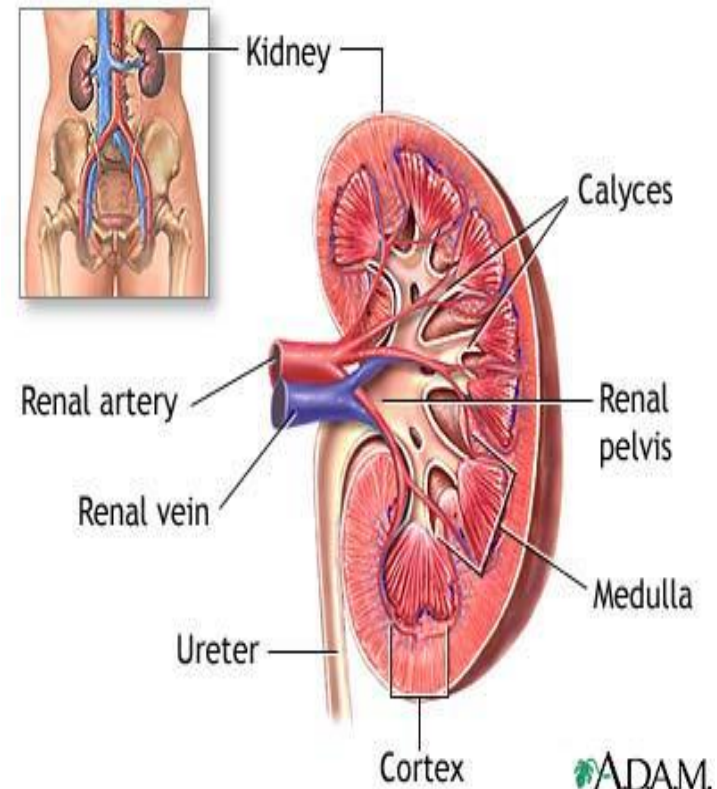


# DIURETICS

## Part 1

Prof. Hanan Hagar  
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 **sodium excretion** in the urine



# INDICATIONS of DIURETICS

```
graph TD; A[INDICATIONS of DIURETICS] --> B[Edema of any origin]; A --> C[Congestive heart failure]; A --> D[Hypertension]; A --> E[Elimination of toxins];
```

**Edema of  
any origin**

**Congestive  
heart failure**

**Hypertension**

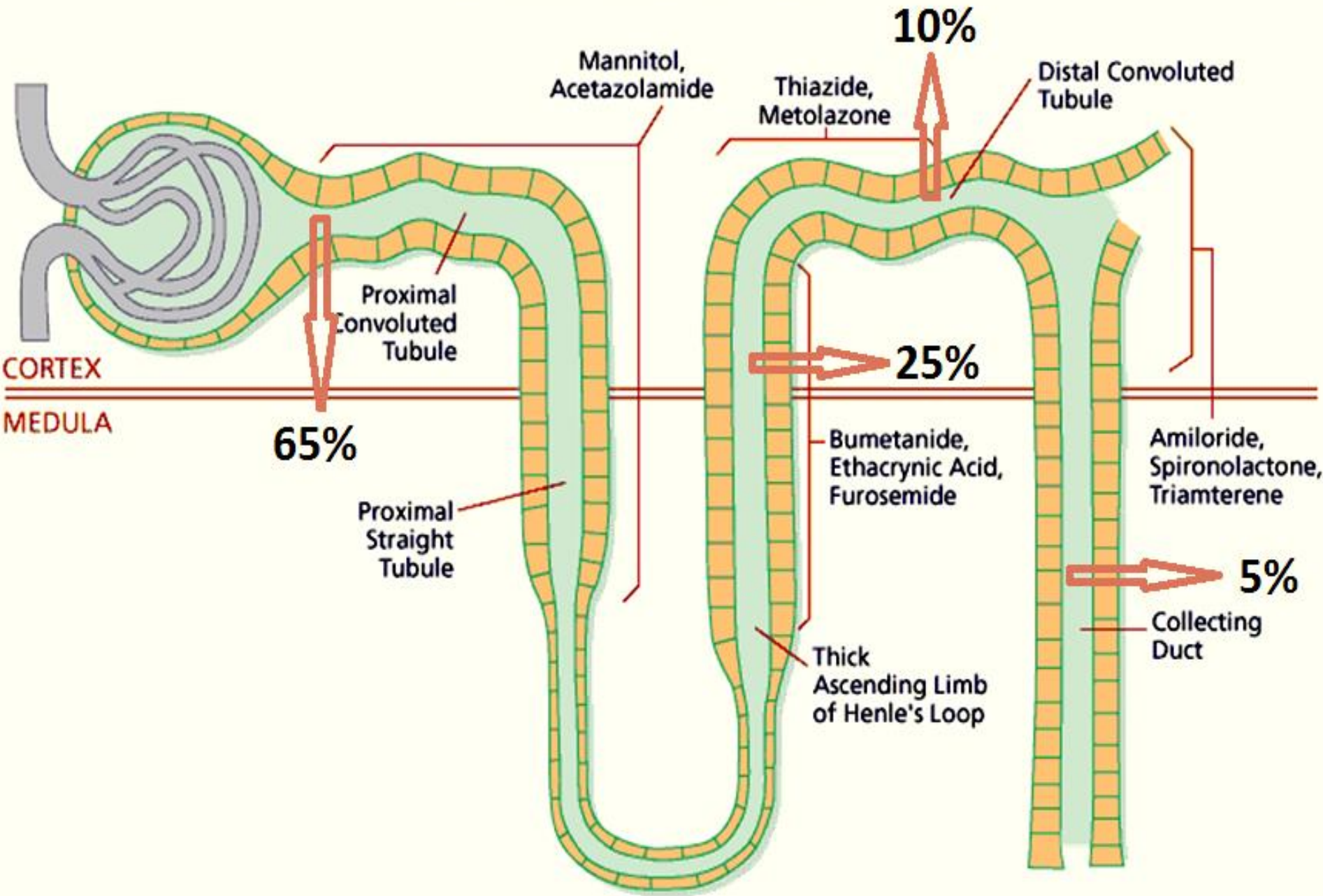
**Elimination  
of toxins**

# 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.



# Diuretic Sites of Action



# 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

<b>Nephron Segment</b>	<b>Na<sup>+</sup> Transporter</b>	<b>Filtered Na<sup>+</sup> re-absorbed</b>
<b>Proximal convoluted tubules</b>	<b>Na<sup>+</sup>/H<sup>+</sup> transporter Carbonic anhydrase enzyme</b>	<b>65 % As NaHCO<sub>3</sub></b>
<b>Ascending Loop of Henle</b>	<b>Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup> cotransporter</b>	<b>20-30% Active reabsorption Na, K, Cl</b>
<b>Distal convoluted tubules</b>	<b>Na<sup>+</sup>/Cl<sup>-</sup> transporter</b>	<b>5-10% Active reabsorption Na, Cl</b>
<b>Cortical Collecting Tubules</b>	<b>Na<sup>+</sup> channel Aldosterone Antidiuretic hormone</b>	<b>5% Na reabsorption K &amp; H secretion</b>



# 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 <sub>3</sub>	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

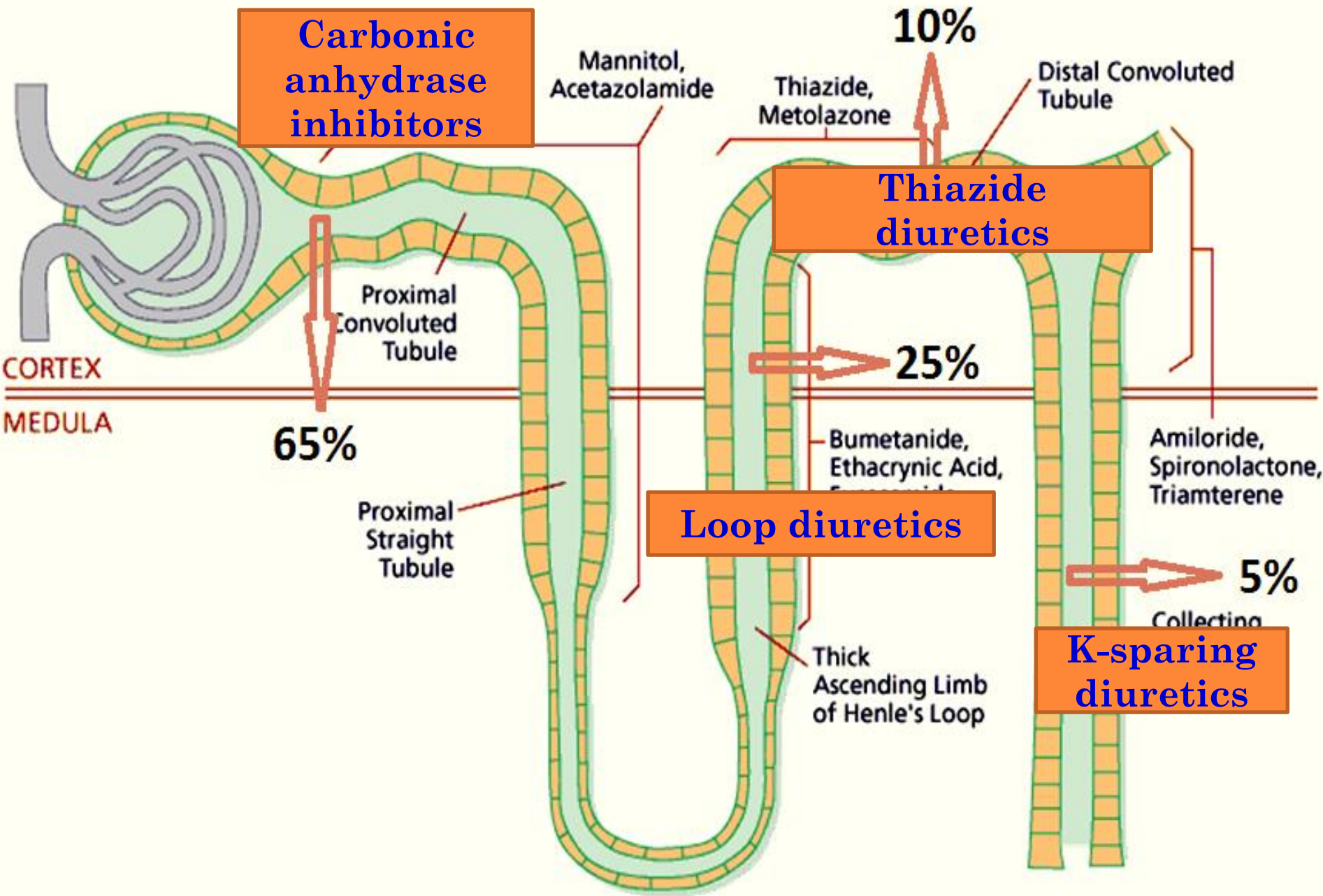
<b>Nephron Segment</b>	<b>Na<sup>+</sup> Transporter</b>	<b>Diuretics</b>
<b>Proximal convoluted tubules</b>	<b>Na<sup>+</sup>/H<sup>+</sup> transporter</b> <b><u>Carbonic anhydrase enzyme</u></b>	<b>Carbonic anhydrase inhibitors</b>
<b>Ascending Loop of Henle</b>	<b>Na<sup>+</sup>/K<sup>+</sup>/2Cl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

# Classification of diuretics

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



# Diuretic Sites of Action



**Carbonic anhydrase inhibitors**

Mannitol, Acetazolamide

Thiazide, Metolazone

10%

Distal Convoluted Tubule

**Thiazide diuretics**

Proximal Convoluted Tubule

25%

Bumetanide, Ethacrynic Acid, Furosemide

**Loop diuretics**

Amiloride, Spironolactone, Triamterene

65%

Proximal Straight Tubule

5%

**K-sparing diuretics**

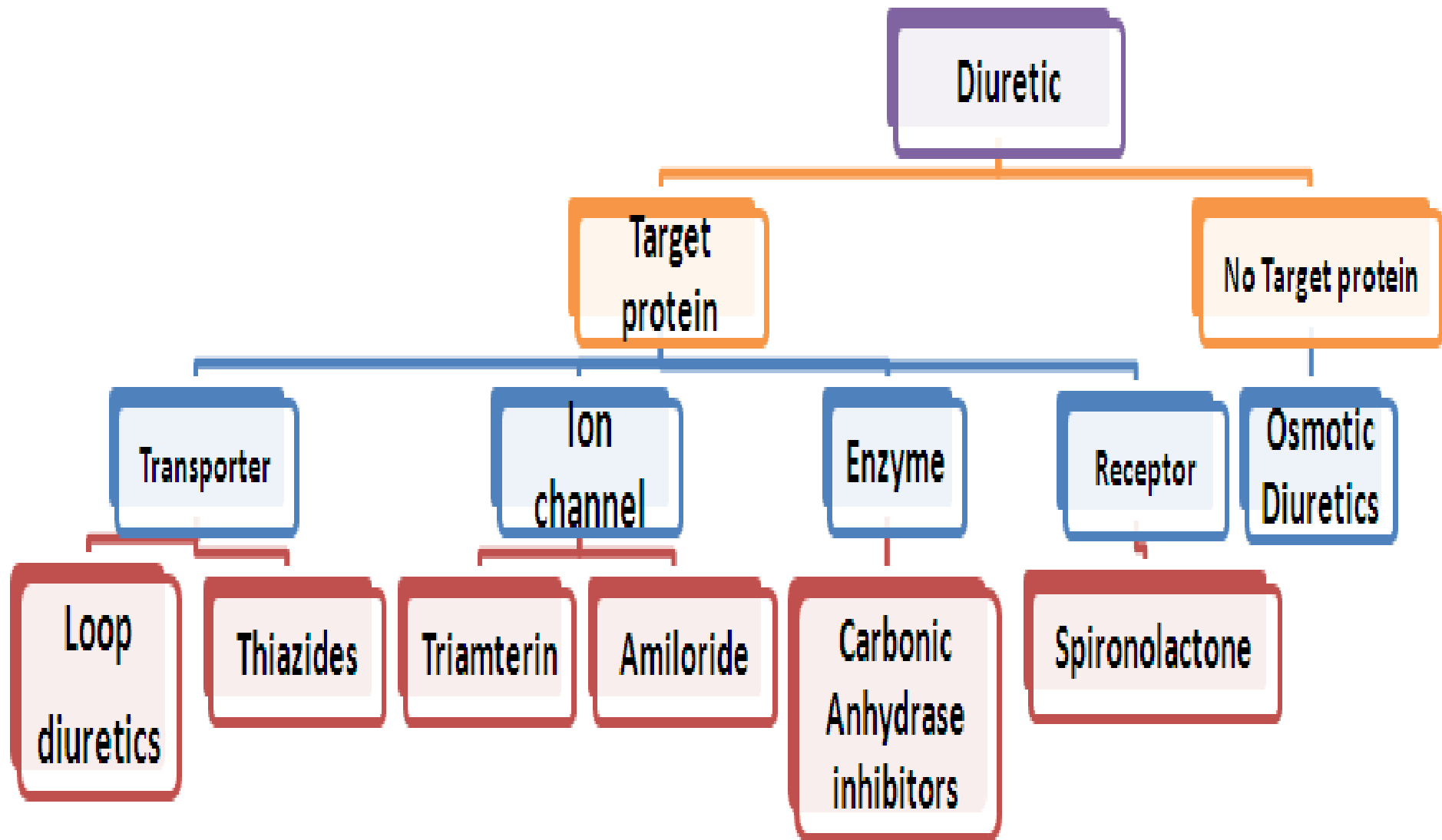
Collecting Duct

Thick Ascending Limb of Henle's Loop

CORTEX

MEDULA

# Classification of diuretics



# Classification of diuretics

**Diuretics**

```
graph TD; Diuretics[Diuretics] --> HighEfficacy[High efficacy]; Diuretics --> ModerateEfficacy[Moderate efficacy]; Diuretics --> LowEfficacy[Low efficacy]; HighEfficacy --> LoopDiuretics[Loop diuretics]; ModerateEfficacy --> Thiazides[Thiazides]; LowEfficacy --> KplusSparing[K+ sparing]; LowEfficacy --> Osmotic[Osmotic]; KplusSparing --> Spironolactone[Spironolactone]; KplusSparing --> Triamterin[Triamterin]; KplusSparing --> Amiloride[Amiloride]; Osmotic --> CarbonicAnhydraseInhibitors[Carbonic anhydrase inhibitors];
```

**High efficacy**

**Loop diuretics**

**Moderate efficacy**

**Thiazides**

**Low efficacy**

**K<sup>+</sup> sparing**

**Spironolactone  
Triamterin  
Amiloride**

**Osmotic**

**Carbonic anhydrase inhibitors**

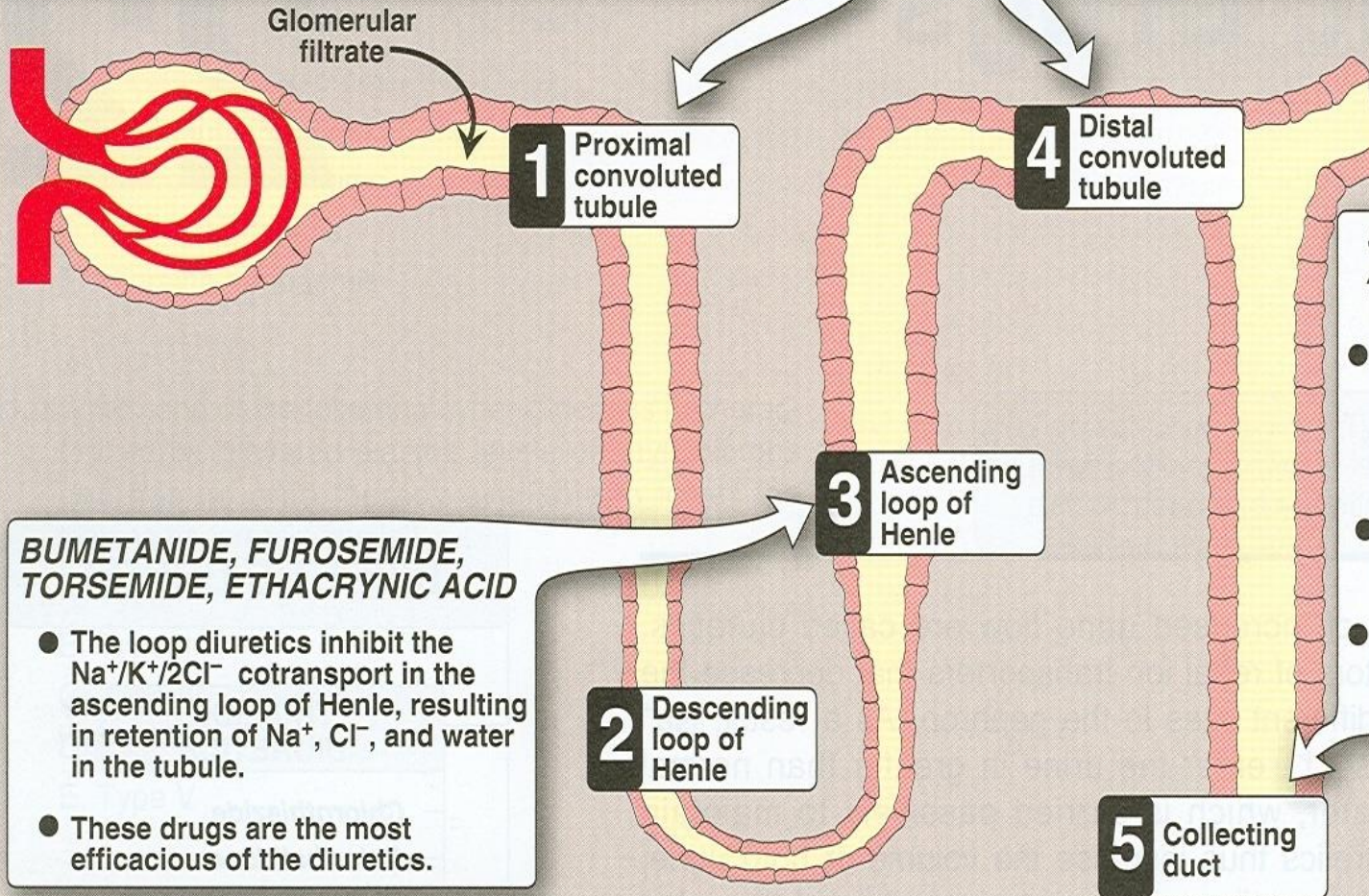


## ACETAZOLAMIDE

- A carbonic anhydrase inhibitor that inhibits the reabsorption of  $\text{HCO}_3^-$  in the proximal convoluted tubule.
- Weak diuretic properties.

## THIAZIDES

- Inhibit reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  in the distal convoluted tubule, resulting in retention of water.
- Most commonly used diuretics.



## BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID

- The loop diuretics inhibit the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  cotransport in the ascending loop of Henle, resulting in retention of  $\text{Na}^+$ ,  $\text{Cl}^-$ , and water in the tubule.
- These drugs are the most efficacious of the diuretics.

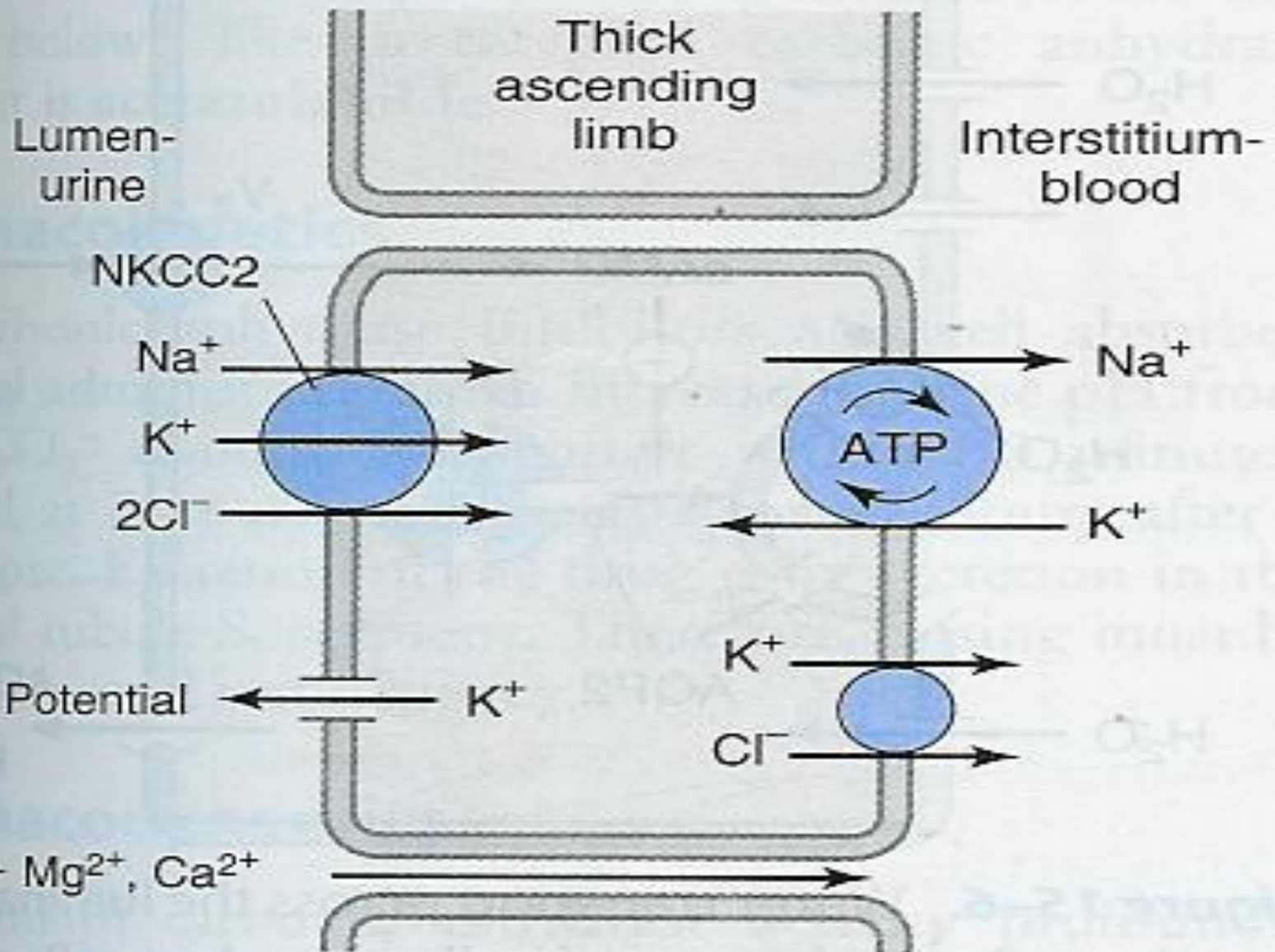
## SPIRONOLACTONE, AMILORIDE, TRIAMTERENE

- *Spironolactone*, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of  $\text{Na}^+$  and secretion of  $\text{K}^+$ .
- *Amiloride* and *triamterene* block  $\text{Na}^+$  channels.
- These agents can prevent loss of  $\text{K}^+$  that occurs with thiazide or loop diuretics.

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

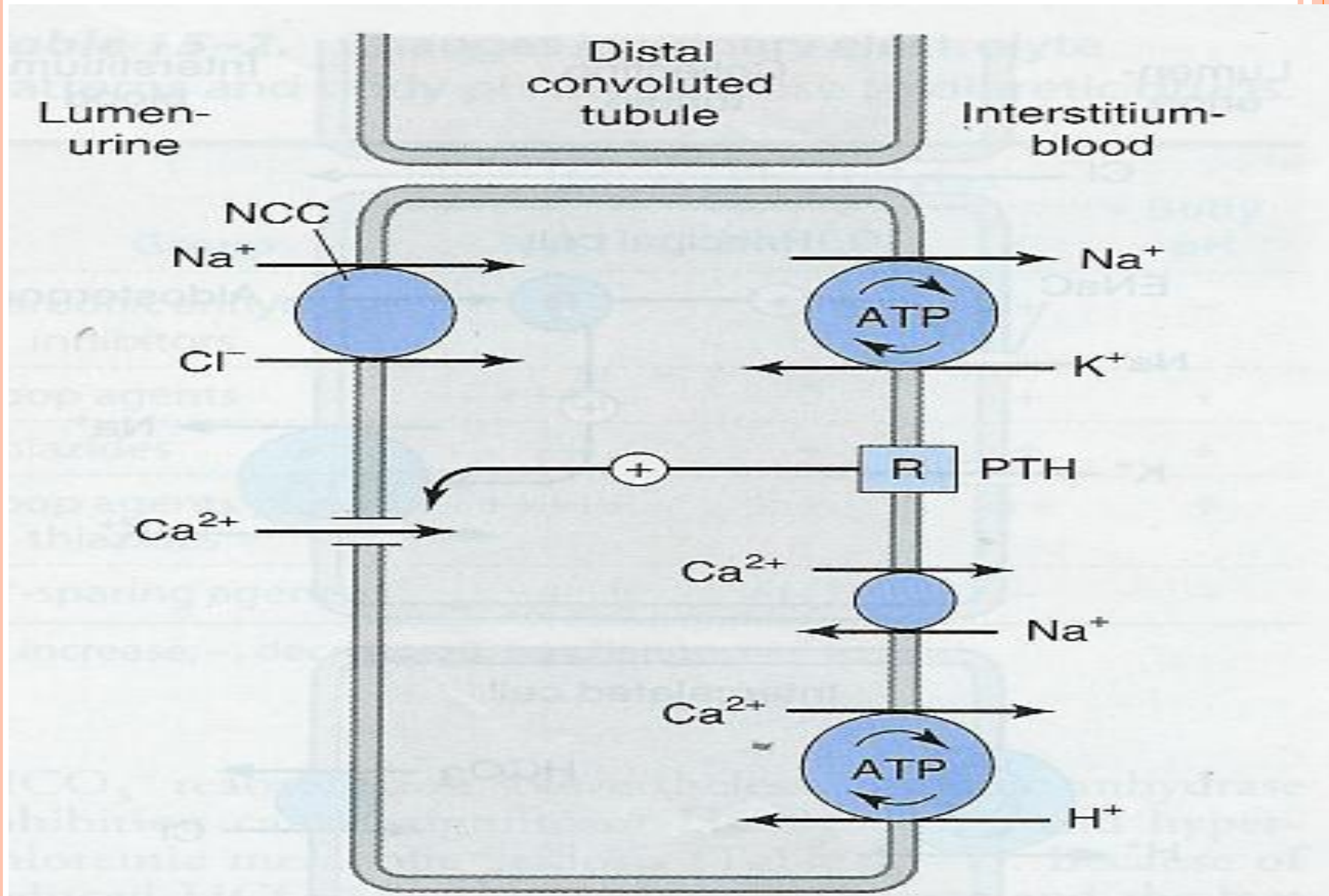


# ASCENDING LOOP OF HENLE

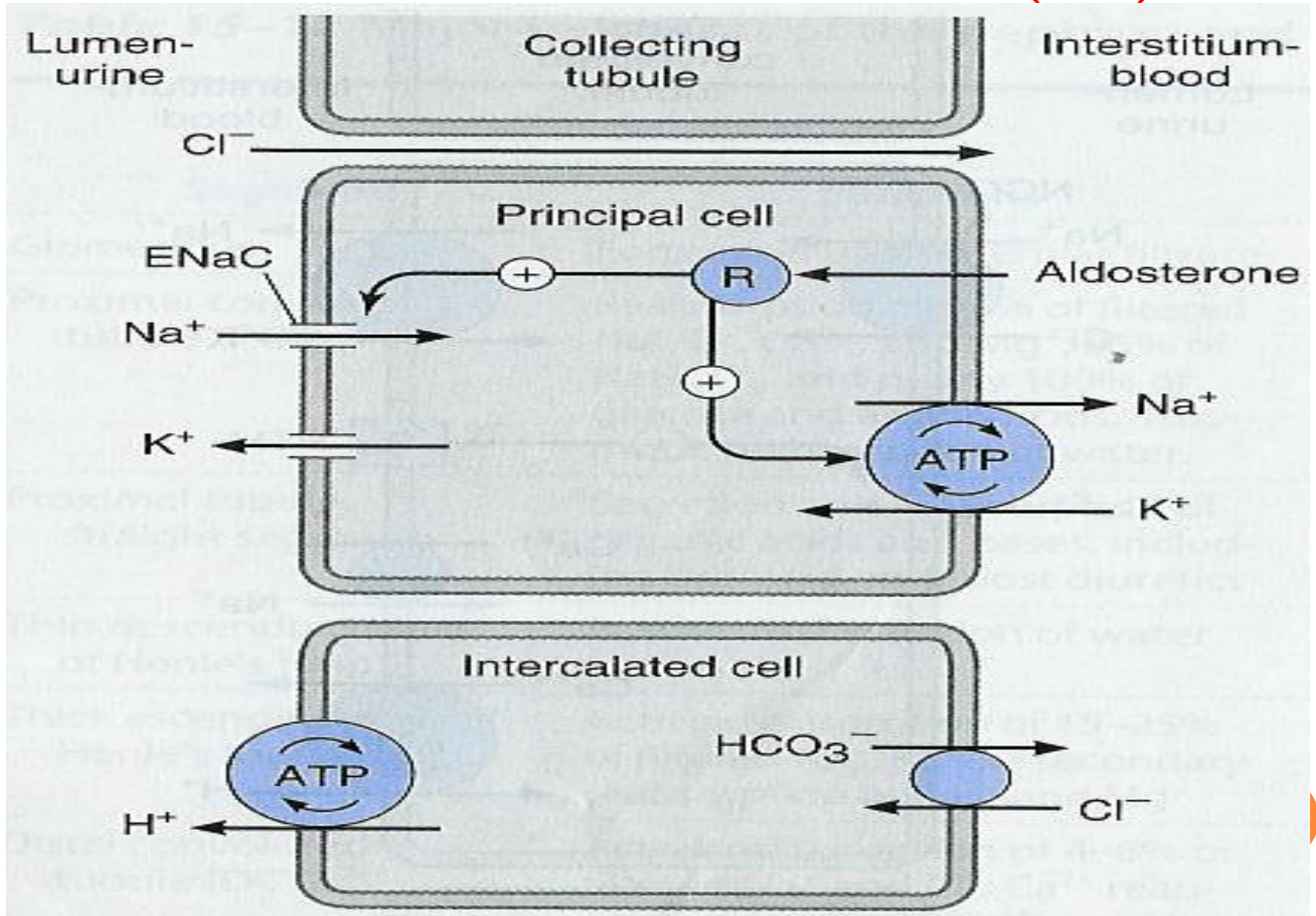




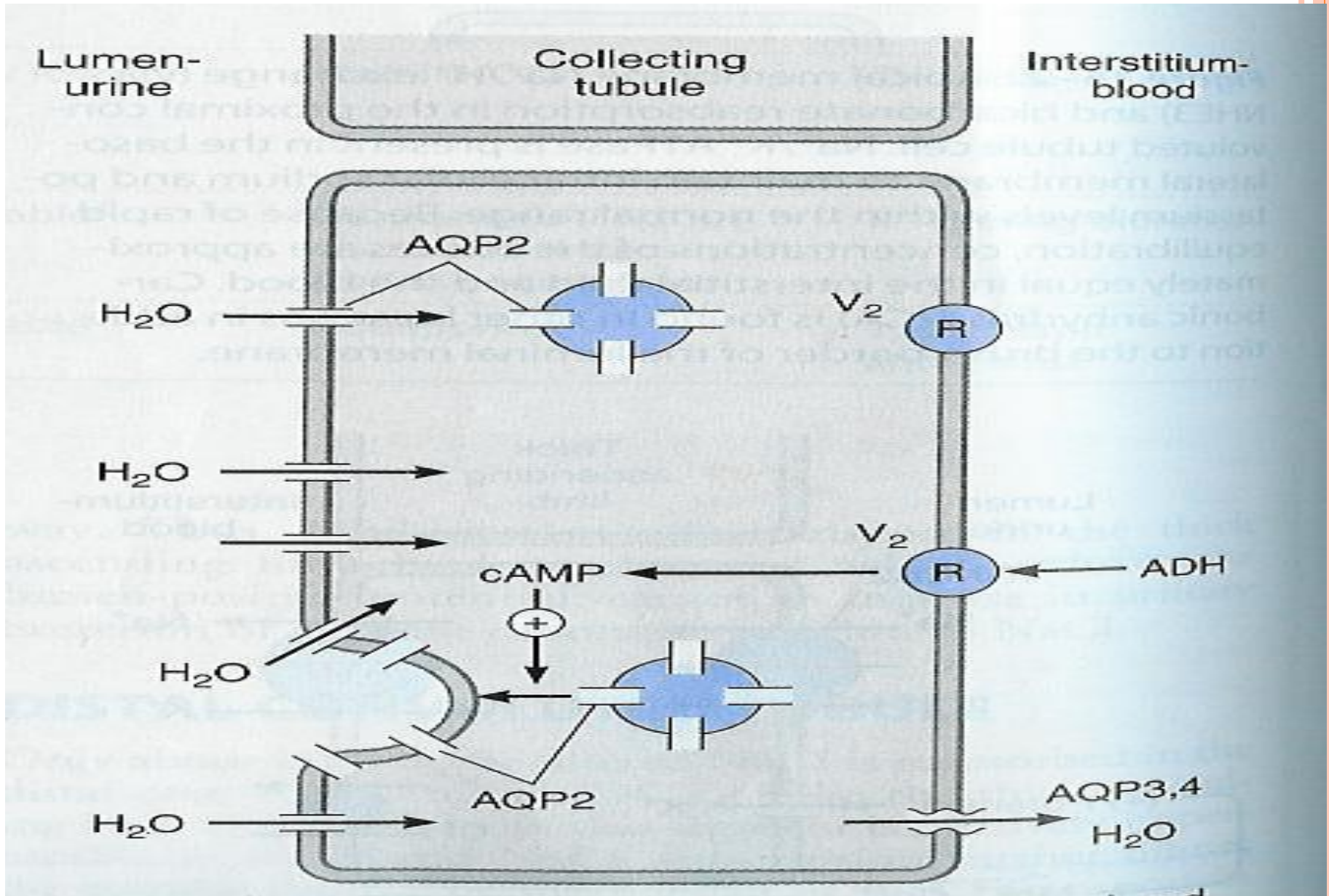
# Distal convoluted tubules (DCT)



# 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 **NaHCO<sub>3</sub> re-absorption** and causes diuresis.





# Carbonic Anhydrase Inhibitors

**Carbonic anhydrase** is required for reversible reaction in which

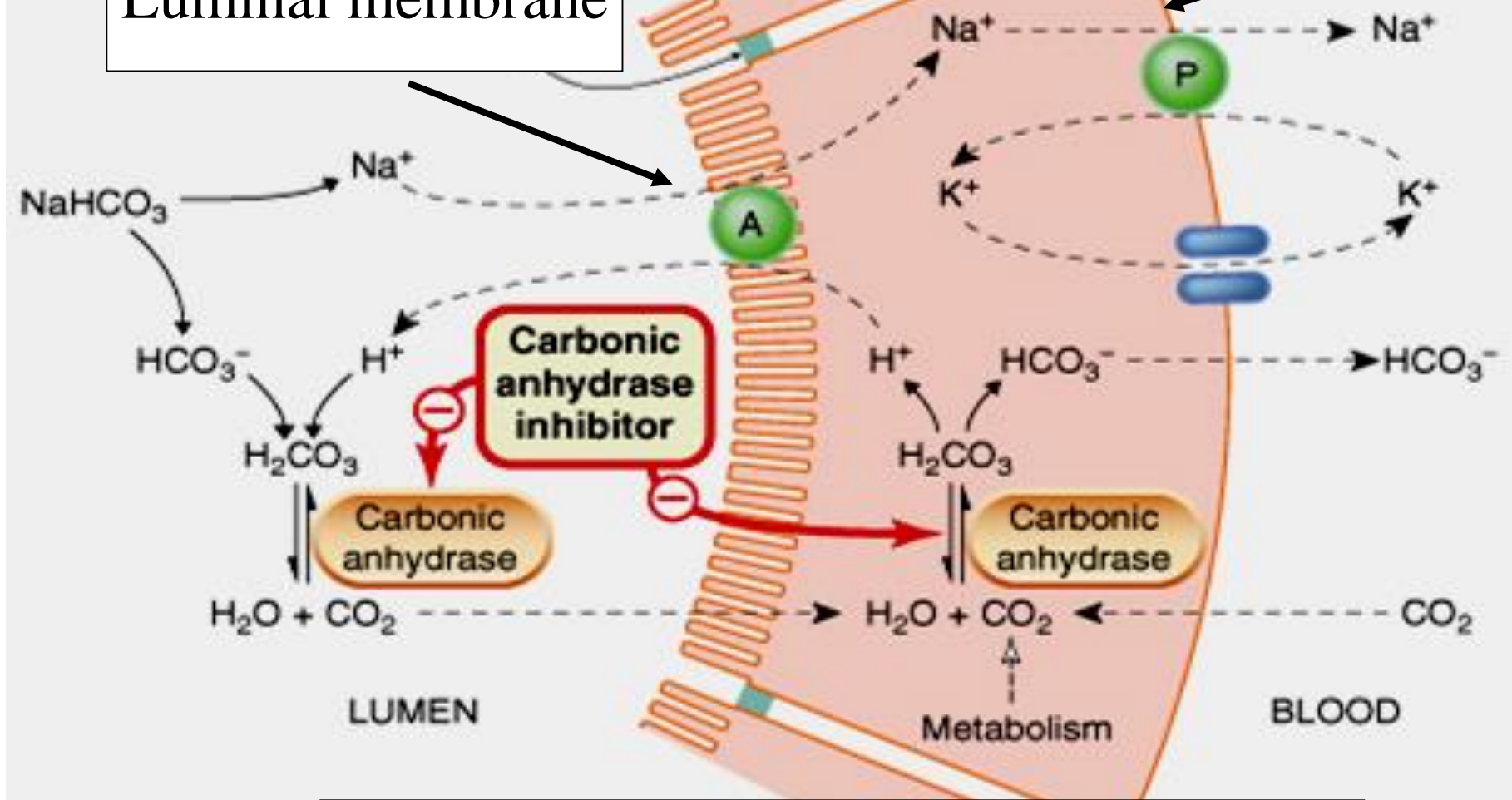


**Lumen**

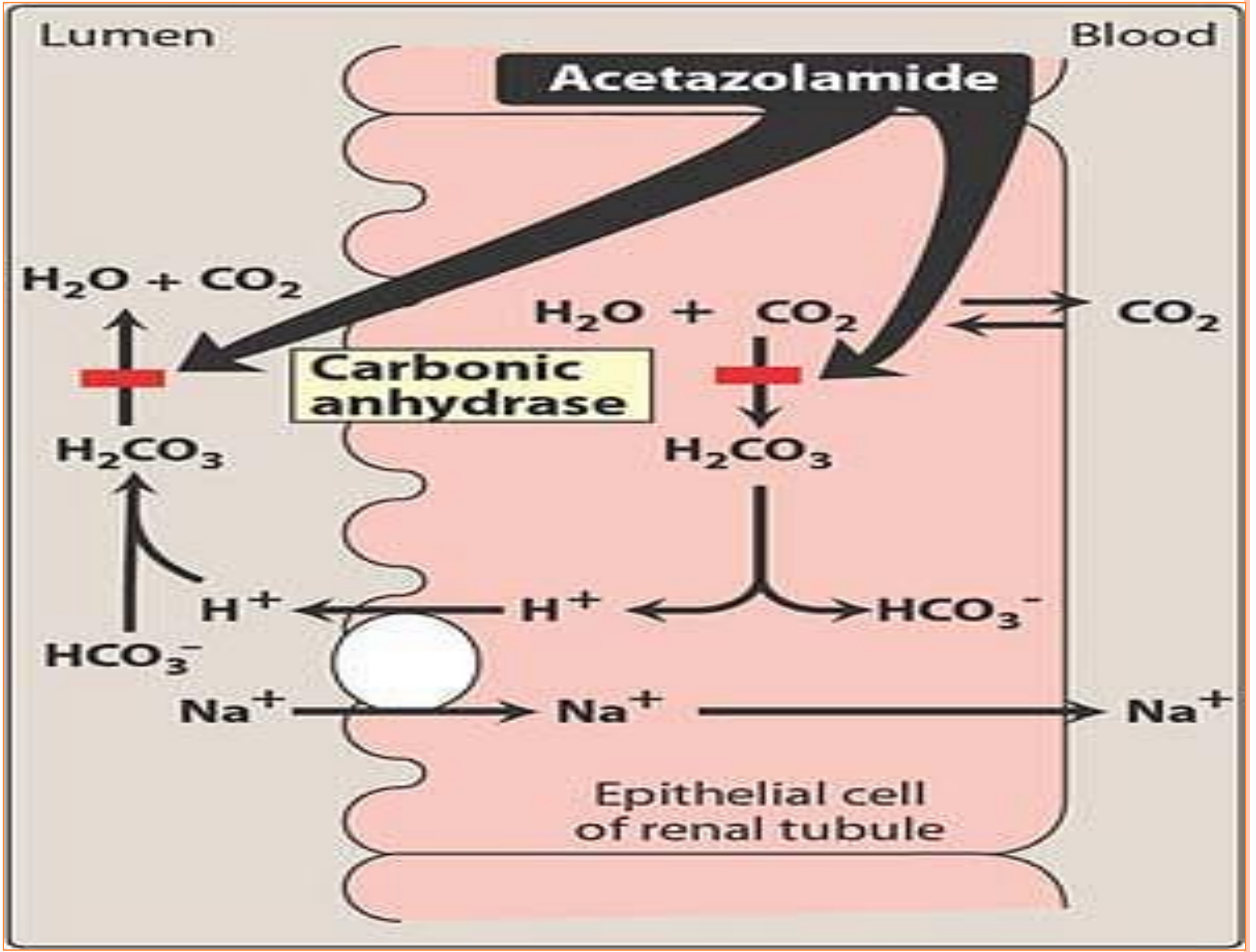
**Blood**

**Basolateral membrane**

**Luminal membrane**



**Proximal tubules**





# 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**



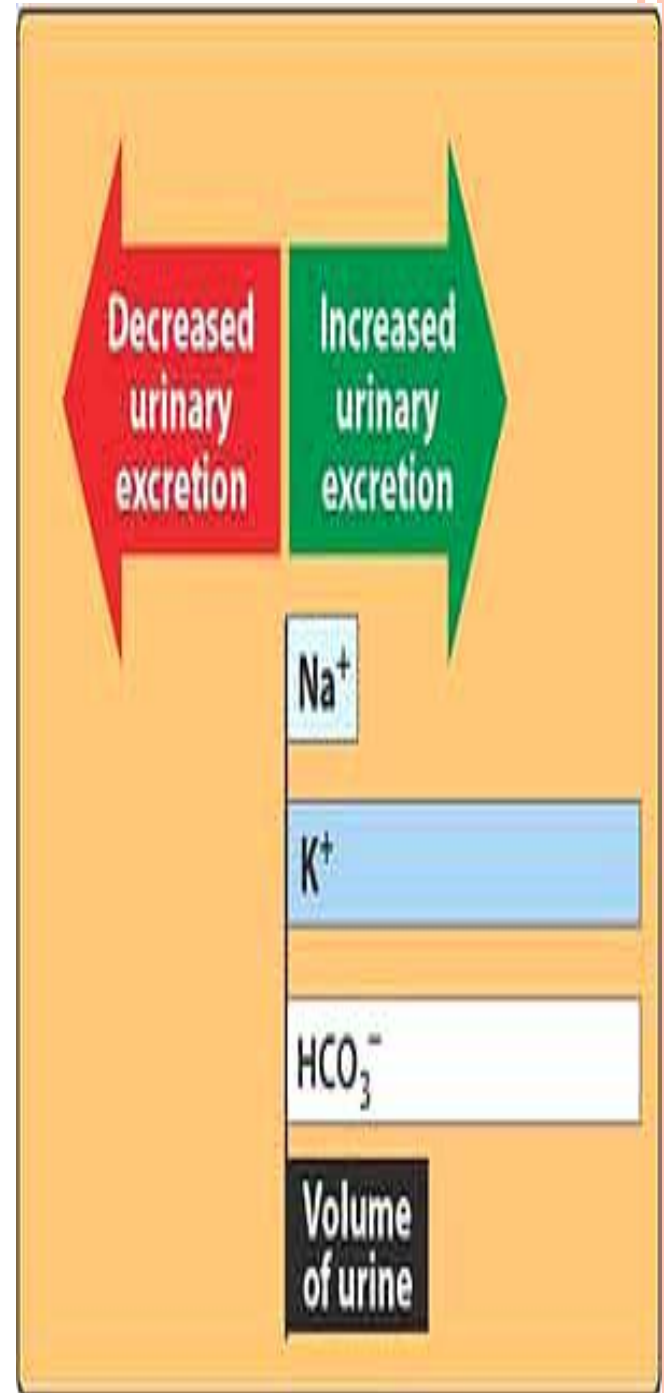
## Pharmacological actions:

- **↑ 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 alkalization 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.



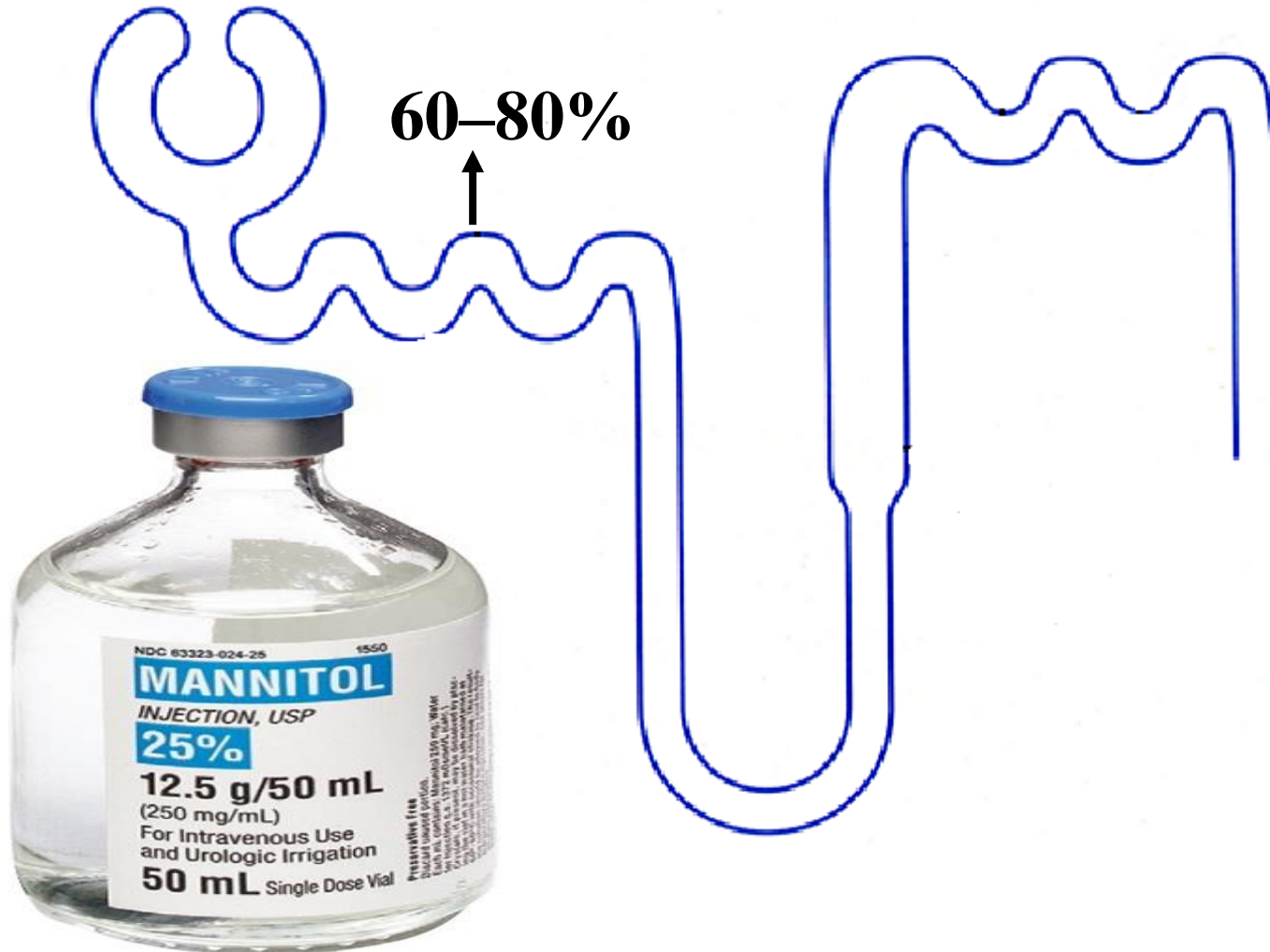
## **Adverse effects:**

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





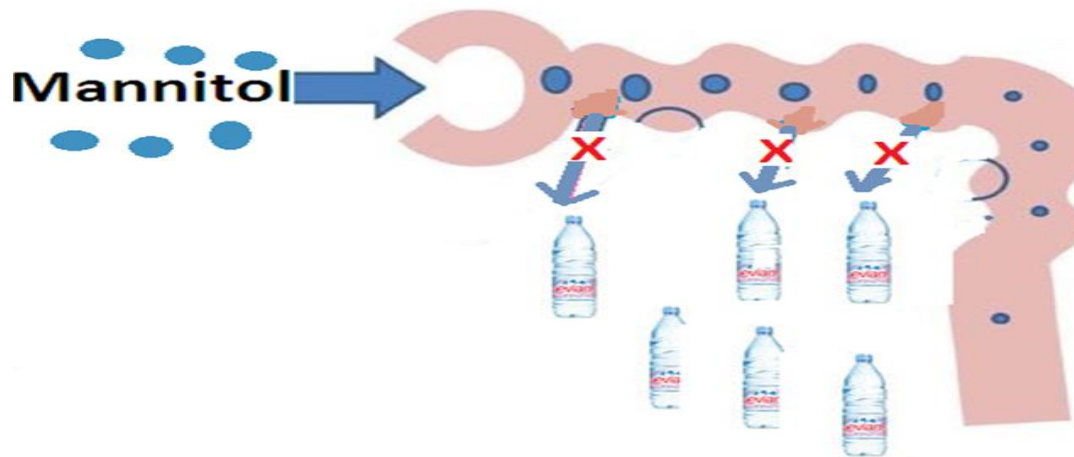
# Osmotic diuretics



# Osmotic diuretics

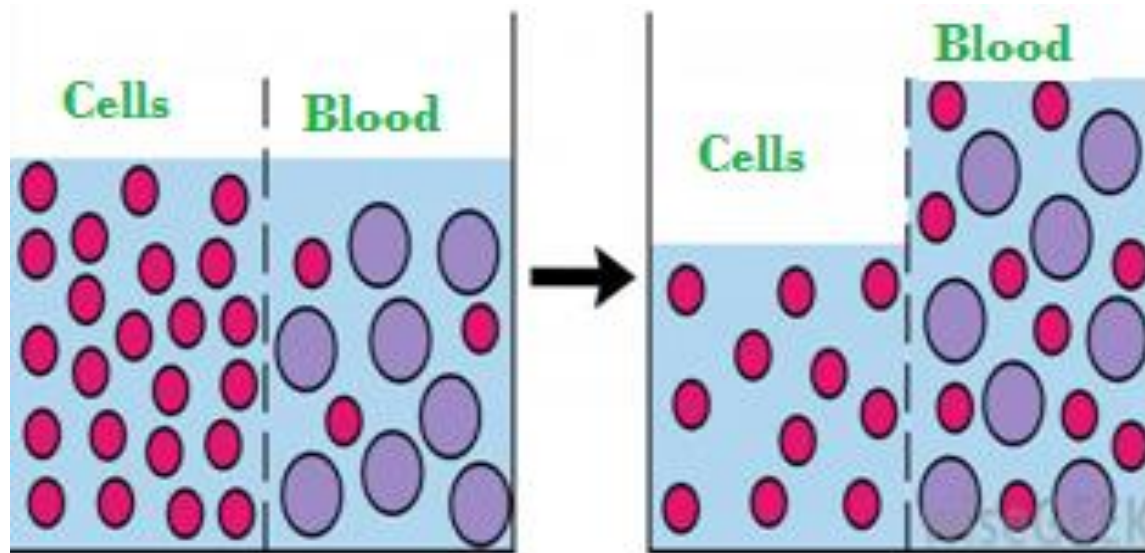
## Mannitol:

- Poorly absorbed
- If given orally  $\longrightarrow$  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<sup>+</sup> reabsorption.**
- ↑water excretion with relatively less effect on Na<sup>+</sup>.
- **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

