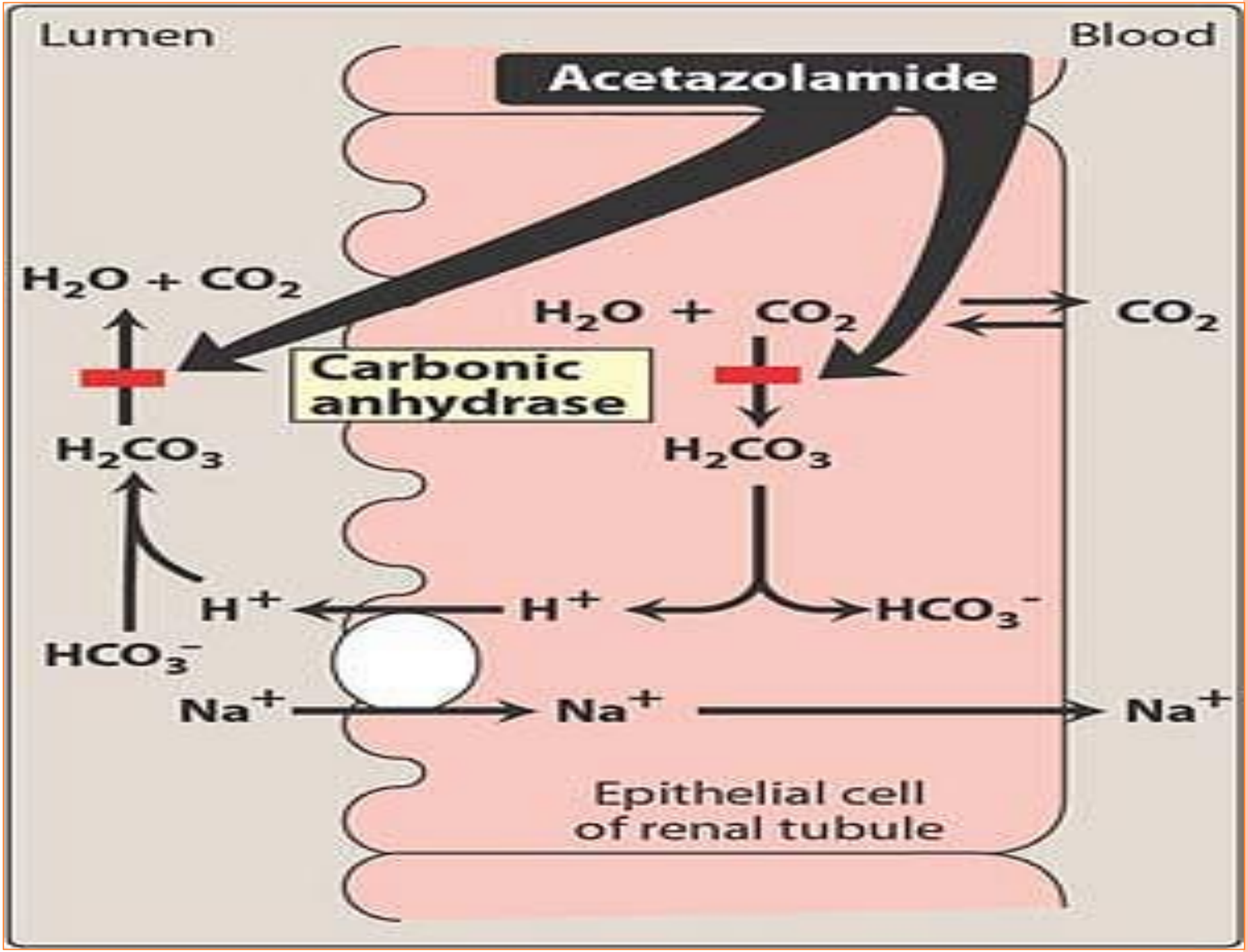
Mechanism of action:

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:

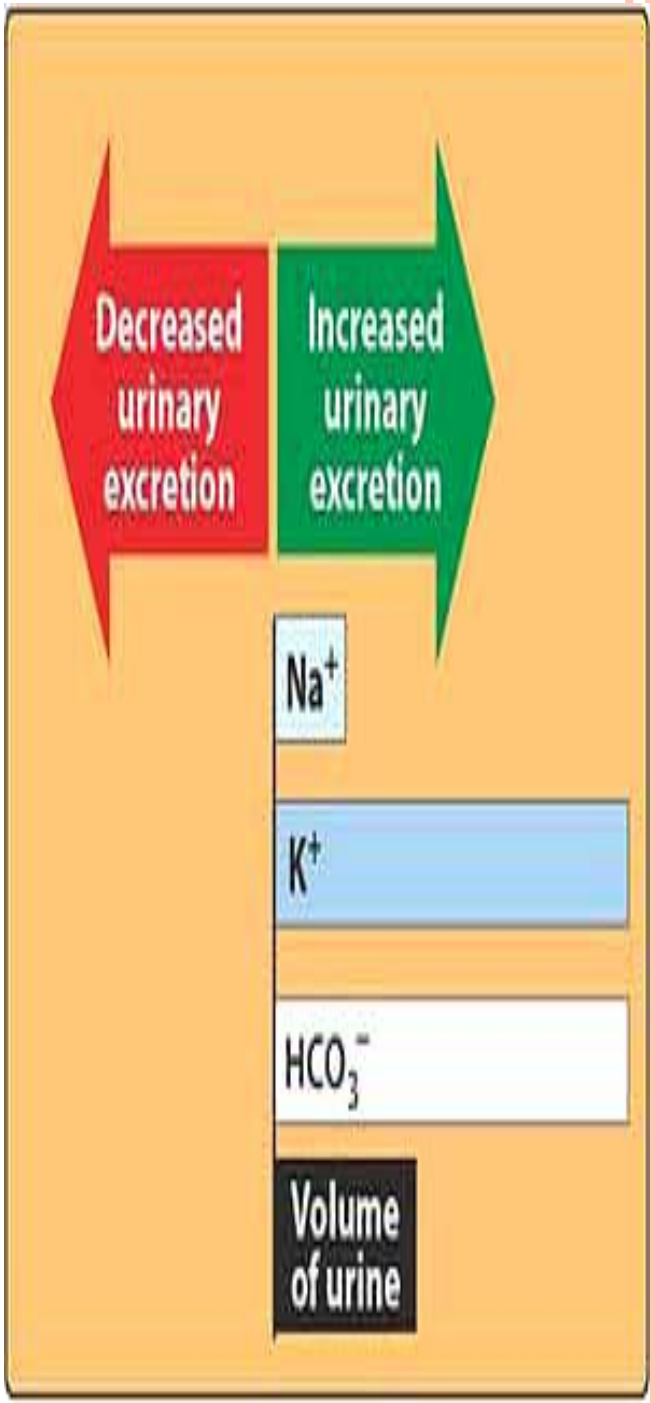
- given orally once a day.
- Onset of action is rapid (30 min).
- Duration of action (9-12 h).
- Excreted by active secretion in proximal convoluted tubules.
- Produces alkaline urine

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.

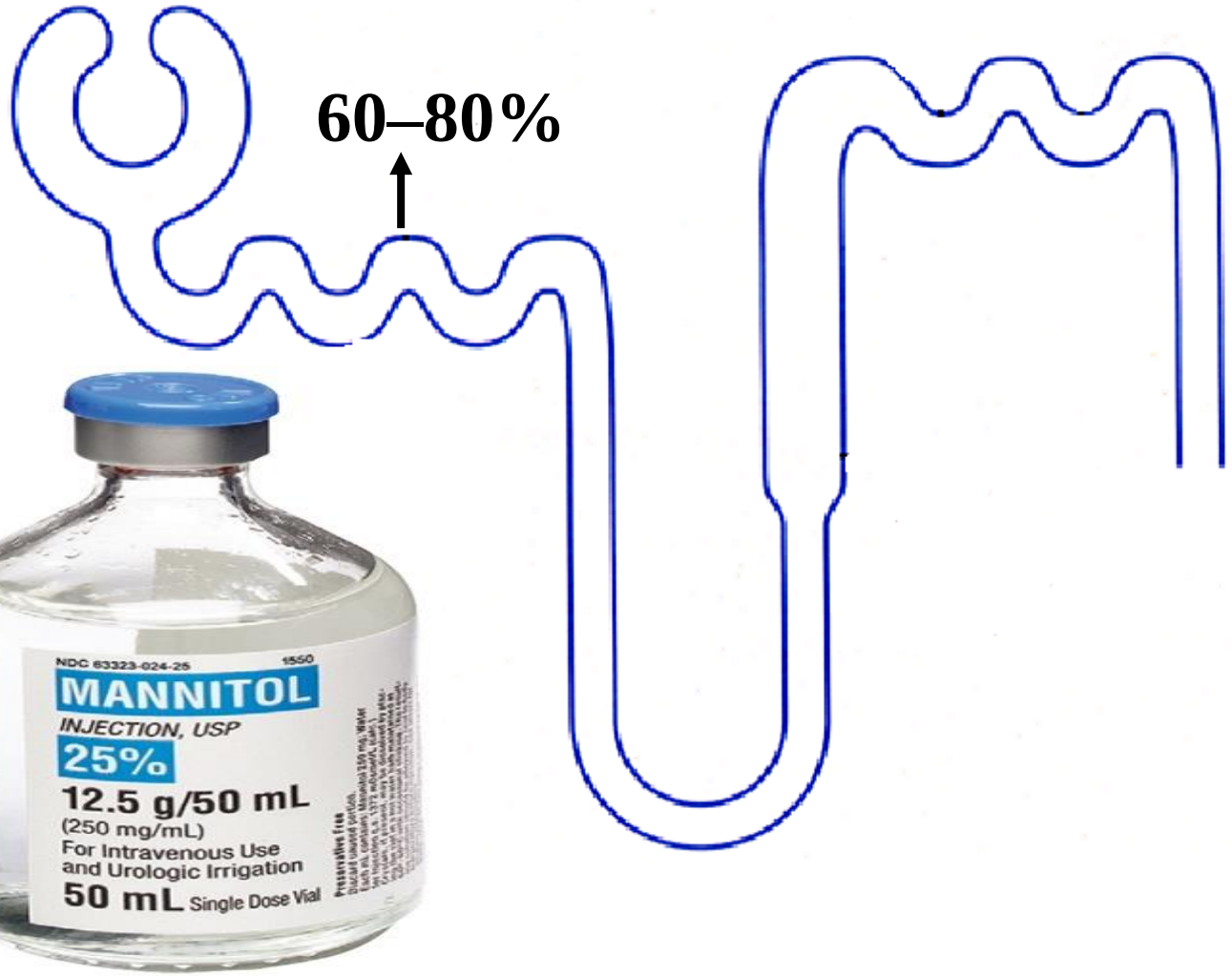
Metabolic alkalosis

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.**

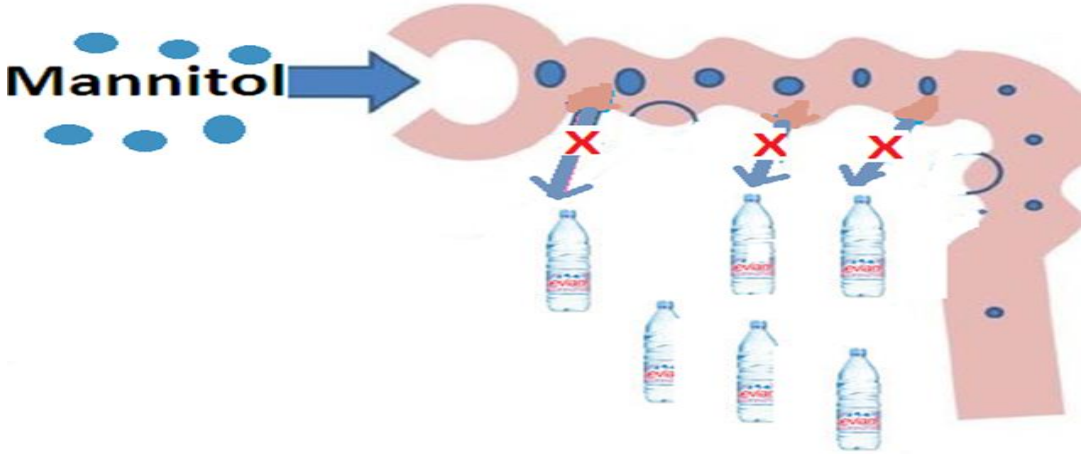
Osmotic diuretics



Osmotic diuretics

Mannitol:

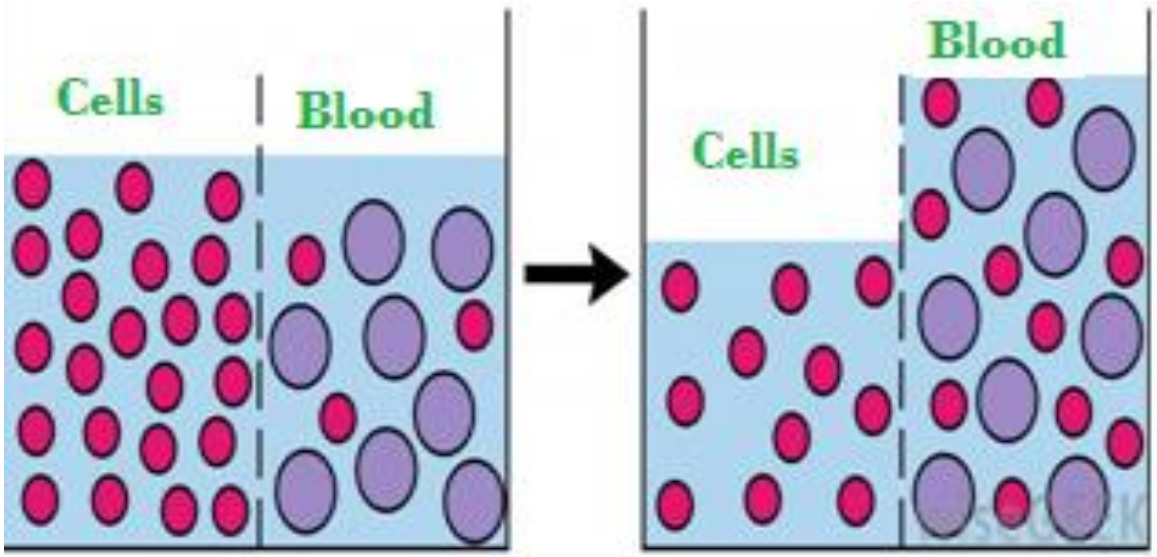
- Poorly absorbed
- If given orally ⟶ osmotic diarrhea
- Given intravenously
- Not metabolized
- Excreted by glomerular filtration **without being re-absorbed or secreted within 30-60 min**



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. haemolysis, rhabdomyolysis

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

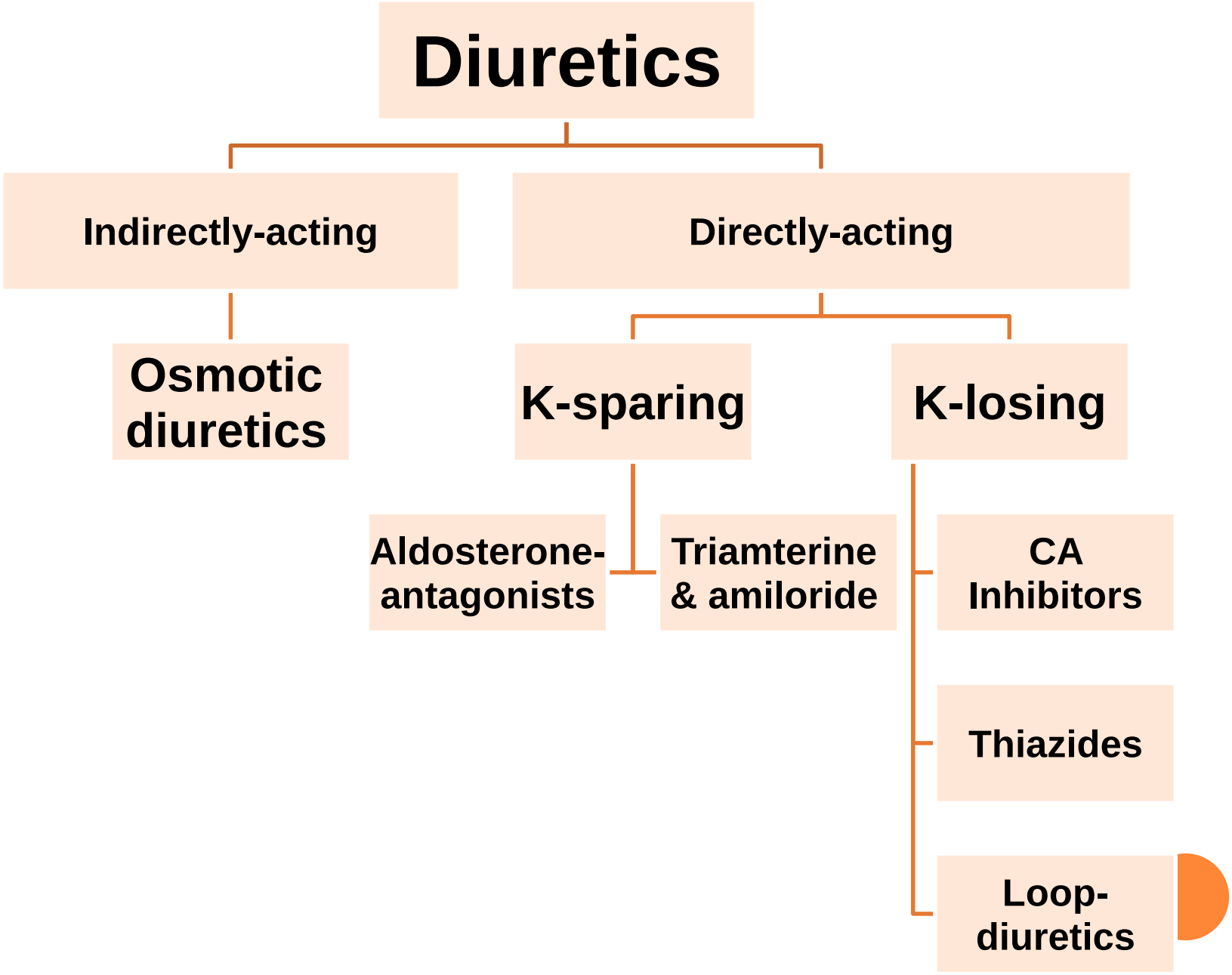
- To ↓ intracranial & intraocular pressure before ophthalmic or brain procedures (**cerebral edema**).

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


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