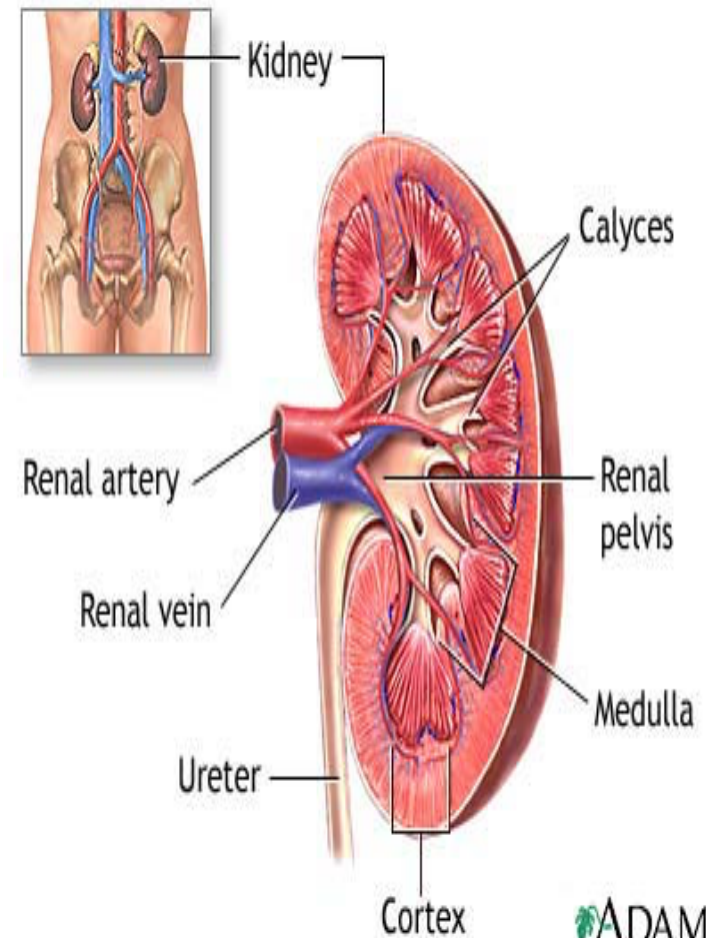


# DIURETICS

Prof. Hanan Hagar  
Pharmacology Unit

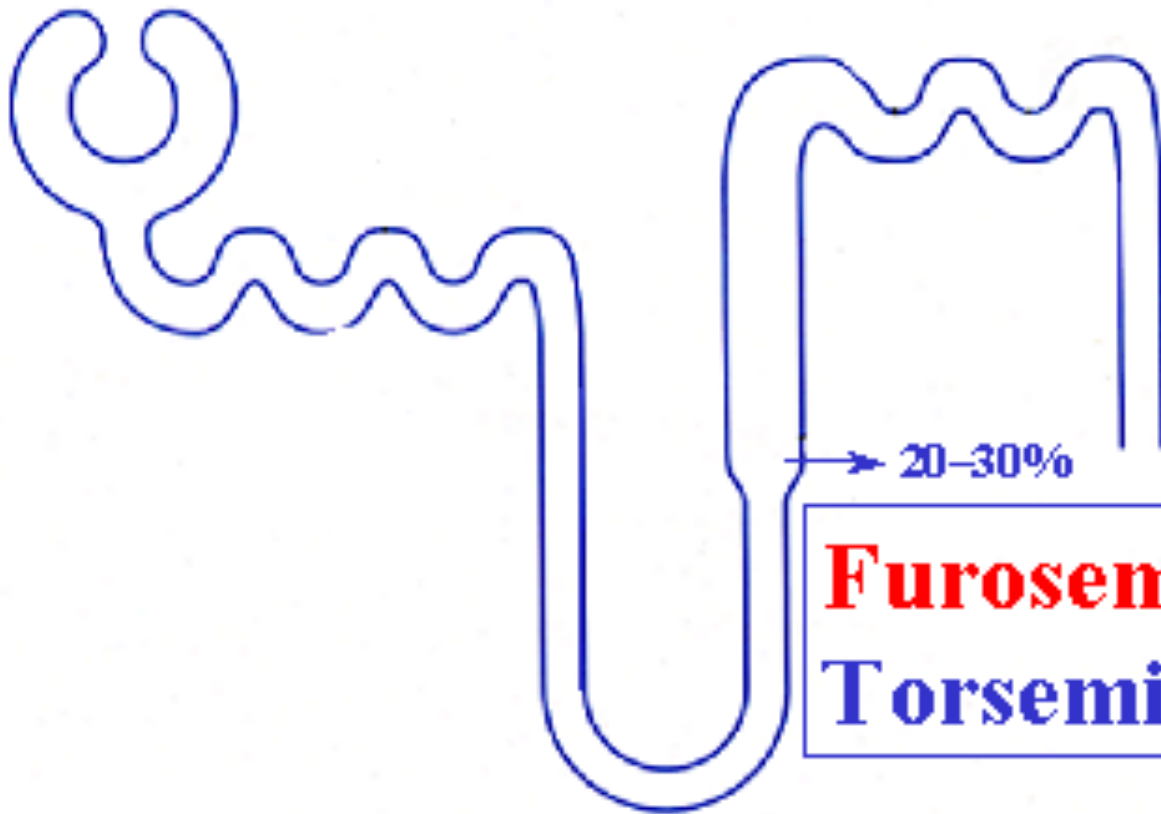


# Classification of diuretics

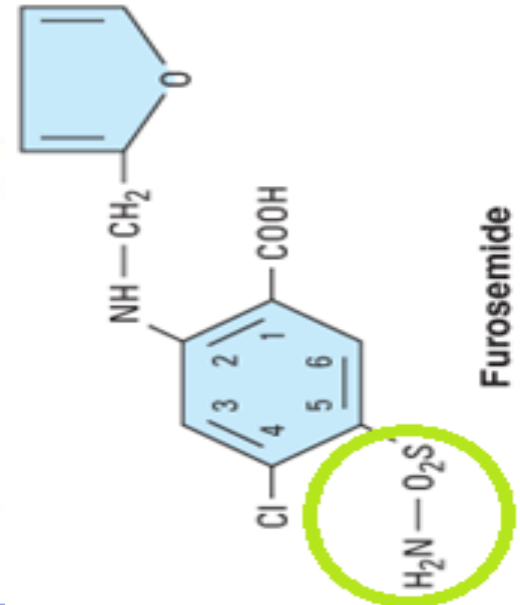
- **Carbonic Anhydrase Inhibitors**
- **Loop Diuretics**
- **Thiazides**
- **Potassium-Sparing Diuretics**
- **Osmotic Diuretics**



# Loop Diuretics



**Furosemide**  
**Torseamide**



# LOOP DIURETICS

## High Ceiling diuretics

- The most potent diuretic, termed “**high ceiling diuretic**”

**Efficacy:** High natriuresis as 25-30%  $\text{Na}^+$  is reabsorbed.

- **Drugs as:**

- Furosemide - Torsemide
- Bumetanide – Ethacrynic acid





# Loop Diuretics

## High Ceiling Diuretics

**Bumetanide**

Potency 40,  $t_{1/2}$  0.8 h

**Ethacrynic**

**Acid**

Potency 0.7,  $t_{1/2}$  1h

**Furosemide**

Potency 1,  $t_{1/2}$  1.5h

**Torsemide**

Potency 3,  $t_{1/2}$  3.5h



# LOOP DIURETICS

## **Mechanism:**

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

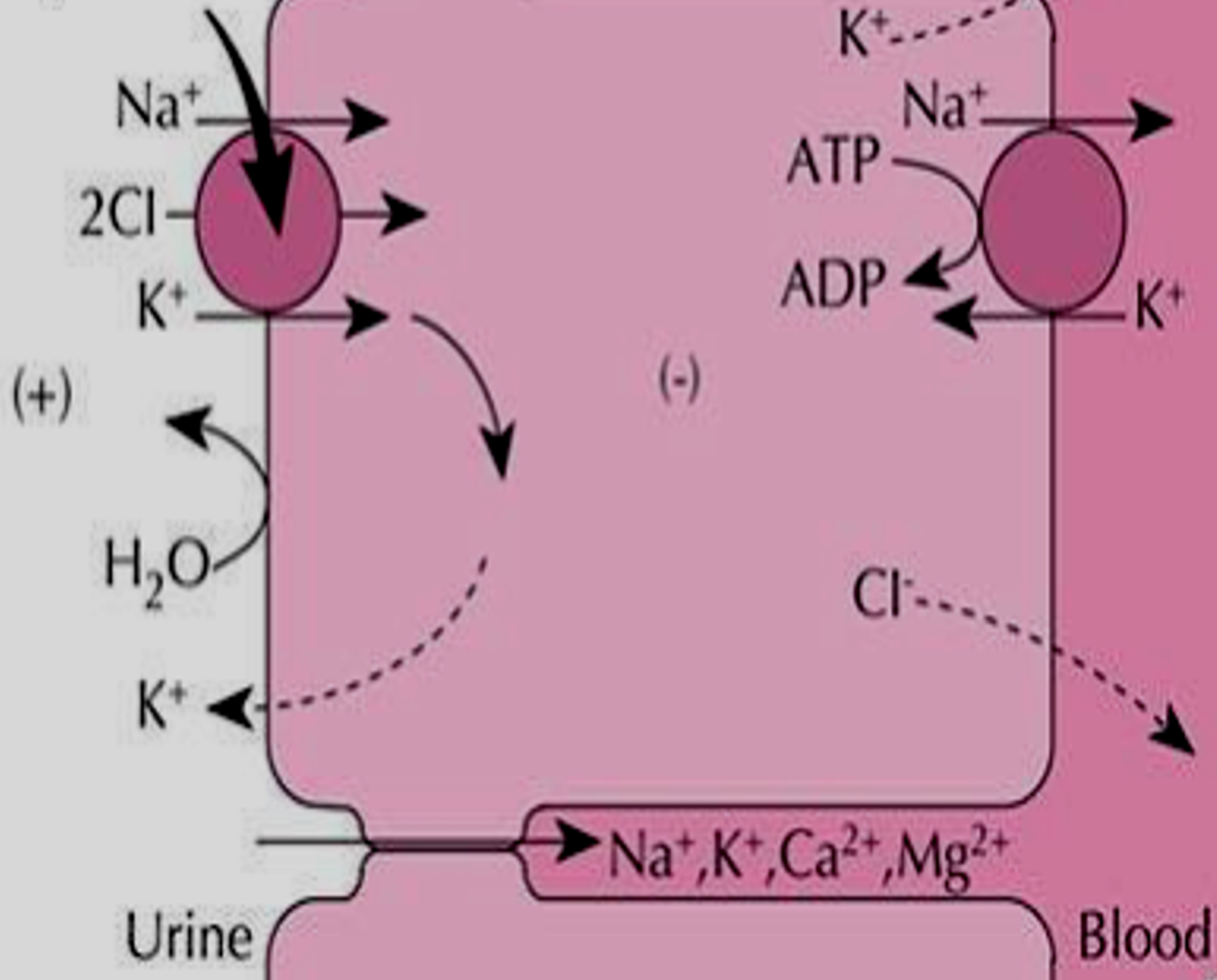


# Ascending loop of Henle

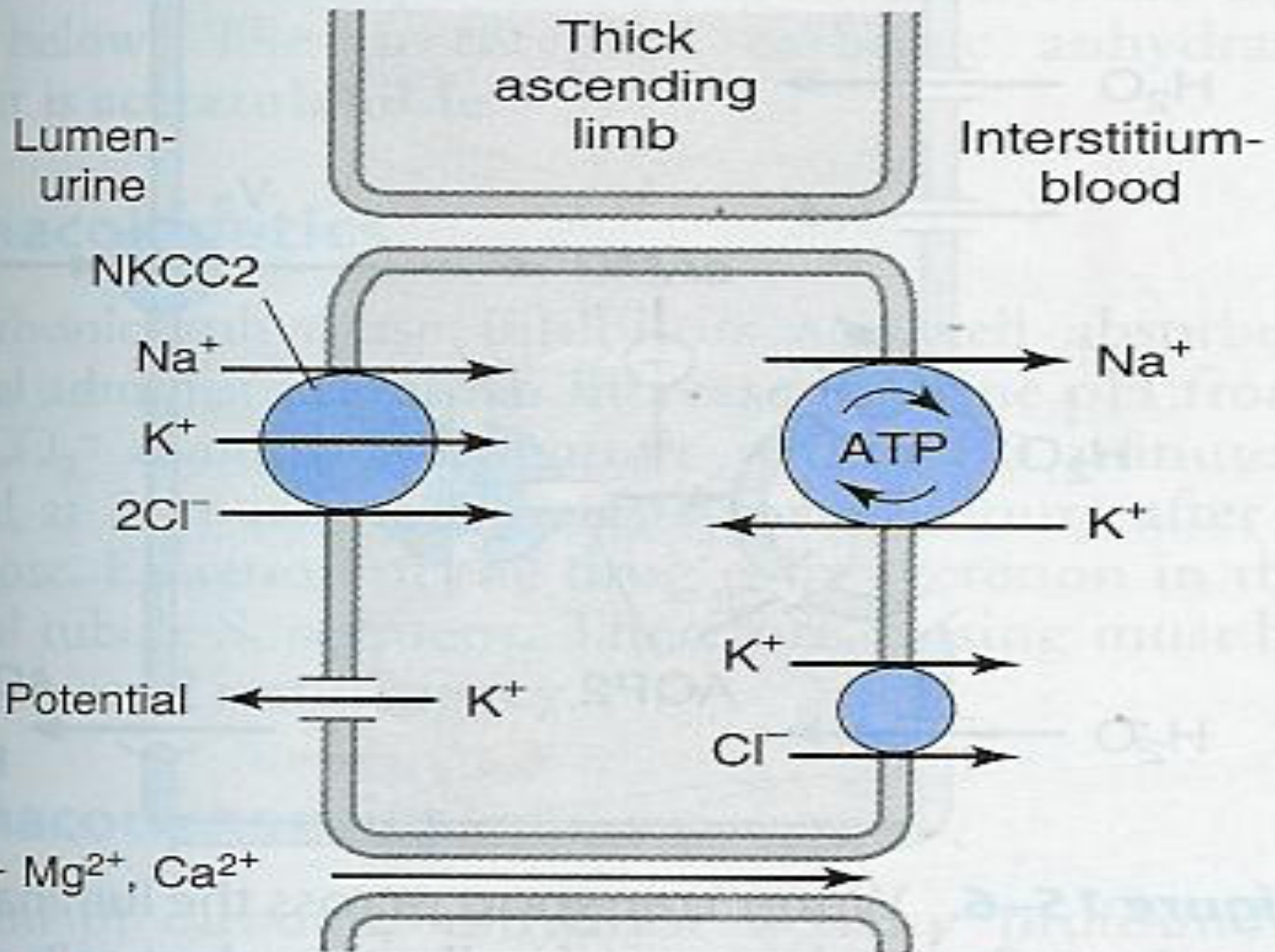
- Is impermeable to water
- **In thick ascending loop of Henle (TAL)** is responsible for active re-absorption of Na, K and Cl (**25-30% Na<sup>+</sup> is reabsorbed**) via transport system in luminal membrane called **Na<sup>+</sup>/ K<sup>+</sup> / 2Cl<sup>-</sup> co-transporter**
- Ca and Mg are reabsorbed and enter the interstitial fluid via paracellular pathway

# Ascending loop of Henle

Loop diuretics



# ASCENDING LOOP OF HENLE



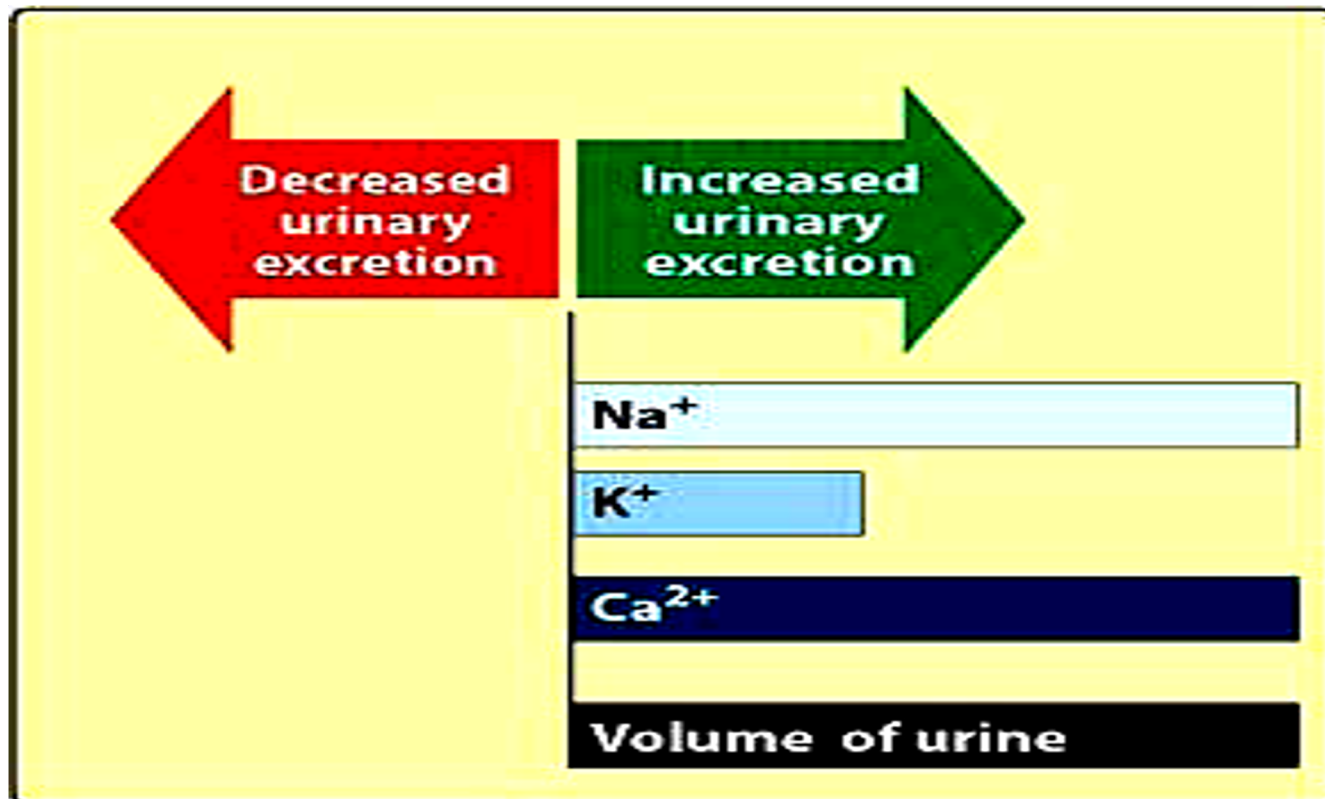
# Pharmacokinetics

- 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  $\text{Na}^+$  and  $\text{K}^+$
- ↑ urinary excretion  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$
- ↑ 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





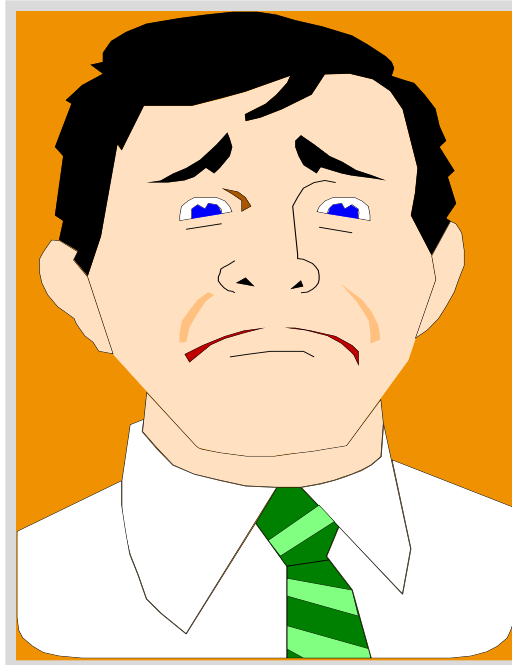
# ADVERSE EFFECTS

**Volume  
Depletion**

**Hypokalemia**

**Hypocalcaemia**

**Hypomagnesaemia**



**Metabolic  
Alkalosis**

**Ototoxicity**

**Hyperuricemia**

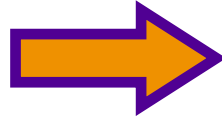
**Hyperglycemia**



# LOOP DIURETICS

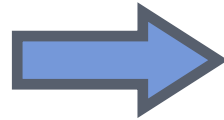
# DRUG- DRUG INTERACTIONS

NSAIDS



↓ Diuretic Response

Digitalis



Arrhythmias

Aminoglycosides

↑ Ototoxicity of Loop Diuretic



# Adverse effects :

- Hypovolemia
- Hyponatraemia ( $\downarrow$  blood  $\text{Na}^+$ ).
- Hypokalemia ( $\downarrow$  blood  $\text{K}^+$ )
- Hypomagnesaemia ( $\downarrow$  blood  $\text{Mg}^{2+}$ )
- Hypocalcaemia ( $\downarrow$  blood  $\text{Ca}^{2+}$ )
- 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,  $t_{1/2}$  2h

**Chlorthalidone**

Potency 10,  $t_{1/2}$  26h

**Metolazone**

Potency 5,  $t_{1/2}$  5h

**Hydrochlorothiazide**

Potency 1,  $t_{1/2}$  3h

**Indapamide**

Potency 20,  $t_{1/2}$  16h

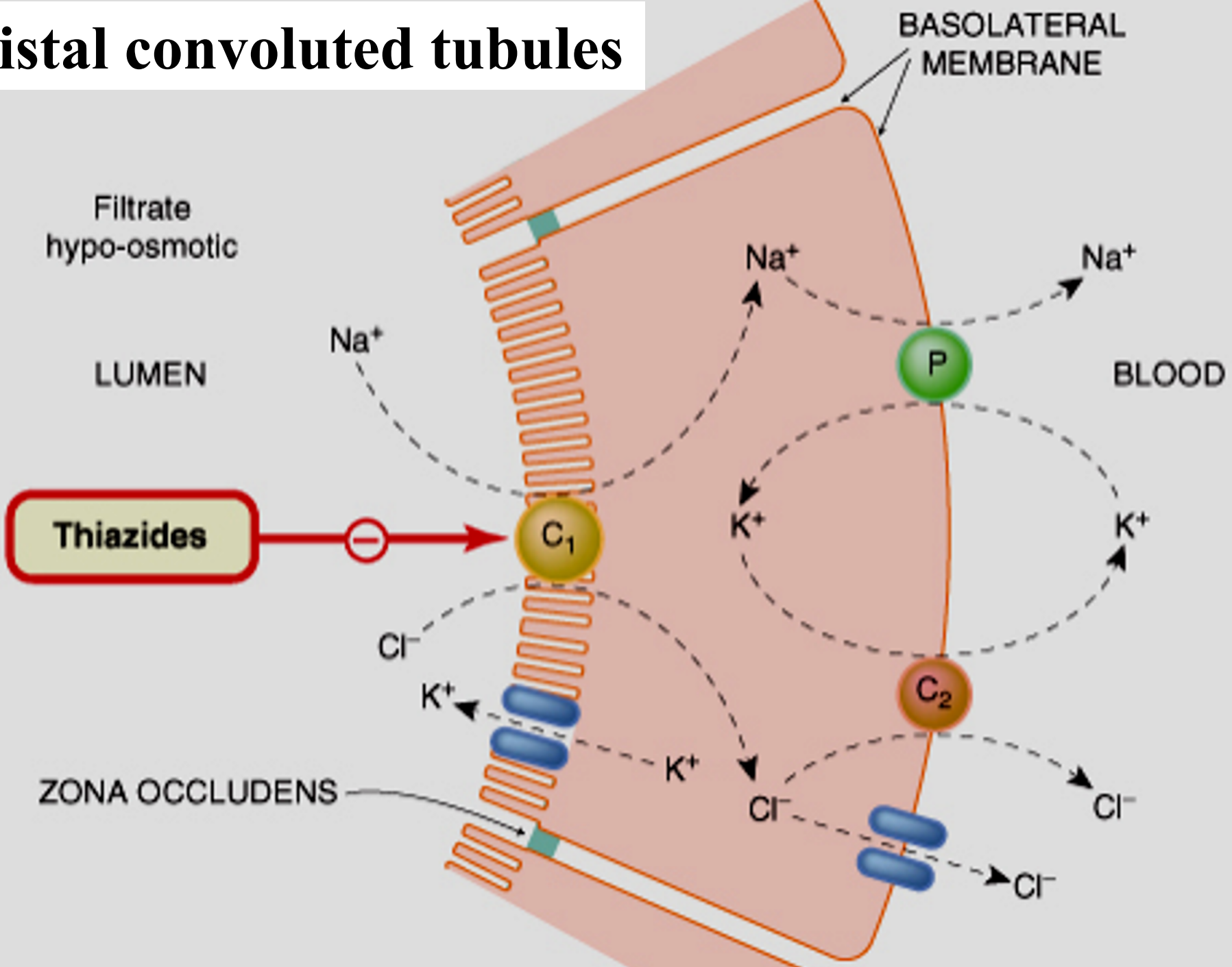
# Thiazide diuretics

## 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).

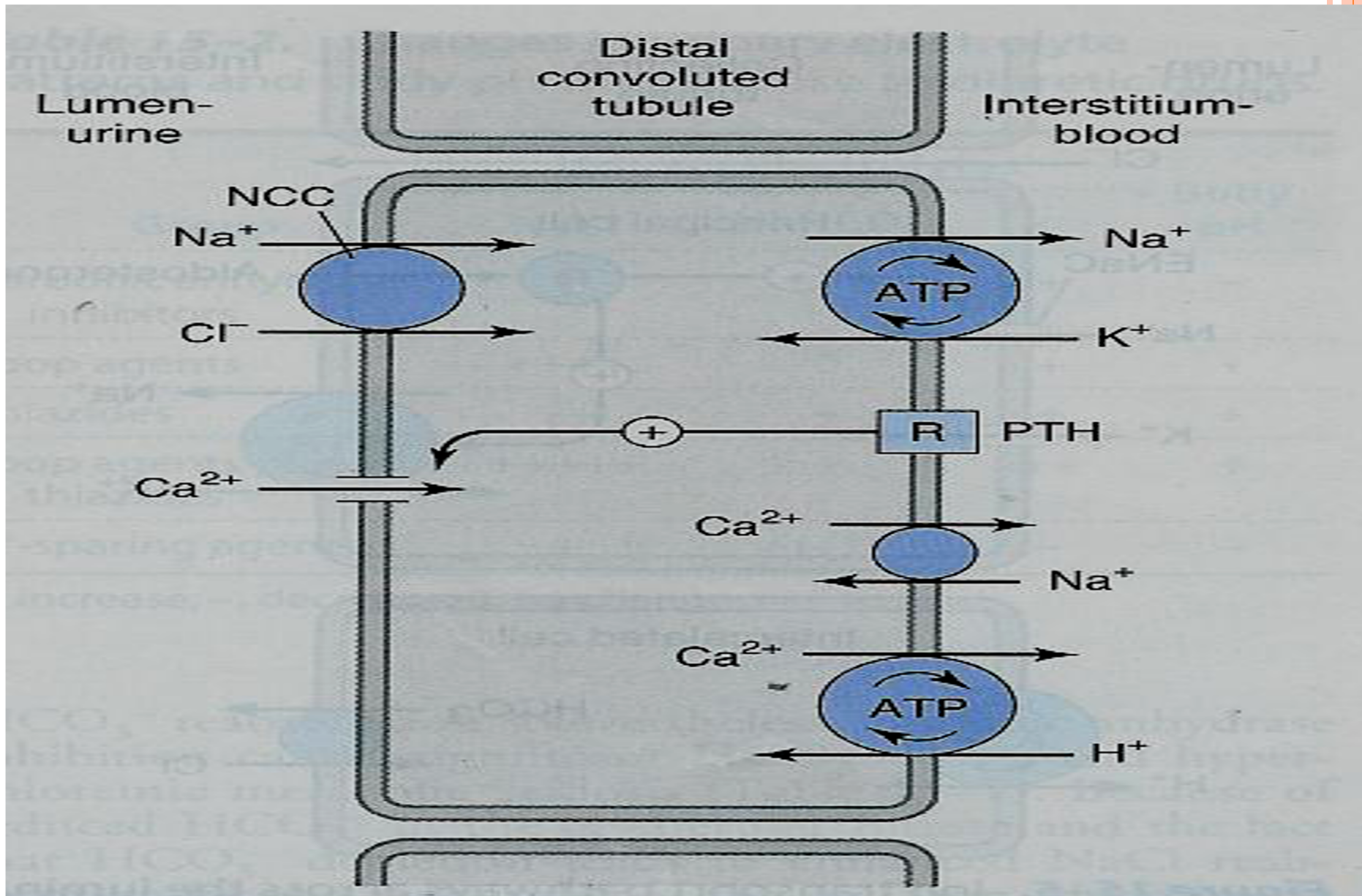


# Distal convoluted tubules





# 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)**

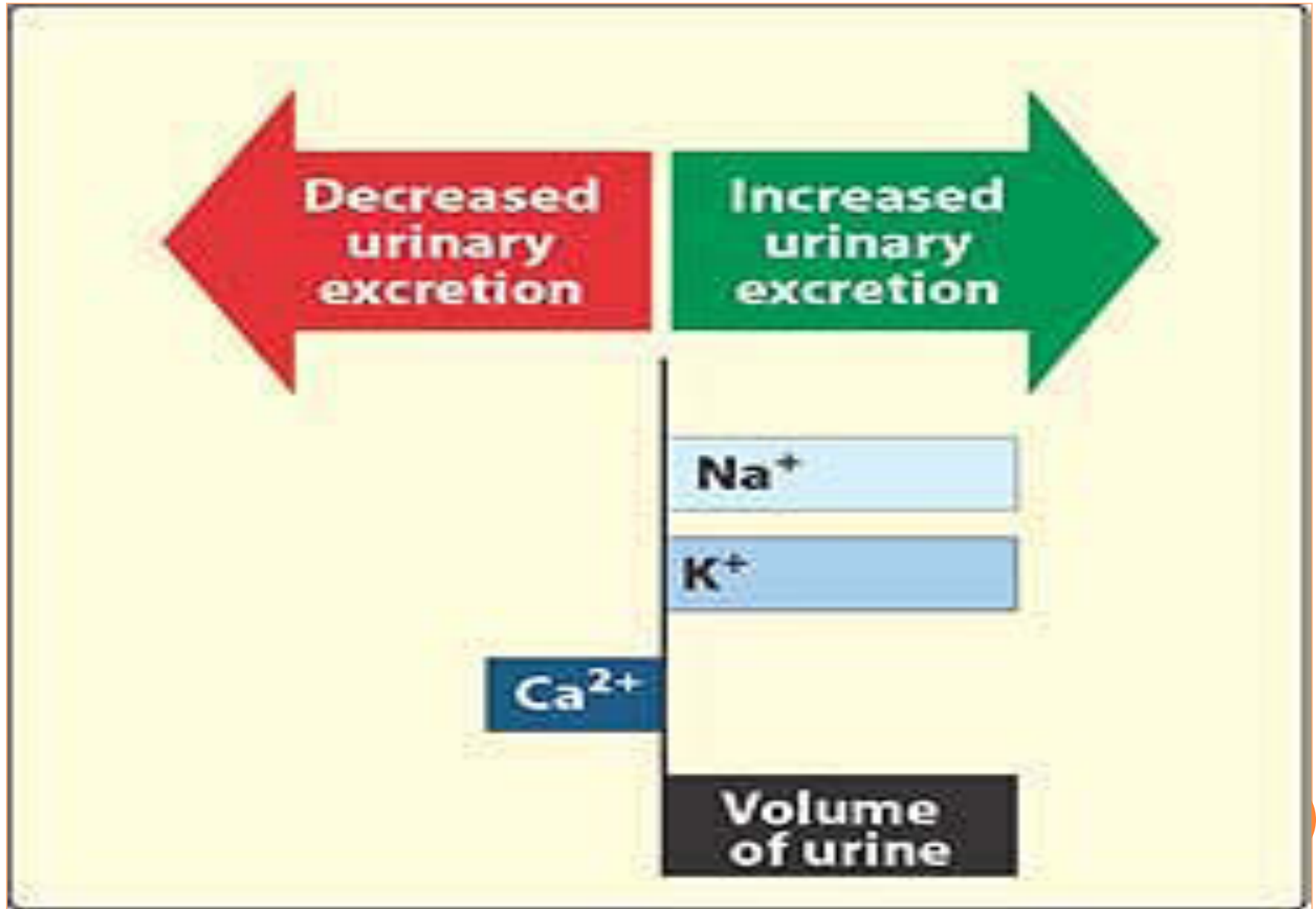
**↑ urinary magnesium excretion**

**↓ 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*).
- Treatment of osteoporosis

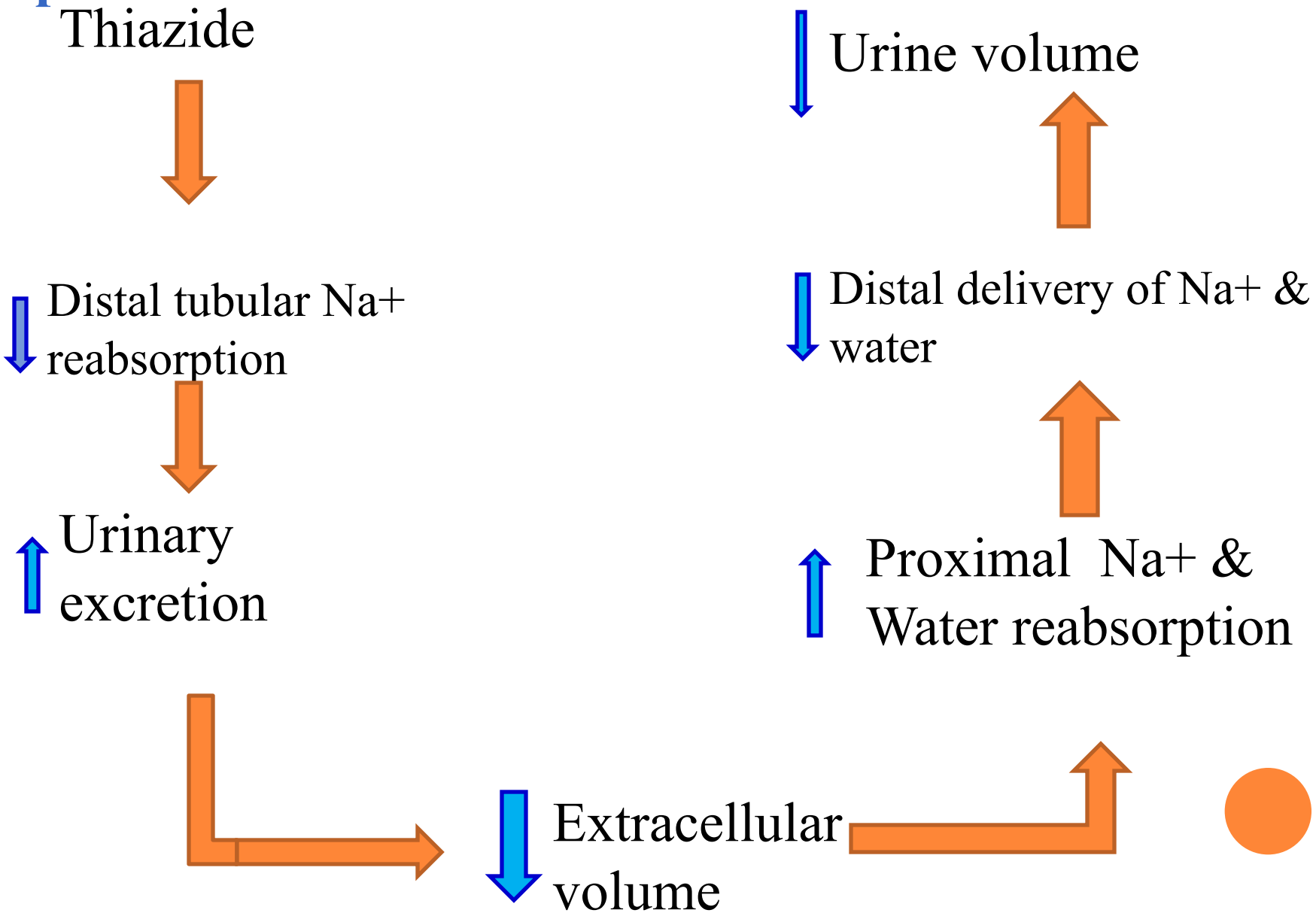


# Uses:

- 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**

**Hypocalcaemia**

**Hypomagnesaemia**

**Metabolic  
Alkalosis**

**Hyperuricemia**

**Hyperglycemia**



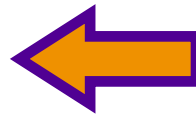
**Hyperlipidemia**



# THIAZIDE DIURETICS

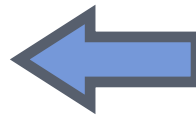
## DRUG- DRUG INTERACTIONS

**Uricosurics  
Sulphonylurea**



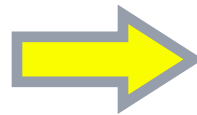
**Thiazides  
Diminish  
effect**

**Digitalis  
Diazoxide**



**Thiazides  
Increase effect**

**NSAIDs**



**Reduce thiazide  
efficacy**