DIURETICS
Part 1

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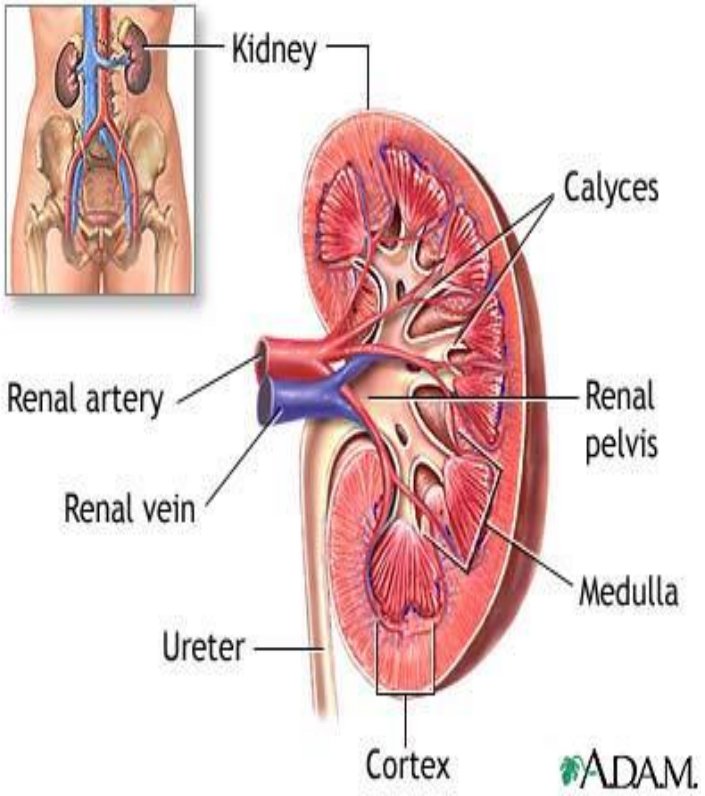


Diuretics

- 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	85 % Na , HCO3
Ascending Loop of Henle	20-30% Active reabsorption Na, K, Cl Ca an Mag
Distal convoluted tubules	5-10% Active reabsorption Na, Cl
Cortical Collecting Tubules	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- Ca, Mg absorption	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

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**

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.

Types of diuretics

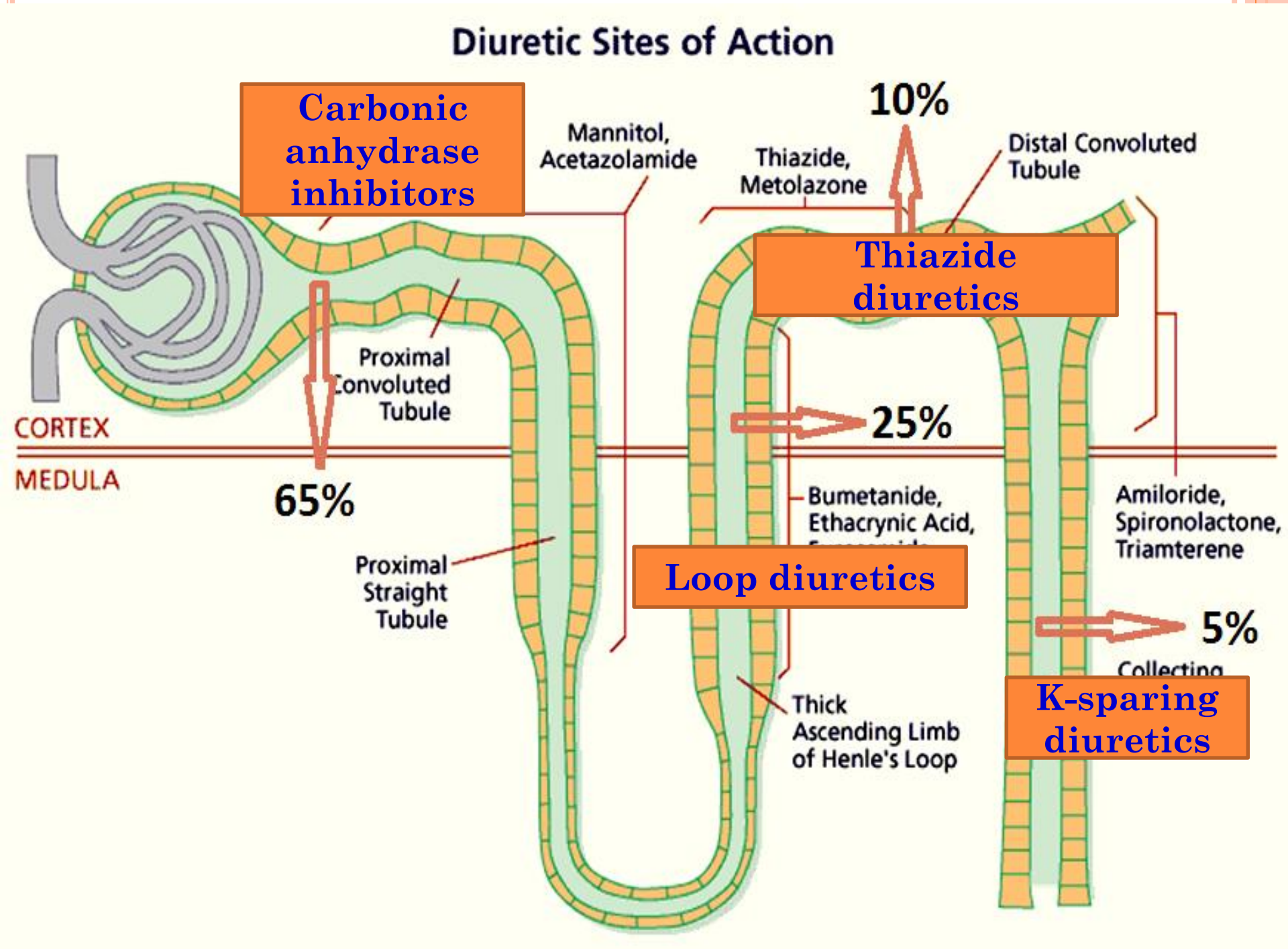
Nephron Segment	Na^+ Transporter	Diuretics
Proximal convoluted tubules	Na^+/H^+ transporter Carbonic anhydrase enzyme	**Carbonic anhydrase inhibitors**
Ascending Loop of Henle	$Na^+/K^+/2Cl^-$ cotransporter	**Loop diuretics**
Distal convoluted tubules	Na^+/Cl^- transporter	**Thiazide diuretics**
Cortical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

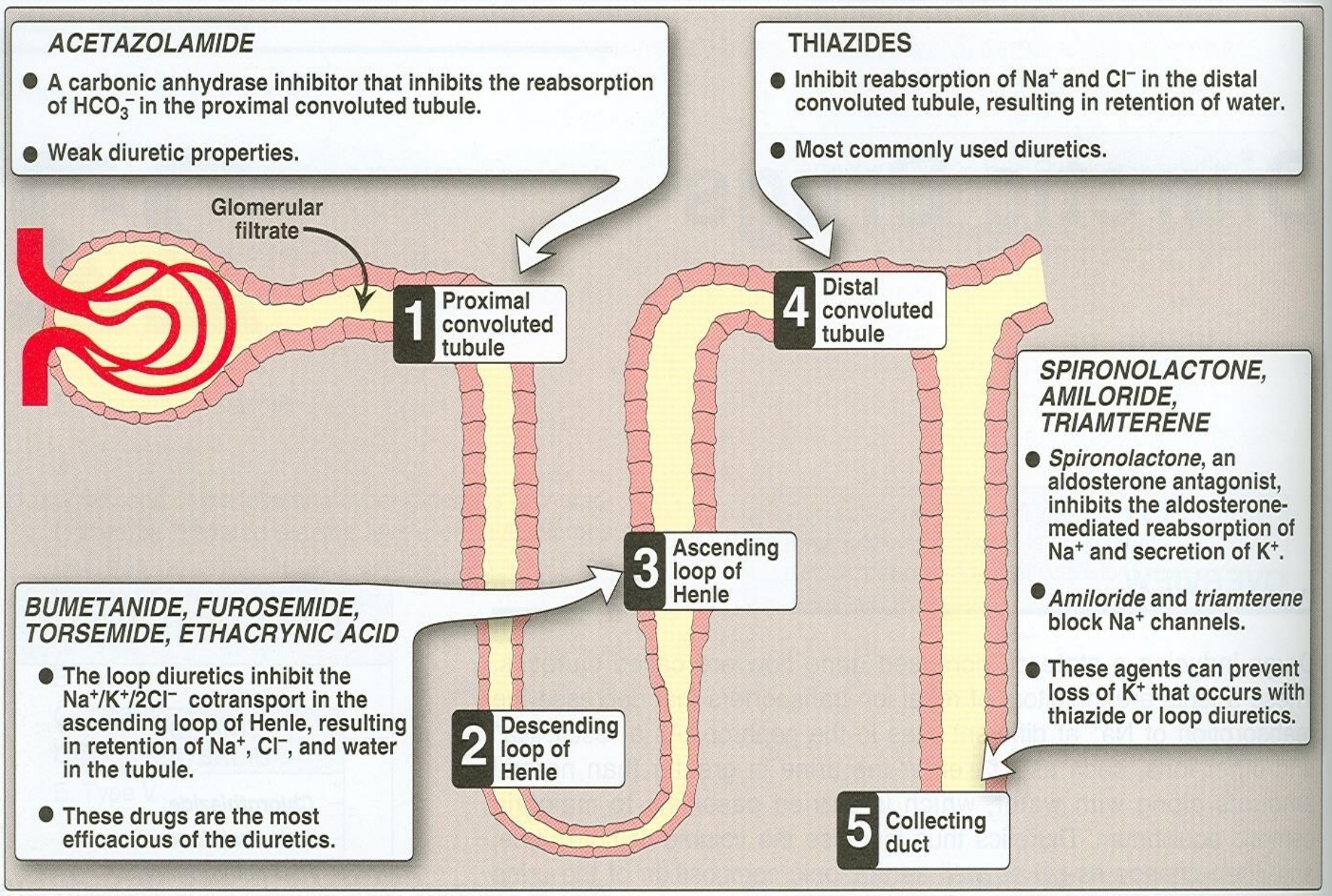
Site of action of diuretics

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

Classification of diuretics

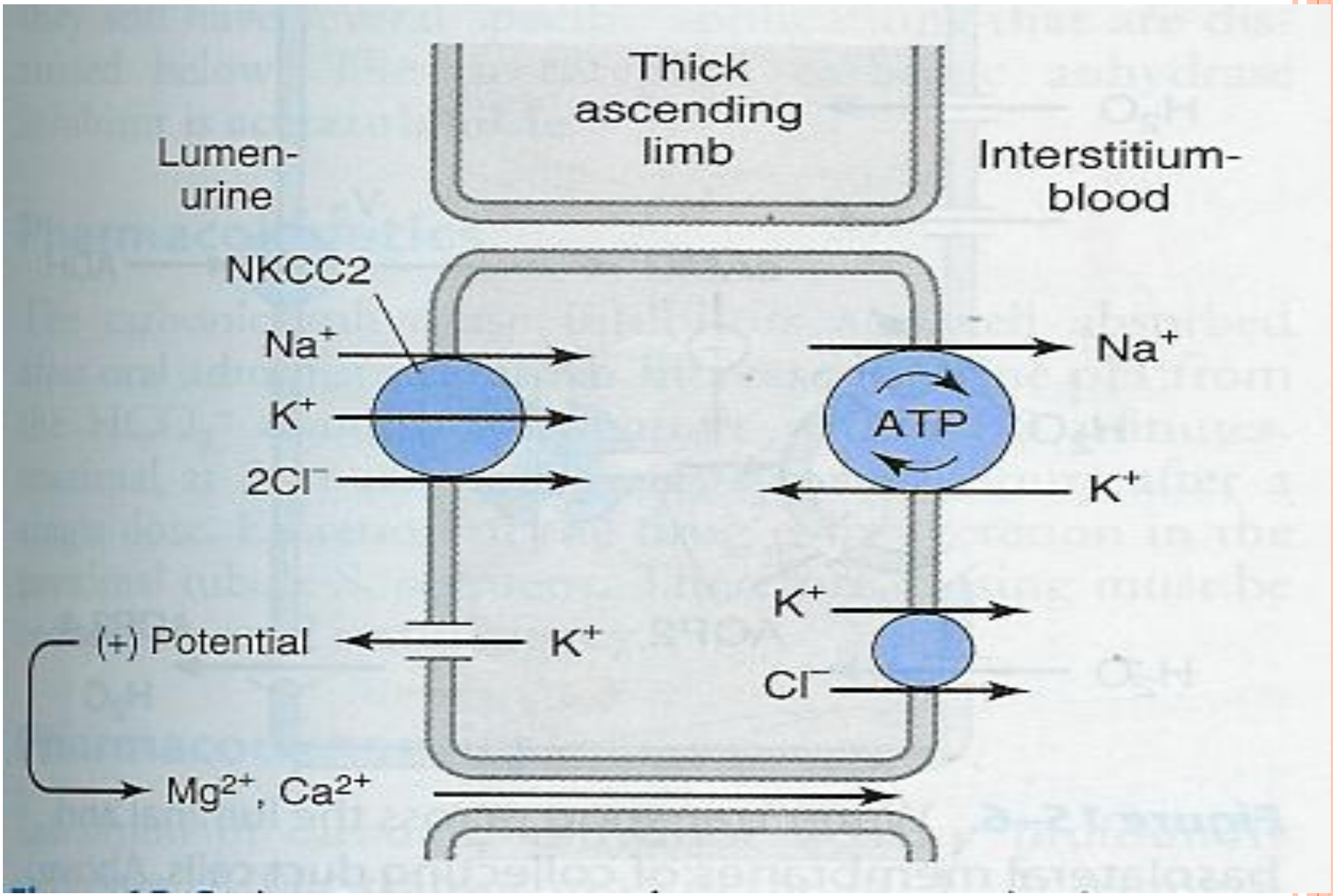
- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazide diuretics
- Potassium-sparing diuretics
- Osmotic diuretics


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

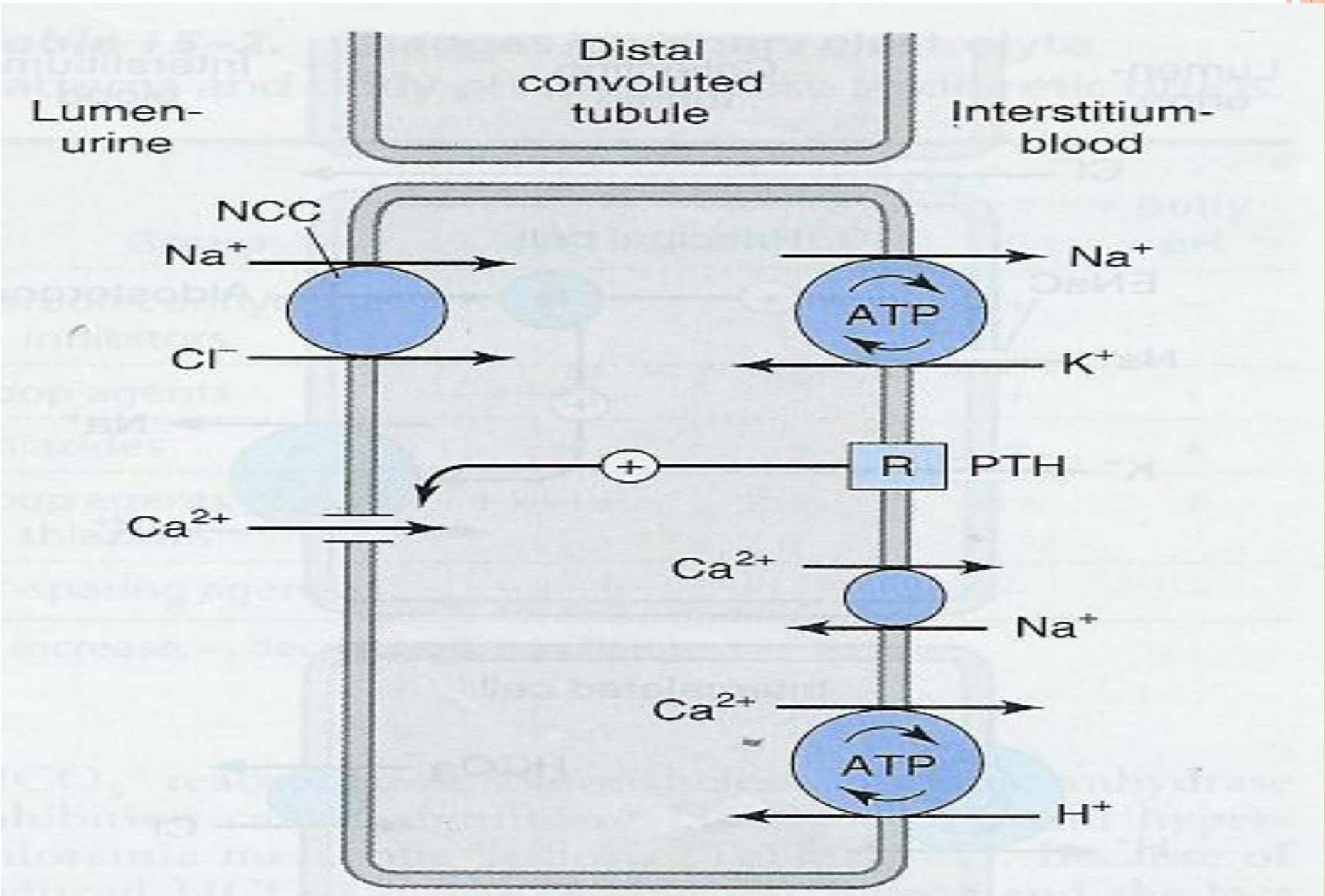


Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

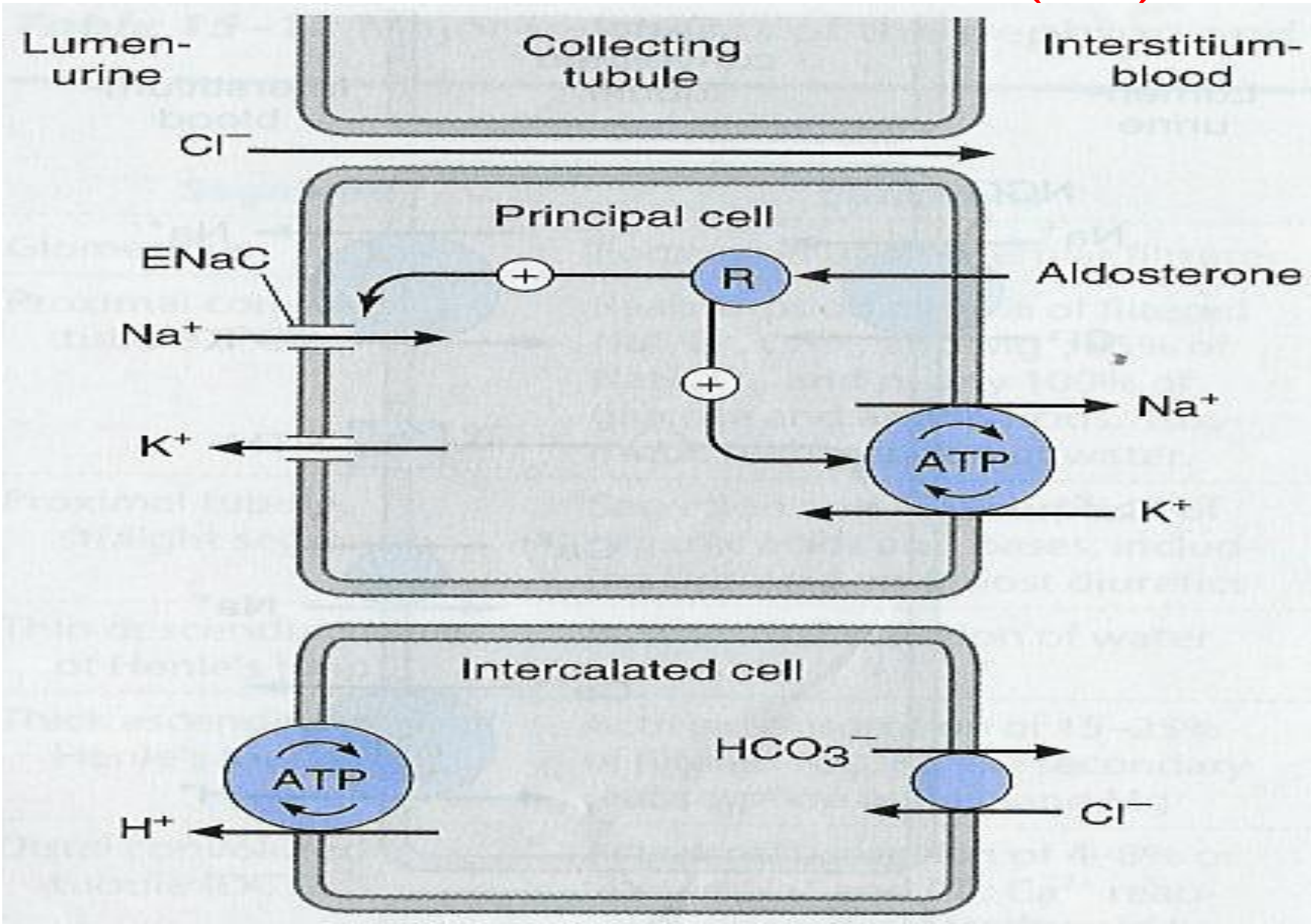
Ascending loop of Henle



Distal convoluted tubules (DCT)



COLLECTING TUBULES (CT)



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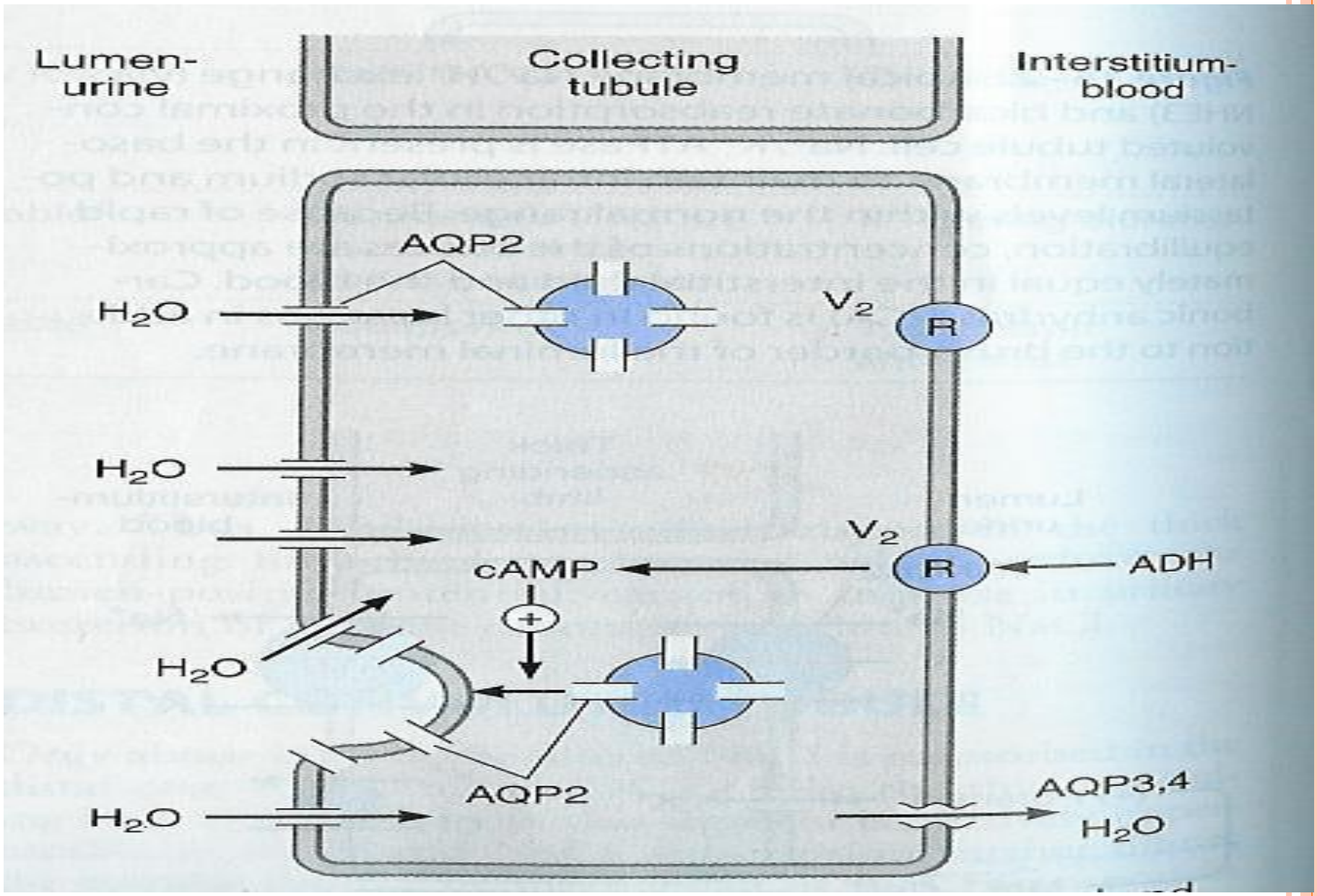


Carbonic Anhydrase Inhibitors

Carbonic Anhydrase Inhibitors

Acetazolamide – dorzolamide

Mechanism of action:

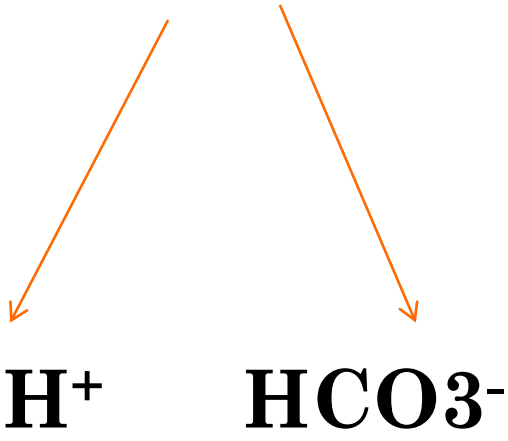
Site of action: proximal convoluted tubules

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

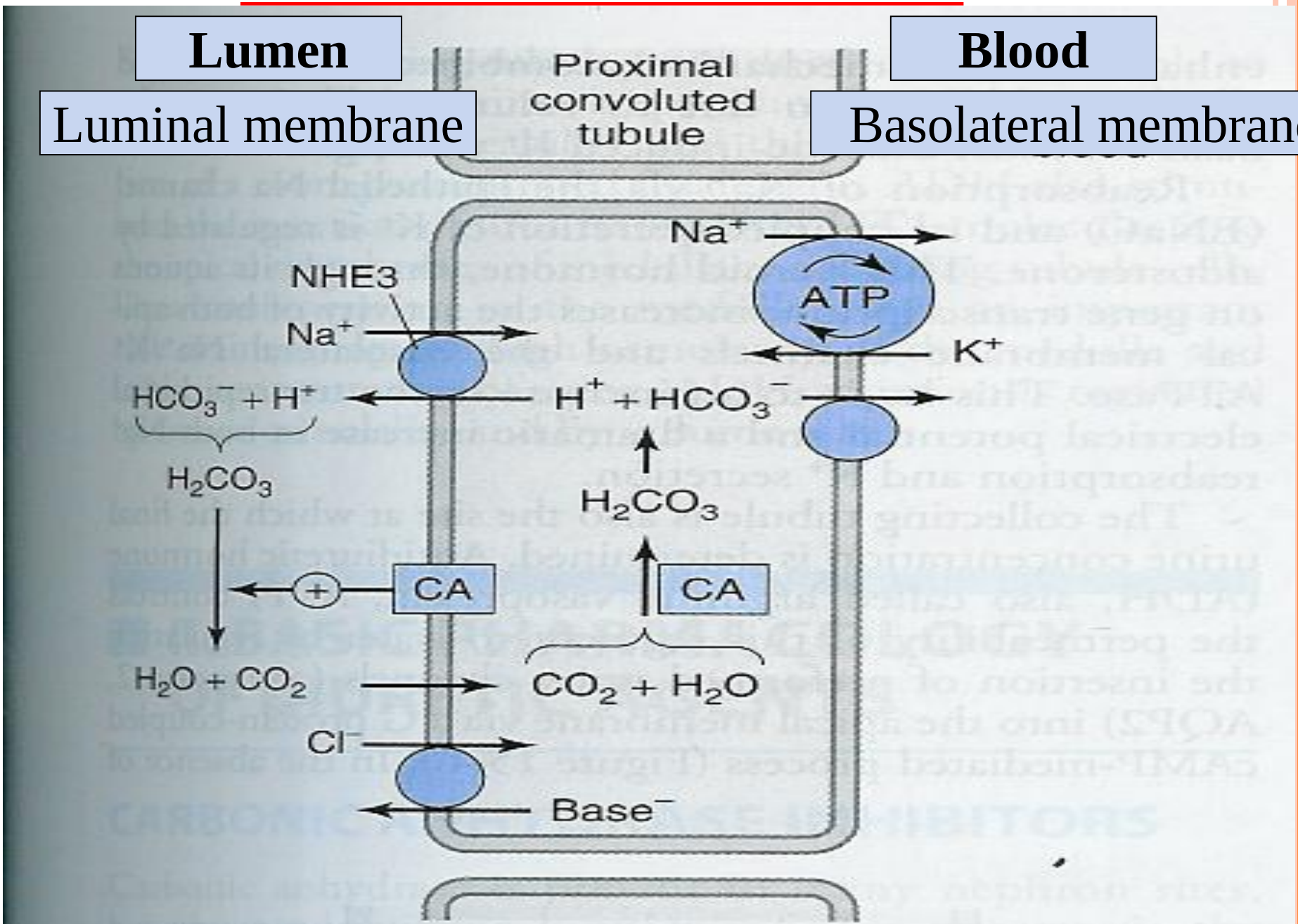
Carbonic Anhydrase Inhibitors

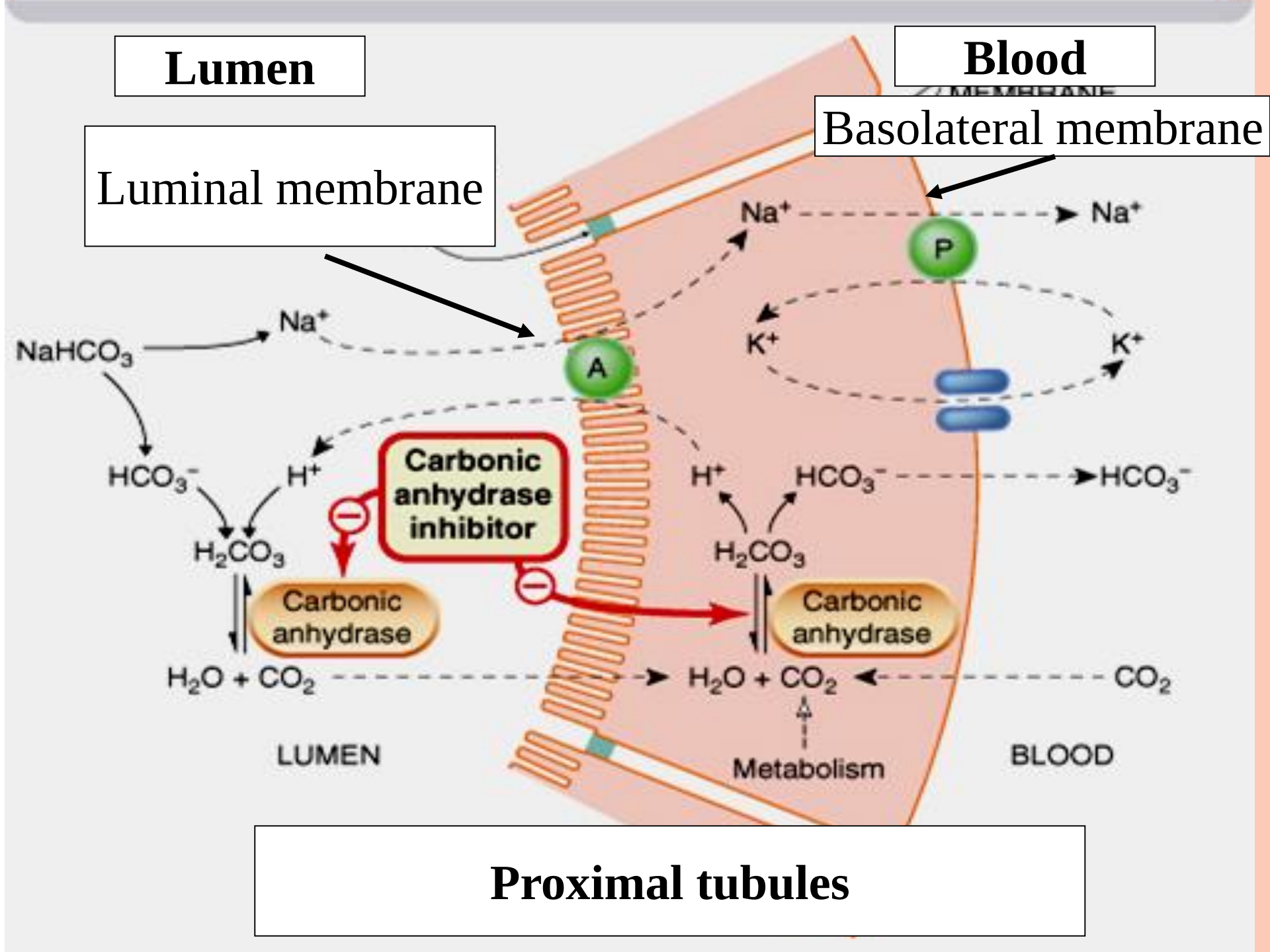
CA is required for reversible reaction,

in which $CO_2 + H_2O \rightleftharpoons H_2CO_3$

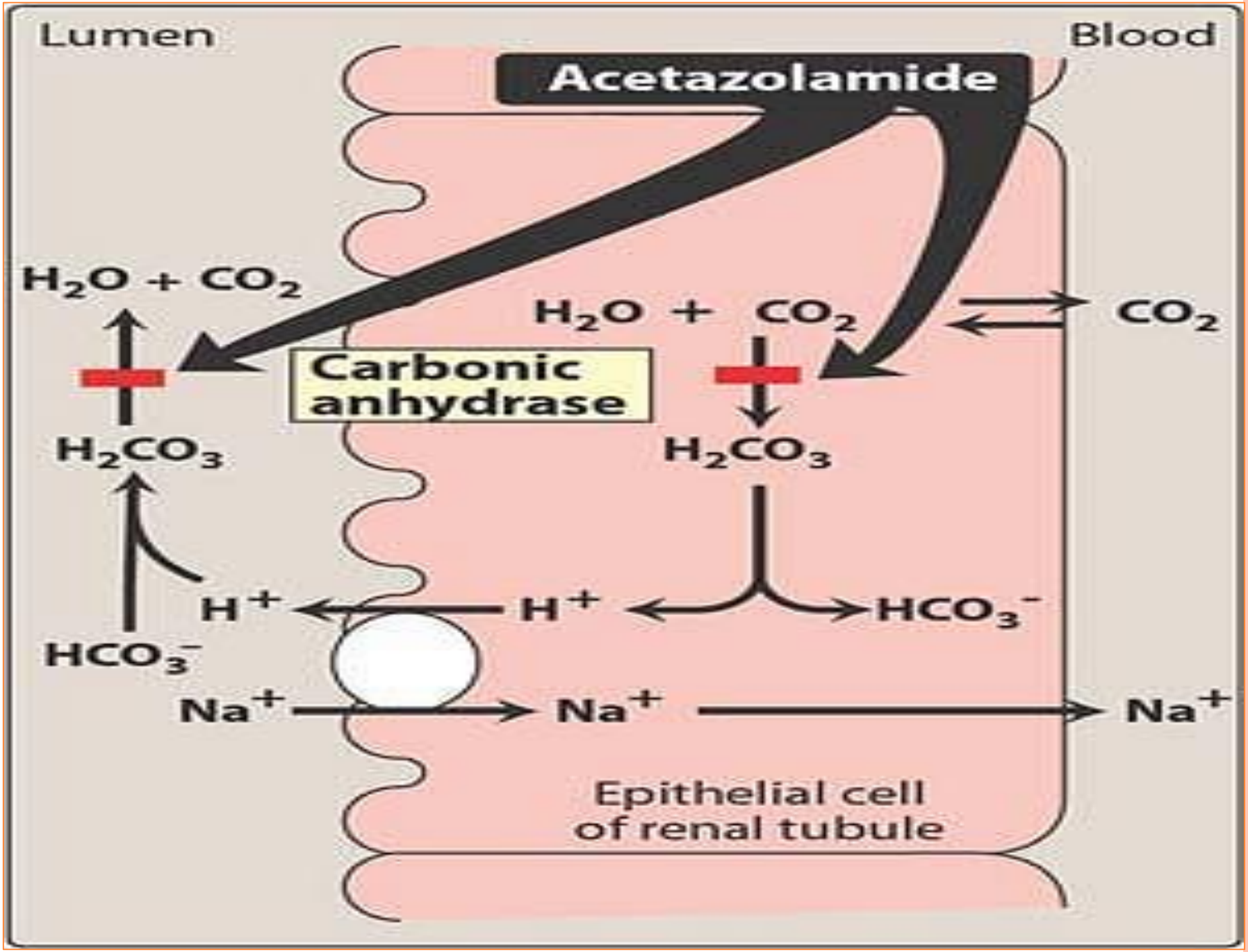


CARBONIC ANHYDRASE





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:

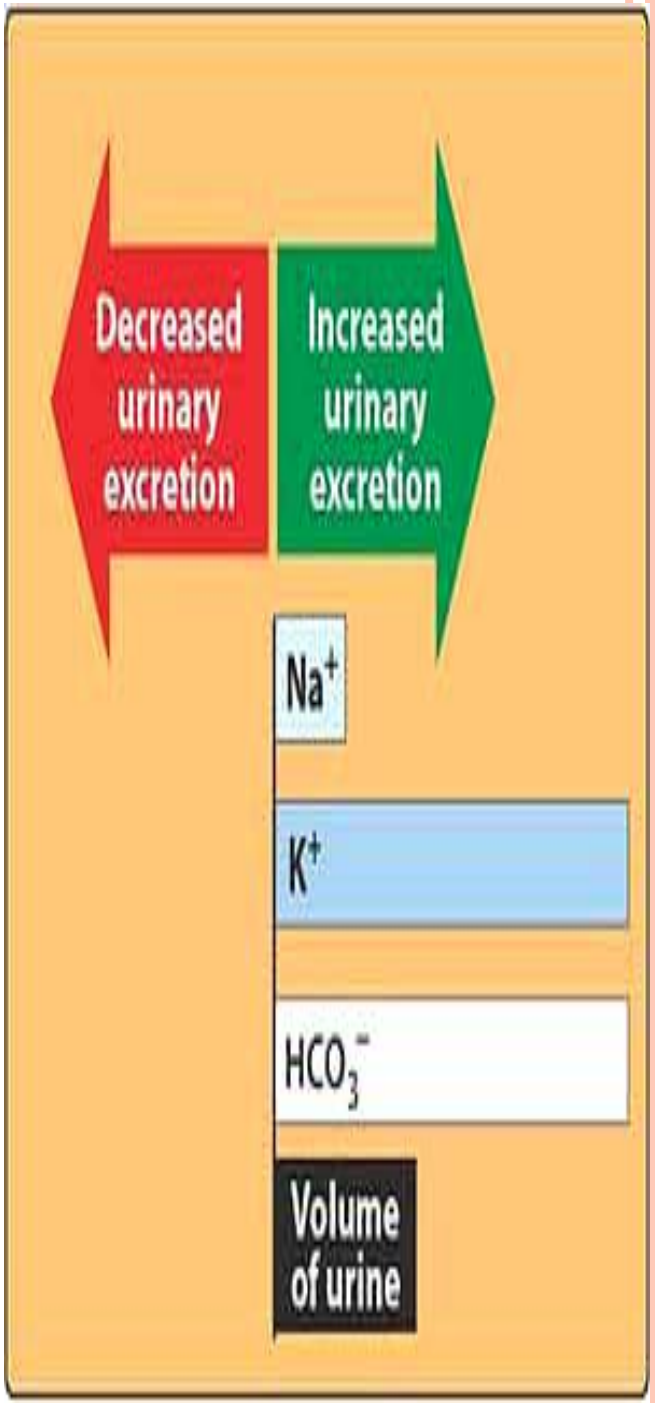
- given orally once a day.
- Onset of action is rapid (30 min).
- Duration of action (12 h).
- Excreted by active secretion in proximal convoluted tubules.
- Produces alkaline urine

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).**
- **Urinary alkalinization to enhance renal excretion of acidic substances (cysteine in cystinuria).**
- **Hyperphosphatemia**
- **Metabolic alkalosis**

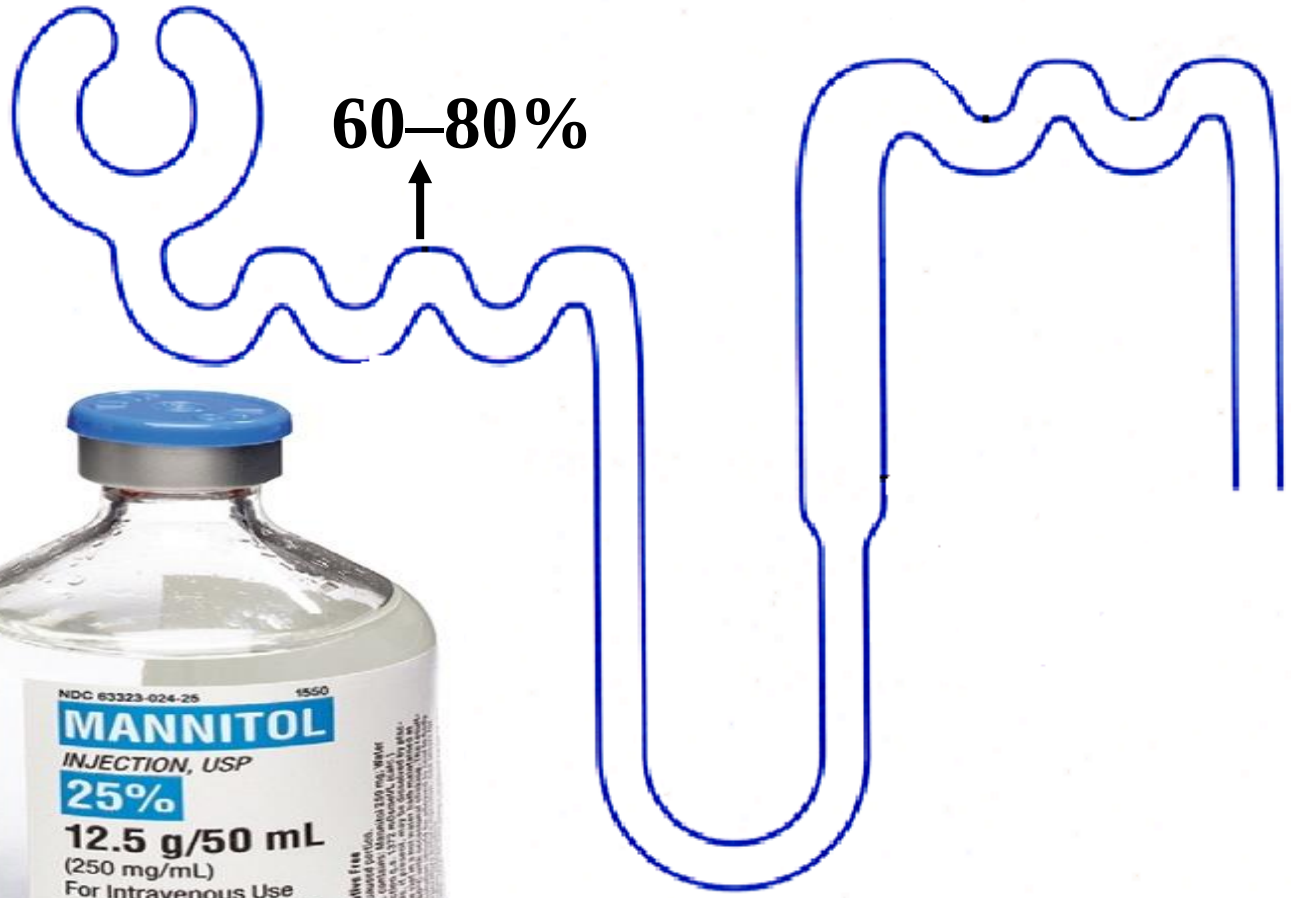
Adverse effects:

- **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?)**

Osmotic diuretics



Osmotic diuretics

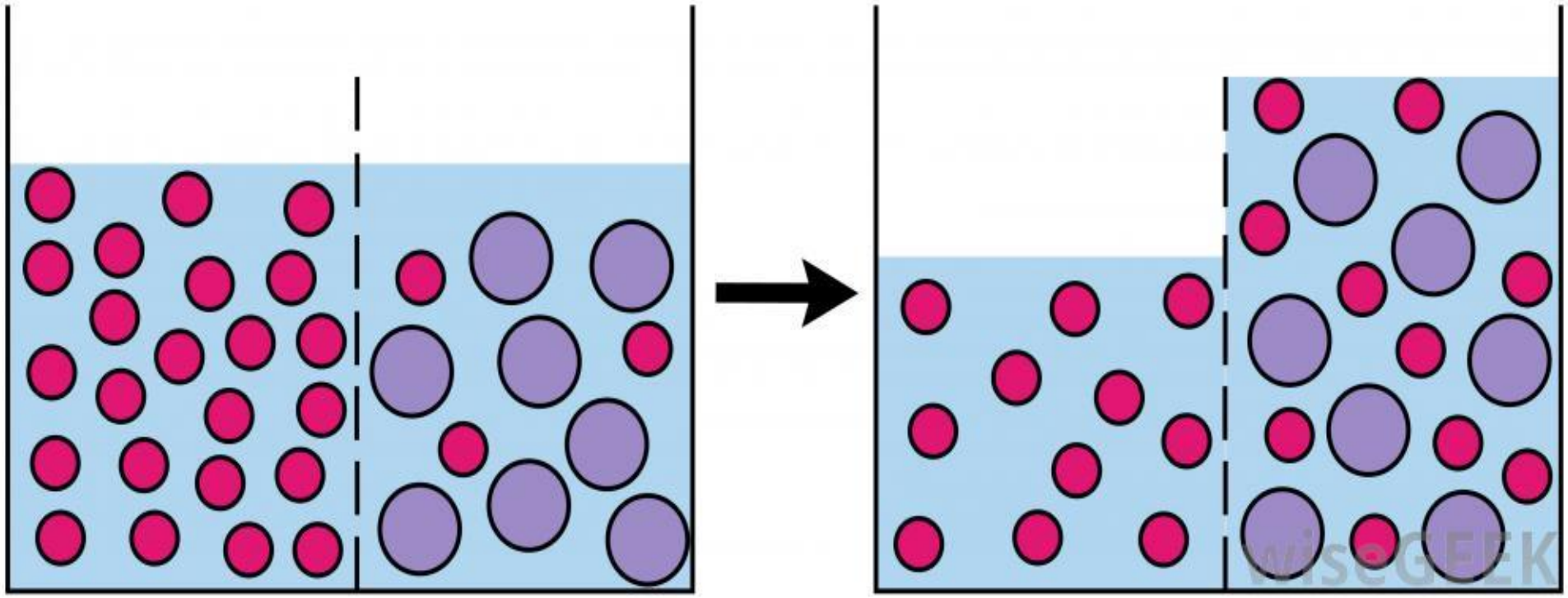
Mannitol:

- 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.**

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



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 & hypernatraemia** (Adequate water replacement is required).