

➤ Diuretic

- A diuretic is any substance that promotes diuresis, the increased production of urine.
- All diuretics increase the excretion of water from bodies.

Diuretic

vs

Antidiuretic

- Increase the excretion of water
- High ceiling/loop diuretic
- Reduces the excretion of water in urine.
- Vasopressin (antidiuretic hormone)

Medical uses

Diuretics are used to treat

- ❖ Heart failure
- ❖ Liver cirrhosis
- ❖ Hypertension
- ❖ Influenza
- ❖ Water poisoning
- ❖ Kidney diseases.

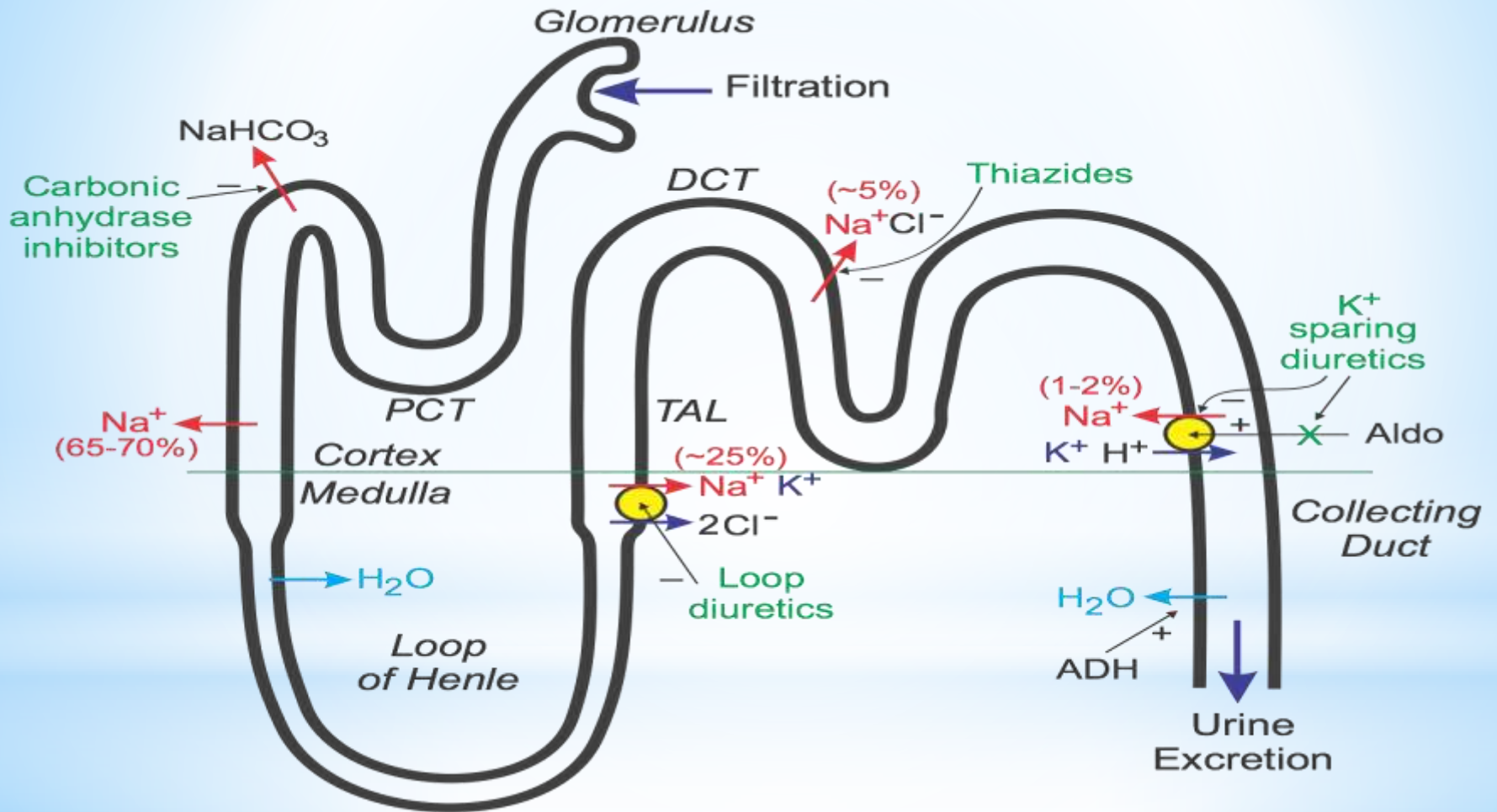
Some diuretics, such as acetazolamide, help to make the urine more alkaline and are helpful in increasing excretion of substances such as aspirin in cases of overdose or poisoning.

The antihypertensive actions of some diuretics (**thiazides and loop diuretics**) in particular) are independent of their diuretic effect.

□ Types

- High ceiling/loop diuretic
- Thiazides
- Potassium-sparing diuretics
- Carbonic anhydrase inhibitor
- Calcium-sparing diuretics
- Osmotic diuretics
- Low ceiling diuretics

❖ Mechanism of action



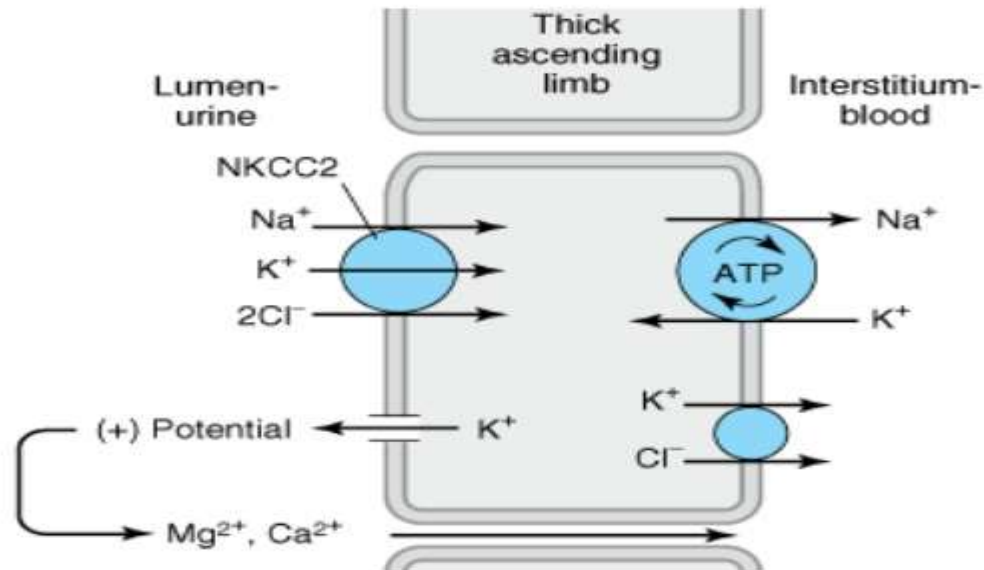
□ High ceiling/loop diuretic

High ceiling diuretics may cause a substantial diuresis - up to 20% of the filtered load of NaCl (salt) and water. This is large in comparison to normal **renal sodium reabsorption** which leaves only about 0.4% of filtered sodium in the urine.

Loop diuretics inhibit the body's ability to reabsorb sodium at the ascending loop in the nephron, which leads to an excretion of water in the urine, whereas water normally follows sodium back into the extracellular fluid. Examples of high ceiling loop diuretics :-

- **Ethacrynic acid**
- **Torsemide**
- **furosemide.**

Mechanism of Action of Loop Diuretic



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- Loop diuretics act on the Na^+ - K^+ - 2Cl^- symporter (NKCC2) in the thick ascending limb of the loop of Henle to inhibit sodium, chloride and potassium reabsorption
- This stimulates the release of renin, which through renin-angiotensin system, increases fluid retention in the body, increases the perfusion of glomerulus, thus increasing glomerular filtration rate (GFR).

■ Thiazides

Derived from benzothiadiazine.


Inhibits reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+ - Cl^- symporter.


Thiazide-like diuretics.


- **chlorthalidone**
- **metolazone.**
- Thiazide diuretics also increase **calcium reabsorption at the distal tubule**. By lowering the sodium concentration in the tubule epithelial cells, thiazides indirectly increase the activity of the basolateral $\text{Na}^+/\text{Ca}^{2+}$ antiporter. This facilitates the transport of Ca^{2+} from the epithelial cells into the renal interstitium. This movement of Ca^{2+} , in turn, decreases the intracellular Ca^{2+} concentration, which allows more Ca^{2+} to diffuse from the lumen of the tubules into epithelial cells via apical Ca^{2+} -selective channels (TRPV5). In other words, less Ca^{2+} in the cell increases the driving force for reabsorption from the lumen.


Mechanism of Action of Thiazide Diuretics


Key

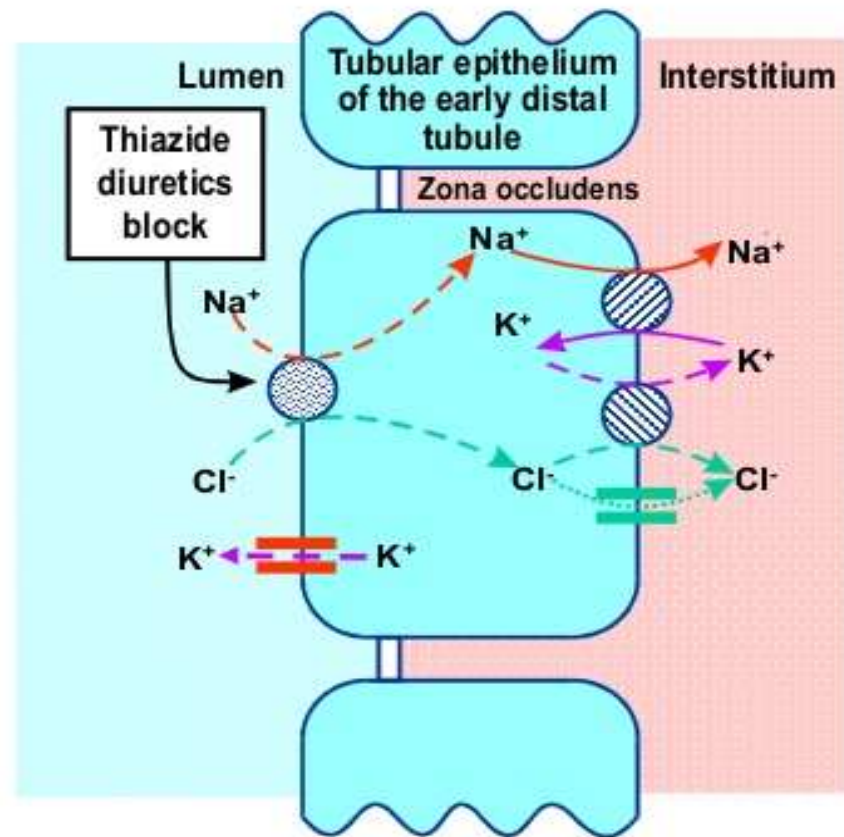
 Na^+/Cl^- co-transporter

 K^+/Cl^- co-transporter

 Na^+/K^+ ATPase

 Cl^- channel

 K^+ channel



■ Potassium-sparing diuretics

These are diuretics which do not promote the secretion of potassium into the urine; thus, potassium is retained and not lost as much as with other diuretics.

Aldosterone antagonists: spironolactone, which is a competitive antagonist of aldosterone.

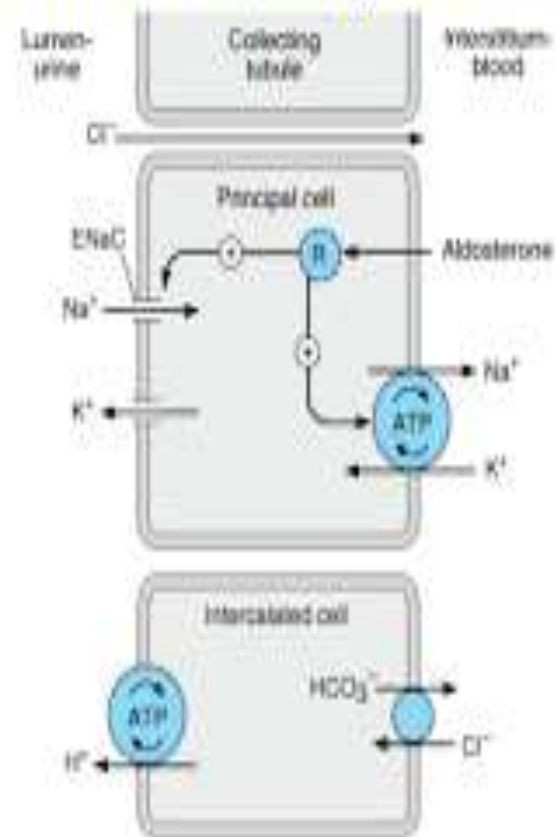
Aldosterone normally adds sodium channels in the principal cells of the collecting duct and late distal tubule of the nephron preventing sodium reabsorption.

Eplerenone

Potassium canrenoate.

Epithelial sodium channel blockers: amiloride and triamterene.

Potassium Sparing Diuretics



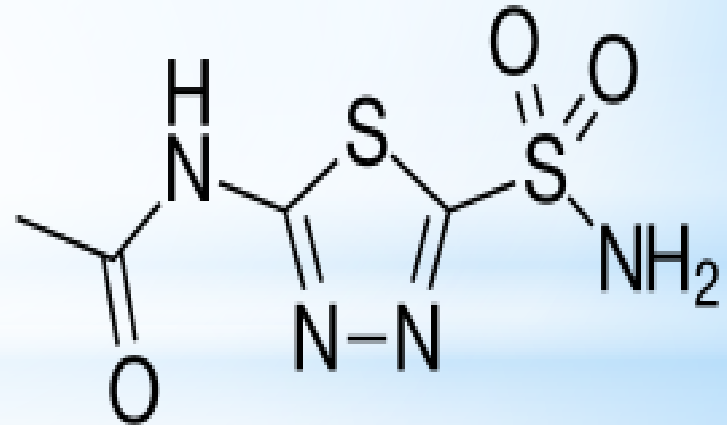
❖ Carbonic anhydrase inhibitor

Carbonic anhydrase inhibitors are a class of pharmaceuticals that suppress the activity of carbonic anhydrase.

Their clinical use has been established as anti glaucoma agents, diuretics, antiepileptics, in the management of mountain sickness, gastric and duodenal ulcers, idiopathic intracranial hypertension, neurological disorders, or osteoporosis.

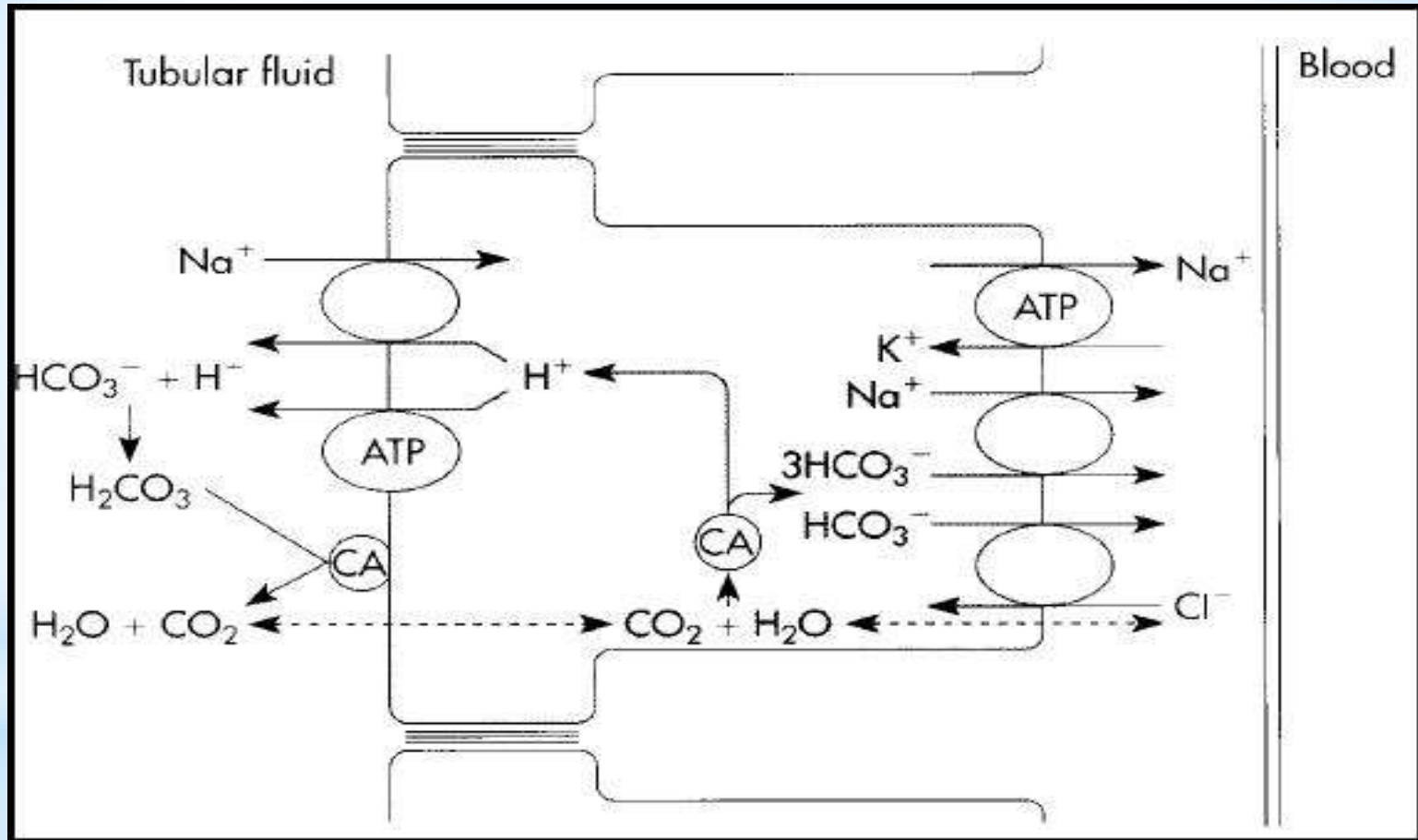
Drugs in this class

:- Acetazolamide
Methazolamide.



Acetazolamide

❖ Mechanism of action



❖ Calcium-sparing diuretics

Agents that result in a relatively low rate of excretion of calcium.

The thiazides and potassium-sparing diuretics are considered to be calcium-sparing diuretics.

The **thiazides** cause a **net decrease** in calcium lost in urine.


The **potassium-sparing** diuretics cause a **net increase** in calcium lost in urine, but the increase is *much smaller* than the increase associated with other diuretic classes.

By contrast, loop diuretics promote a significant increase in calcium excretion. This can increase risk of reduced bone density.

❖ Mechanism of action


Mechanism of Action of Thiazide Diuretics

Key

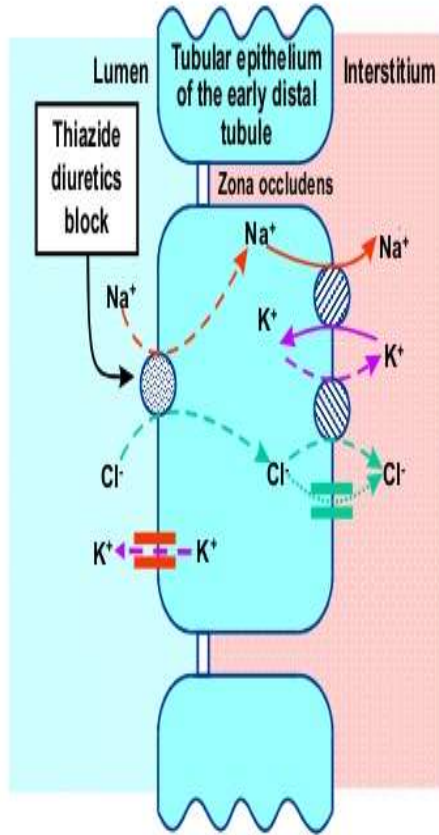
 Na^+/Cl^- co-transporter

 K^+/Cl^- co-transporter

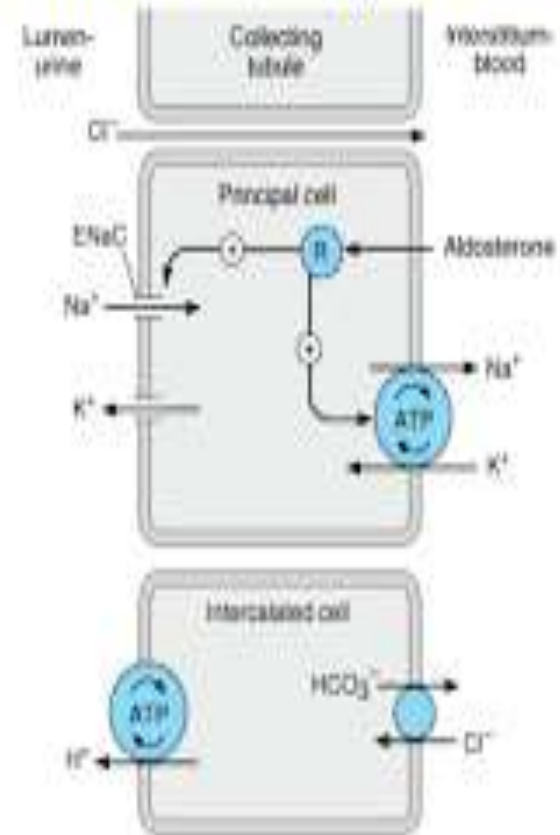
 Na^+/K^+ ATPase

 Cl^- channel

 K^+ channel



Potassium Sparing Diuretics



❖ Osmotic diuretics

Substances that **increase osmolarity** but have **limited tubular epithelial cell permeability**. They expand **extracellular fluid and plasma volume**, therefore increasing blood flow to the kidney.

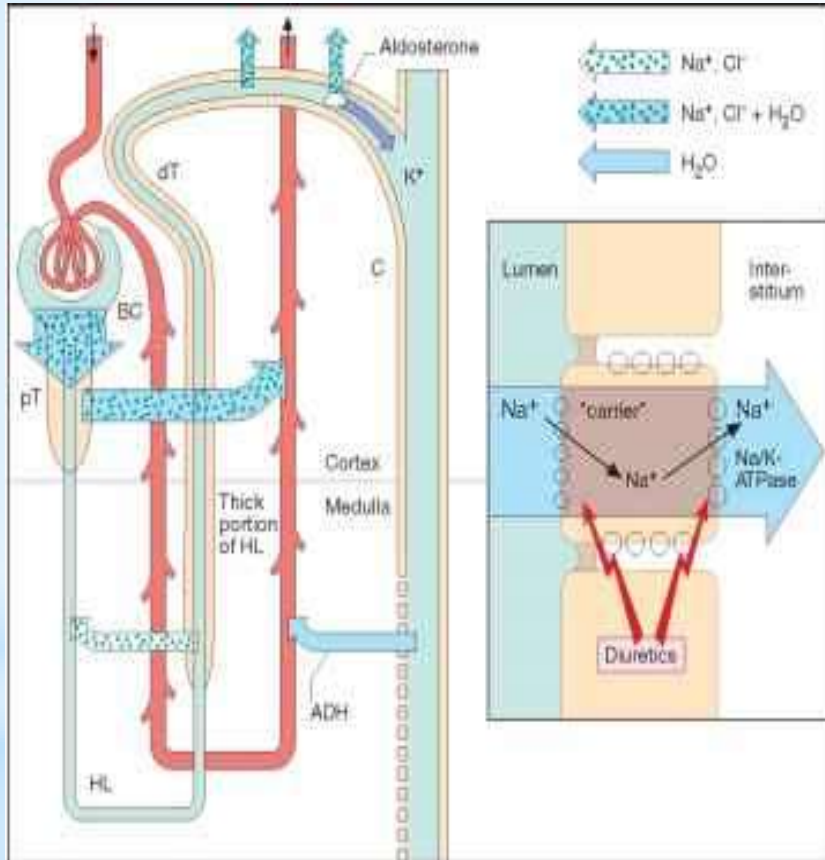
This reduces medullary osmolality and thus impairs the concentration of urine in the loop of Henle (which usually uses the high osmotic and solute gradient to transport solutes and water).

Glucose, like mannitol, is a sugar that can behave as an osmotic diuretic. Unlike mannitol, glucose is commonly found in the blood.

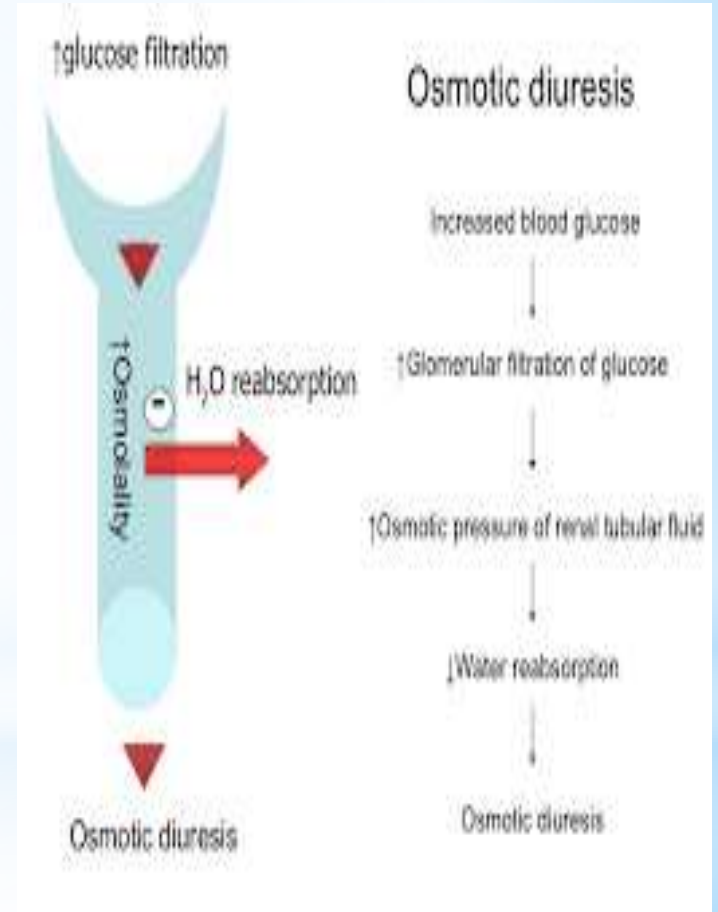
However, in certain conditions, such as diabetes mellitus, the concentration of glucose in the blood (hyperglycemia) exceeds the maximum reabsorption capacity of the kidney. When this happens, glucose remains in the filtrate, leading to the osmotic retention of water in the urine.

Glucosuria causes a loss of hypotonic water and Na^+ , leading to a hypertonic state with signs of volume depletion, such as dry mucosa, hypotension, tachycardia, and decreased turgor of the skin. Use of some drugs, especially stimulants, may also increase blood glucose and thus increase urination.

❖ Mechanism of action



A. Kidney: NaCl reabsorption in nephron and tubular cell



Adverse effect

Diuretic

Symptoms

hypercalcemia

•thiazides

- gout
- tissue calcification
- fatigue
- depression
- confusion
- anorexia
- nausea

Hyperkalemia

•amilorides
•triamterenes
•Spironolactone

- arrhythmia
- muscle cramps
- Paralysis

hyperuricemia

•thiazides
•loop diuretics
•acetazolamides

•Gout

hypokalemia

•loop diuretics
•Thiazides

- muscle weakness
- paralysis
- Arrhythmia

hyponatremia

•thiazides
•Furosemides

- CNS symptoms
 - Coma

Hypovolemia

•loop diuretics
•Thiazides

- lassitude
- thirst
- muscle cramps]
- Hypotension