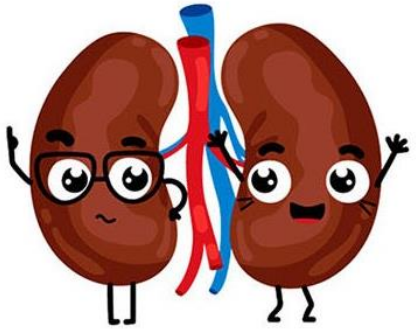
Mustansiriyah University
College of Pharmacy
Depart. of Pharmacology and Toxicology

Diuretics



Pharmacology 4th Stage

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Diuretics

- Diuretics are drugs that increase the volume of urine excreted by inhibiting renal ion transporters that decrease the reabsorption of Na+ at different sites in the nephron.
- As a result, Na+ and other ions enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium.
- Diuretics increase the volume of urine and often change its pH, as well as the ionic composition of the urine and blood.
- Diuretics are most commonly used for management of excessive fluid retention (edema), however, other uses are hypertension (thiazide), glaucoma (carbonic anhydrase inhibitors) and heart failure (aldosterone antagonists.

THIAZIDE DIURETICS

Chlorothiazide DIURIL
Chlorthalidone GENERIC ONLY
Hydrochlorothiazide (HCTZ) MICROZIDE
Indapamide GENERIC ONLY
Metolazone ZAROXOLYN

LOOP DIURETICS

Bumetanide BUMEX
Ethacrynic acid EDECRIN
Furosemide LASIX
Torsemide DEMADEX

POTASSIUM-SPARING DIURETICS

Amiloride MIDAMOR
Eplerenone INSPRA
Spironolactone ALDACTONE
Triamterene DYRENIUM

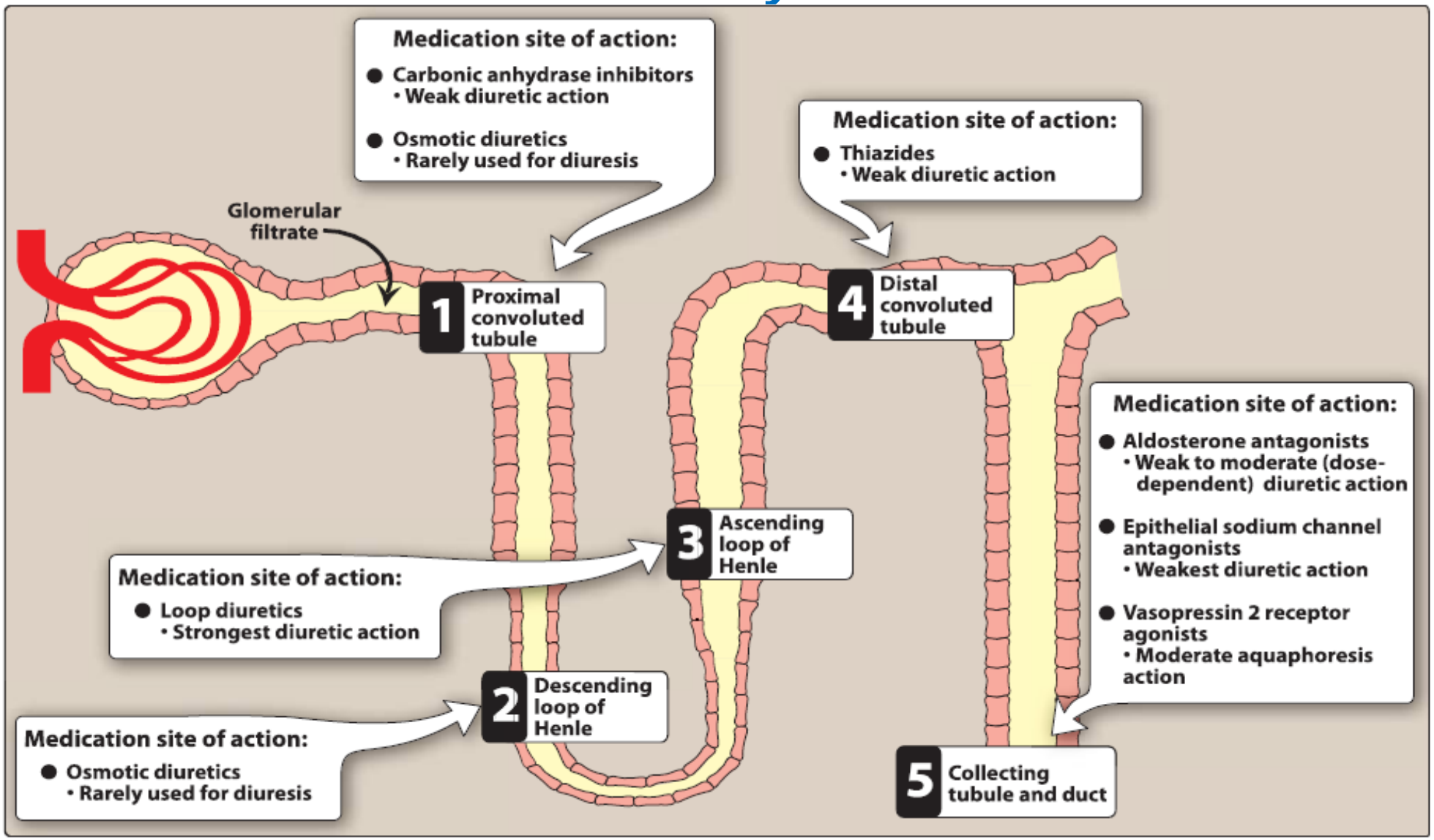
CARBONIC ANHYDRASE INHIBITORS

Acetazolamide DIAMOX

OSMOTIC DIURETICS

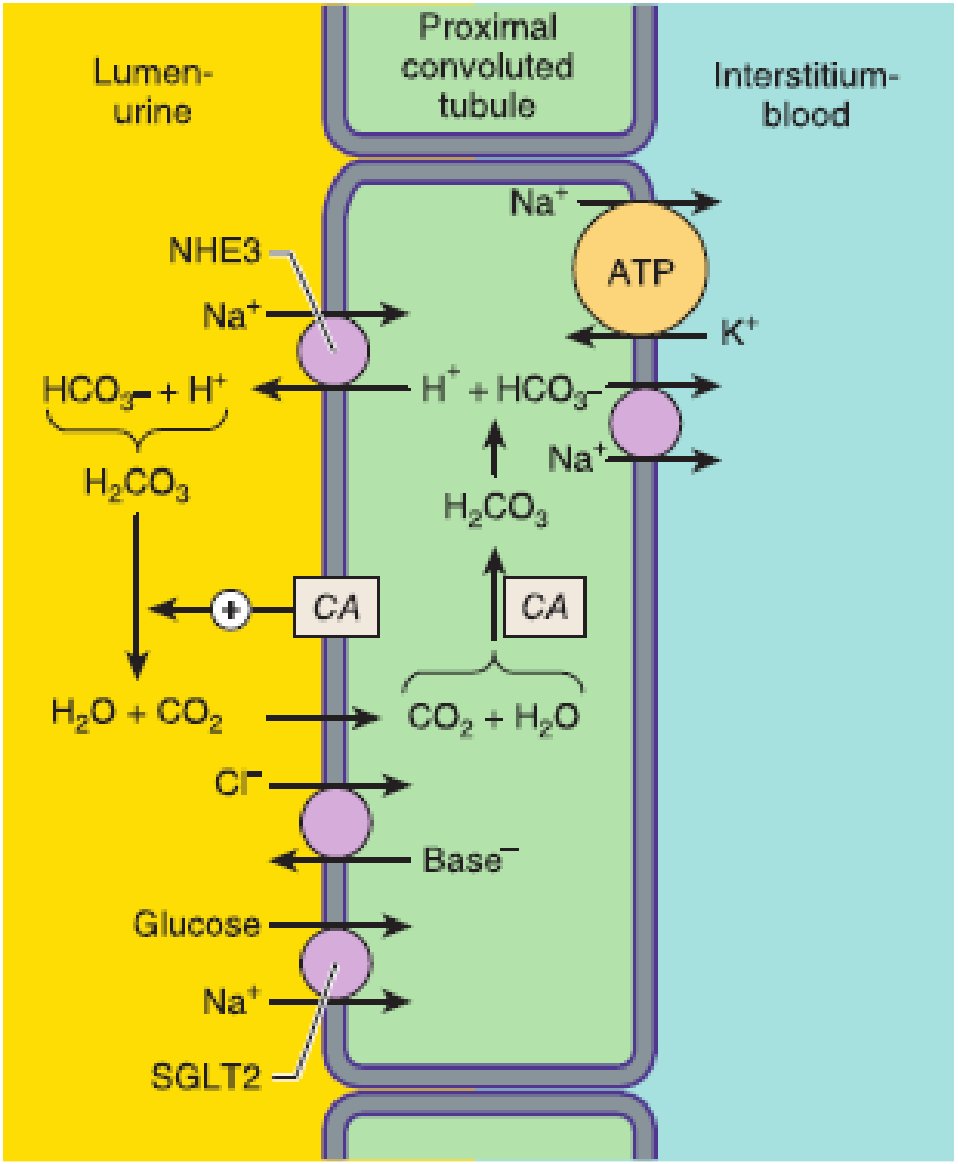
Mannitol OSMITROL

Normal regulation of fluid and electrolytes by the kidneys



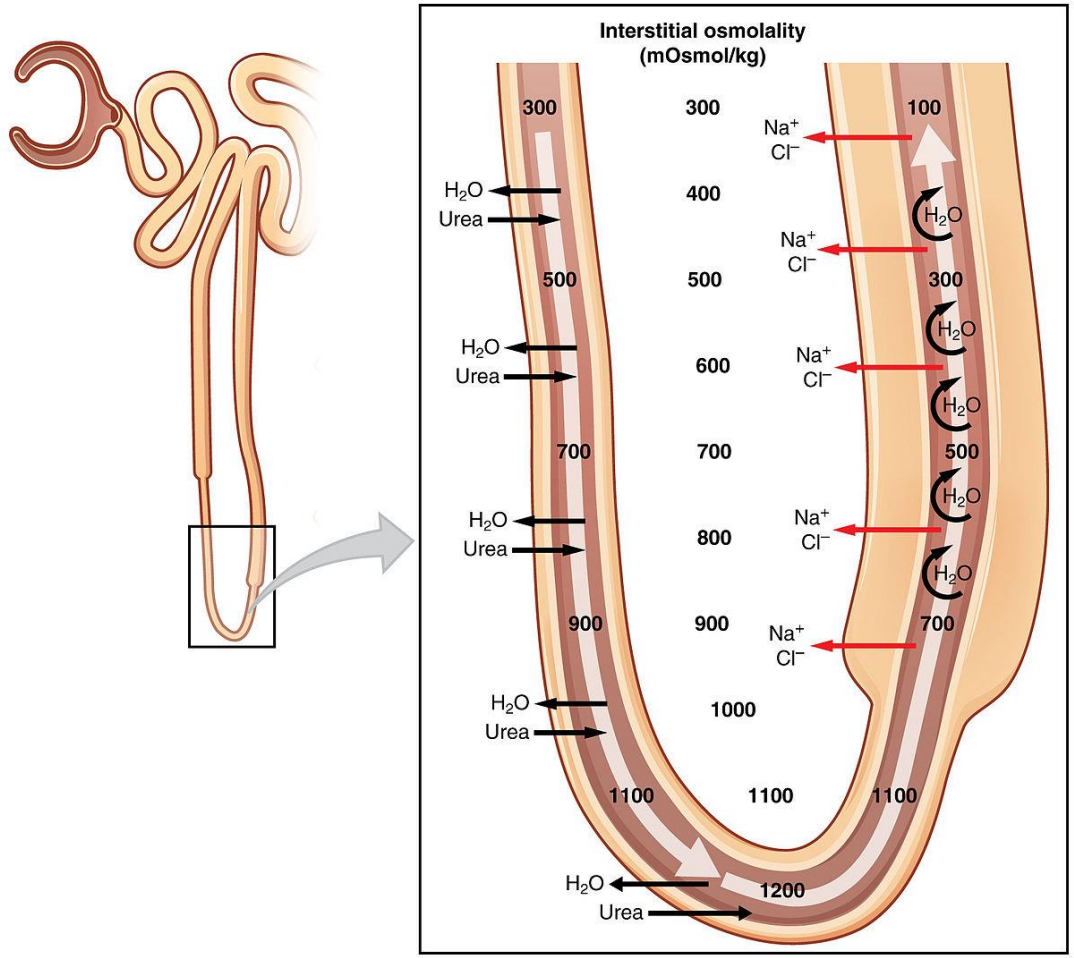
A. Proximal convoluted tubule

- Approximately 65% of the filtered Na+ (and water) is reabsorbed. Given the high water permeability, about 60% of water is reabsorbed from the lumen to the blood to maintain osmolar equality.
- Diuretics working in the proximal convoluted tubule display weak diuretic properties !!!. The presence of a high capacity Na+ and water reabsorption area (loop of Henle) distal to the proximal convoluted tubule allows reabsorption of Na+ and water kept in the lumen by diuretics acting in the proximal convoluted tubule, and limits effective diuresis.



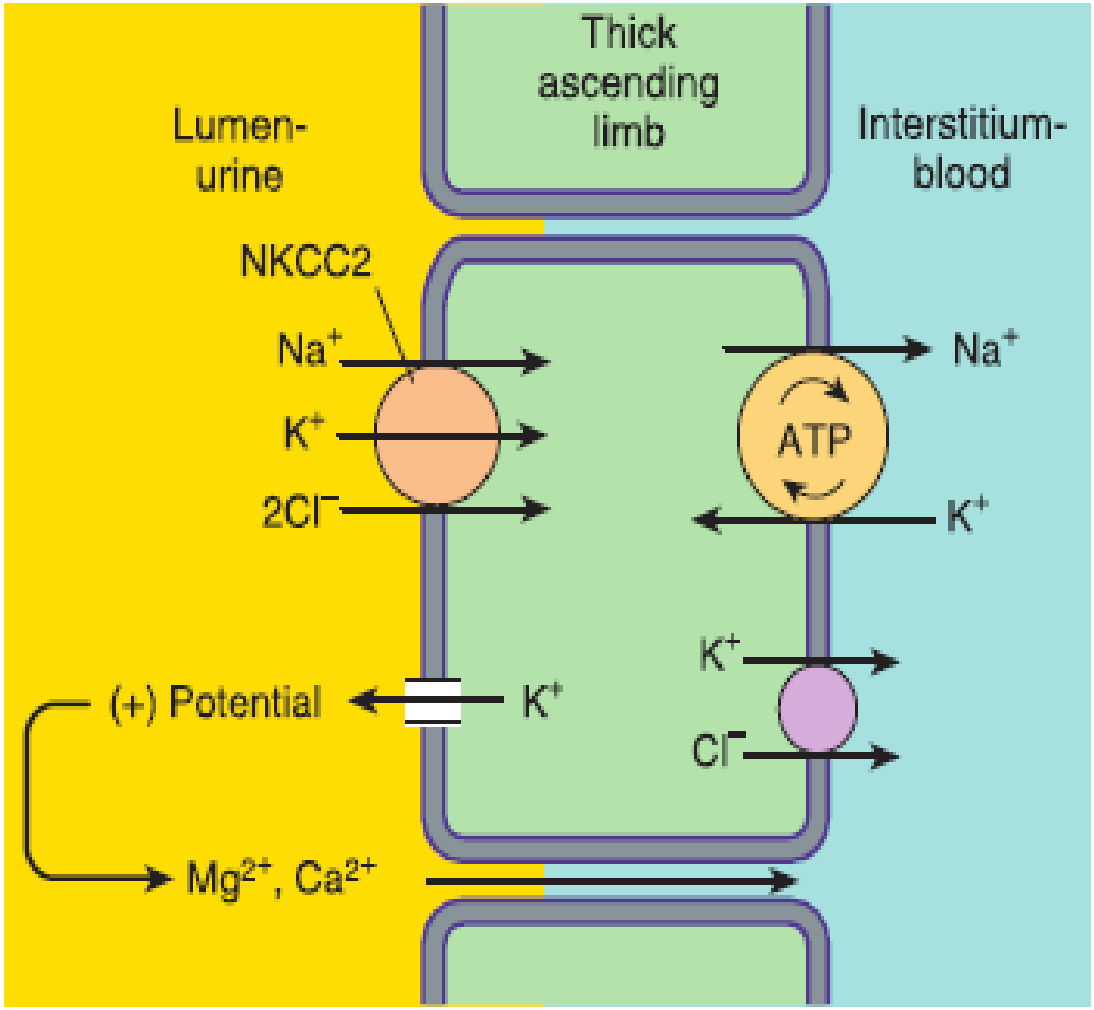
B- Descending loop of Henle

- The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney.
- The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption.
- This results in a tubular fluid with a three-fold increase in Na+ and Cl- concentration.
- Osmotic diuretics exert part of their action in this region.



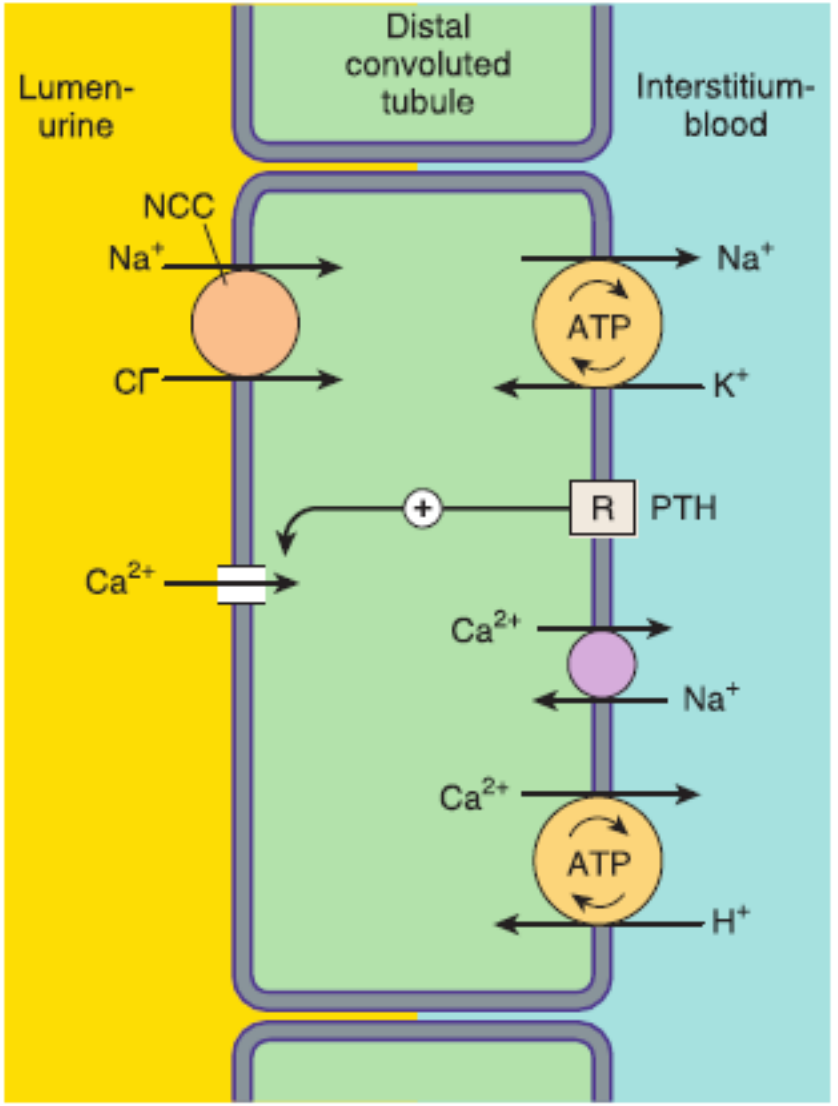
C- Ascending loop of Henle

- The cells of the ascending tubular epithelium are unique in being impermeable to water.
- Active reabsorption of Na+, K+, and Cl- is mediated by a Na+/K+/2CI- cotransporter.
- Both Mg2+ and Ca2+ are reabsorbed via the paracellular pathway. Thus, the ascending loop dilutes the tubular fluid and raises the osmolarity of the medullary interstitium.
- Approximately 25% to 30% of the filtered sodium chloride is absorbed here and have the greatest diuretic effect.



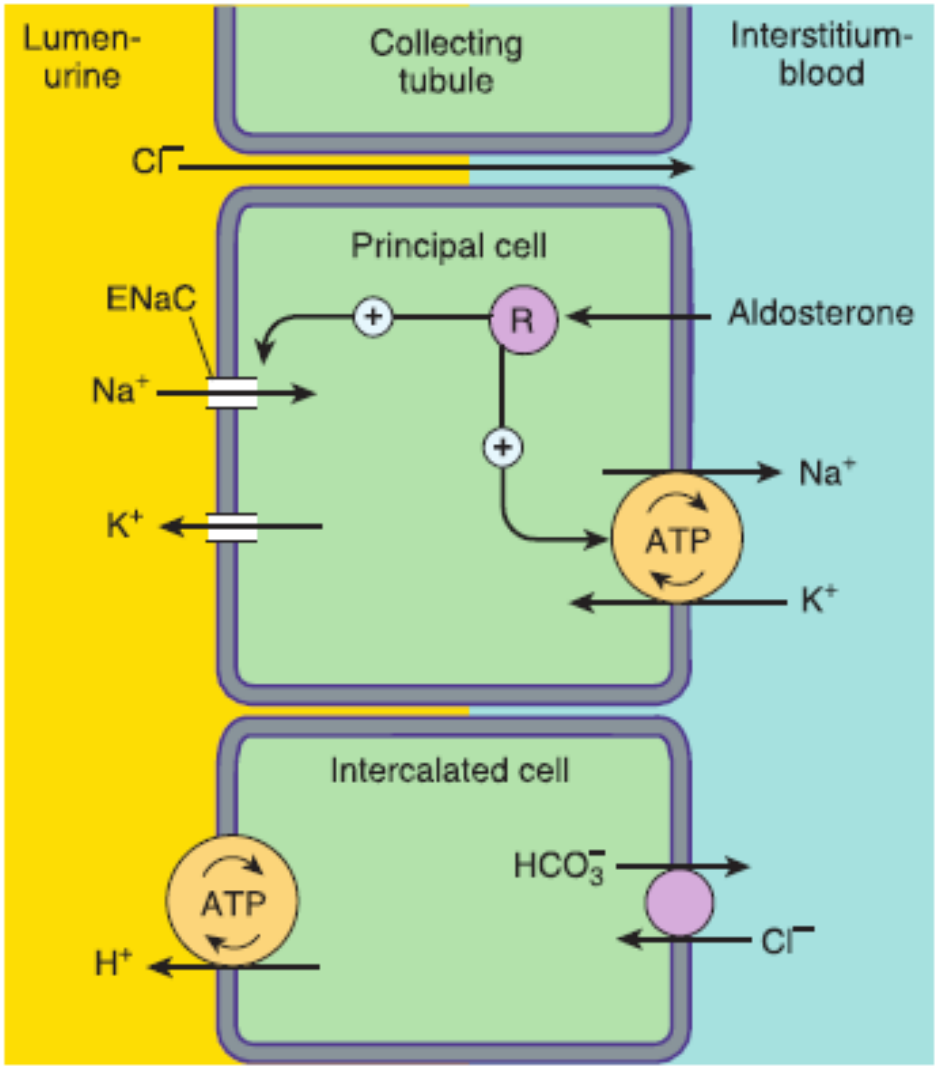
D. Distal convoluted tubule

- The cells of the distal convoluted tubule are also impermeable to water.
- About 5% to 10% of the filtered sodium chloride is reabsorbed via a Na+/Cl- transporter, the target of thiazide diuretics.
- Calcium reabsorption, under the regulation of parathyroid hormone, is mediated by an apical channel and then transported by a Na+/Ca2+ exchanger into the interstitial fluid



E. Collecting tubule and duct

- Approximately 1% to 2% of the filtered sodium enters the principal cells through epithelial sodium channels (ENaC) that are inhibited by amiloride and triamterene.
- Na+ reabsorption relies on a Na+/K+ ATPase pump to be transported into the blood.
- Aldosterone receptors in the principal cells influence Na+ reabsorption and K+ secretion. Aldosterone increases the synthesis of epithelial sodium channels and of the Na+/K+ ATPase pump.
- Antidiuretic hormone (ADH; vasopressin) binds to V2 receptors to promote the reabsorption of water through aquaporin channels.



Diuretic Drugs: A- Thiazides

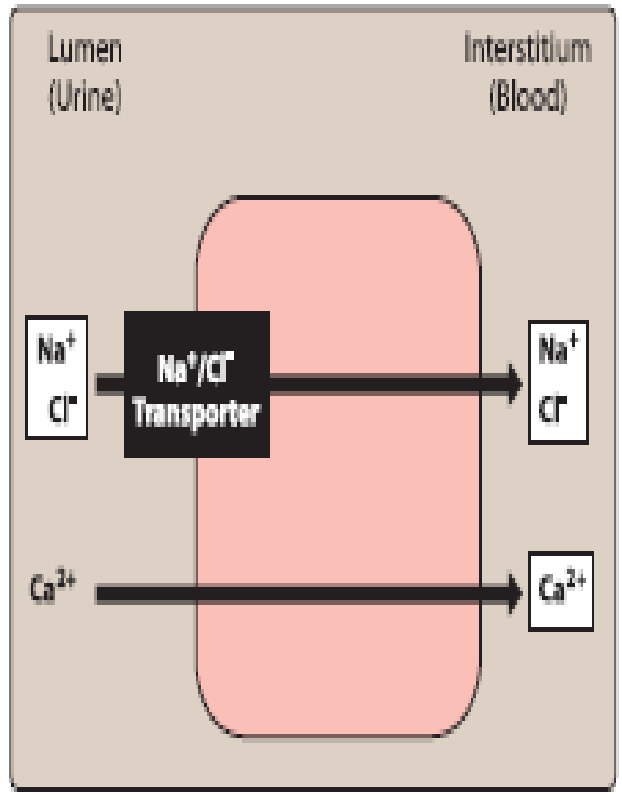
- The thiazides are the most widely used diuretics because of their antihypertensive effects, not only by diuretic effect but also reducing peripheral vascular resistance with long-term therapy.
- All thiazides affect the distal convoluted tubule and all have equal maximum diuretic effects, differing only in potency (low ceiling diuretics).
- Hydrochlorothiazide and chlorthalidone are now used more commonly due to better bioavailability and more potency, so the required dose is considerably lower than that of chlorothiazide.
- **Mechanism of action**

The thiazide and thiazide-like diuretics act mainly in the distal convoluted tubule to decrease the reabsorption of Na+ by inhibition of a Na+/Cl- cotransporter. As a result, these drugs increase the concentration of Na+ and Cl· in the tubular fluid. Thiazides must be excreted into the tubular lumen at the proximal convoluted tubule to be effective. Therefore, decreasing renal function reduces the diuretic effects.

A- Thiazides cont..

- **Action**:

1. **Increased excretion of Na+ and Cl-**: excretion of very hyperosmolar (concentrated) urine.
2. **Decreased urinary calcium excretion**.
3. **Reduced peripheral vascular resistance**: result by relaxation of arteriolar smooth muscle. This effect appear after initial temporary reduction in blood pressure results from a decrease in blood volume and then cardiac output.



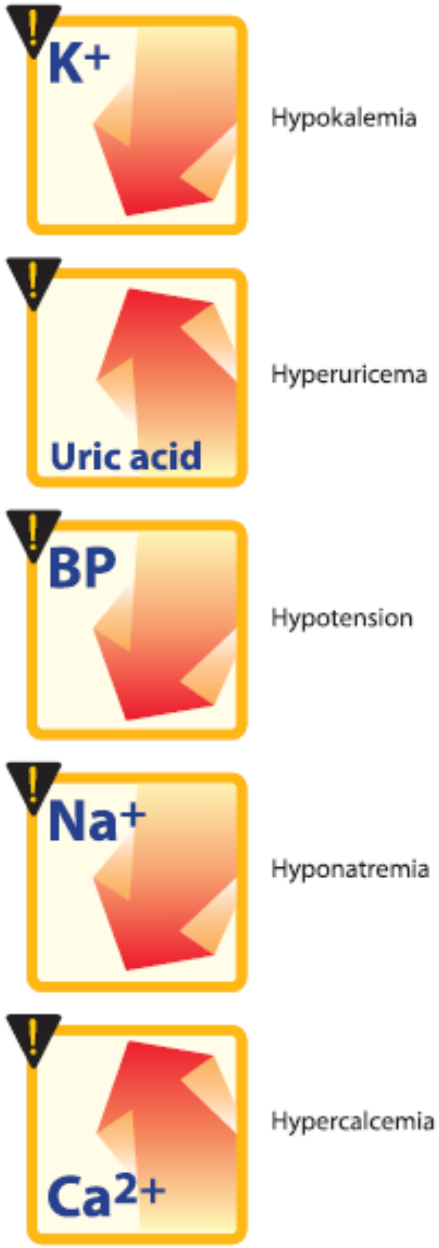
- **Therapeutic uses**

a. **Hypertension**
b. **Heart failure**
c. **Hypercalciuria**
d. **Diabetes insipidus** (disease of increase urine output) !!! : How ???

A- Thiazides cont..

- **Adverse effects:**

1. **Hypokalemia**
2. **Hypomagnesemia**
3. **Hyponatremia**
4. **Hyperuricemia**: by decreasing the amount of acid excreted through competition in the organic acid secretory system
5. **Hypovolemia**: hypotension or light-headedness.
6. **Hypercalcemia**
7. **Hyperglycemia** !!! How???



B- Loop Diuretics

- Bumetanide, furosemide, torsemide, and ethacrynic acid have their major diuretic action on the ascending limb of the loop of Henle. These drugs have the highest efficacy in mobilizing Na+ and Cl- from the body, producing copious amounts of urine.
- Similar to thiazides, loop diuretics do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials such as sulfamethoxazole because of structural differences in their sulfonamide derivative.
- **Mechanism of action**

Loop diuretics inhibit the cotransport of Na+/K+/2Cl- in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions into the renal medulla is decreased. By lowering the osmotic pressure in the medulla, less water is reabsorbed from water permeable segments, like the descending loop of Henle, causing diuresis.

Loop diuretics must be excreted into the tubular lumen at the proximal convoluted tubule to be effective (given with caution with NSAID) Why?

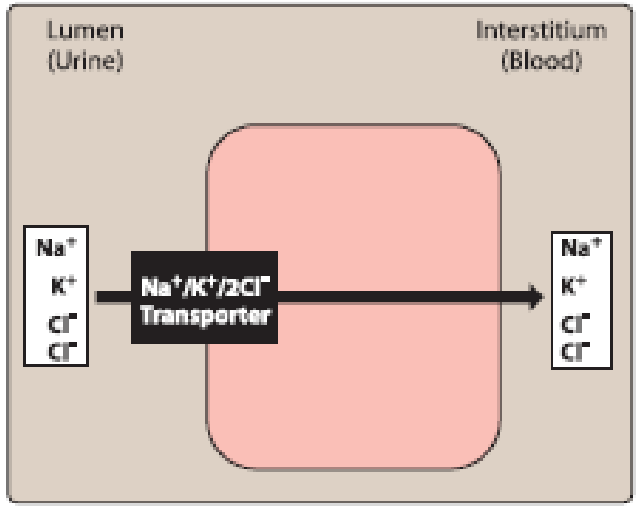
B- Loop Diuretics cont..

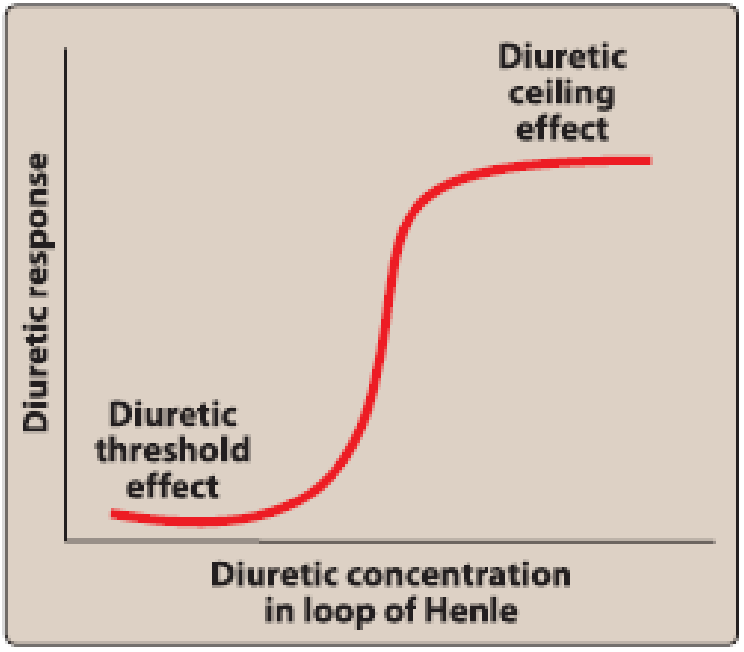
- **Actions**:

a. **Diuresis**: Loop diuretics cause diuresis, even in patients with poor renal function or lack of response to other diuretics. Loop diuretics display a sigmoidal ("S"-shaped) dose-response curve. A dose must be selected to cross the response threshold and avoid the ceiling effect.

b. **Increased urinary calcium excretion:** hypocalcemia does not result, because Ca2+ is reabsorbed in the distal convoluted tubule.

c. **Venodilation**: cause acute venodilation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.





B- Loop Diuretics cont..

- **Therapeutic uses**:

a. **Edema**: Its drug of choice in acute pulmonary edema and also useful in acute/chronic peripheral edema caused from heart failure or renal impairment. Can be used in emergency situations due to rapid onset of action.

b. **Hypercalcemia**:

c. **Hyperkalemia**:

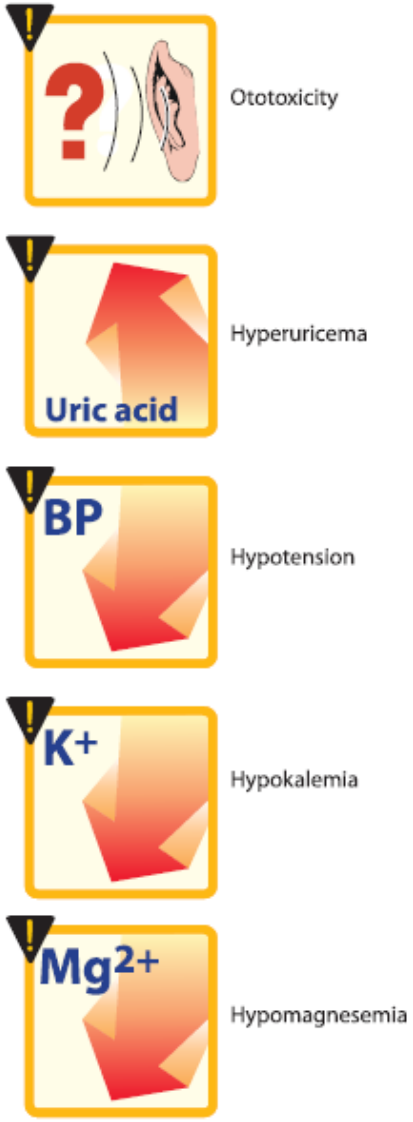
- **Pharmacokinetics**

- Loop diuretics are administered orally or parenterally. Furosemide has unpredictable bioavailability of 10% to 90% after oral administration. Bumetanide and torsemide have reliable bioavailability of 80% to 100%. The duration of action is approximately 6 hours for furosemide and bumetanide, and moderately longer for torsemide, allowing patients to predict the window of diuresis.

B- Loop Diuretics cont..

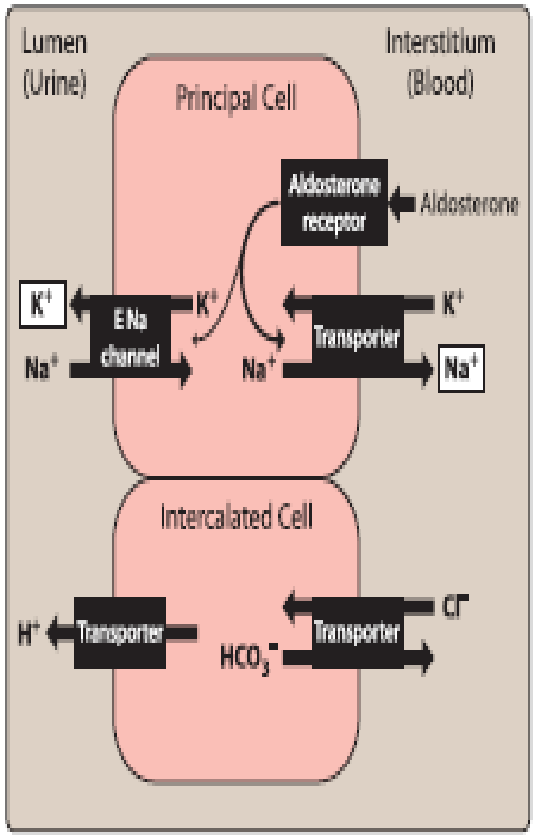
- **Adverse effects:**

1. **Acute hypovolemia**: possibility of hypotension, shock, and cardiac arrhythmias.
2. **Hypokalemia**: The heavy load of Na+ presented to the collecting tubule results in increased exchange of tubular Na+ for K+, leading to hypokalemia. The loss of K+ from cells in exchange for H+ leads to hypokalemic alkalosis.
3. **Hypomagnesemia**
4. **Ototoxicity**: Reversible or permanent hearing loss may occur. Ethacrynic acid is the most likely to cause ototoxicity.
5. **Hyperuricemia**: Loop diuretics compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, may cause or exacerbate gouty attacks.



C- Potassium- Sparing Diuretics

- Potassium-sparing diuretics act in the collecting tubule to inhibit Na+ reabsorption and K+ excretion. Within this class, there are drugs with two distinct mechanisms of action with different indications for use: aldosterone antagonists and epithelial sodium channel blockers.
- **A- Aldosterone antagonist:**
- Mechanism of Action:
- Spironolactone and eplerenone are synthetic steroids that antagonize aldosterone receptors. This prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a lack of intracellular proteins that stimulate the Na+/K+ exchange sites of the collecting tubule. Thus, aldosterone antagonists prevent Na+ reabsorption and, therefore, K+ and H+ secretion. Eplerenone is more selective for aldosterone receptors and causes less endocrine effects (gynecomastia) than spironolactone,



C- Potassium- Sparing Diuretics Cont..

- **Therapeutic uses**

1- **Edema**: used in high doses for edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome

2- **Hypokalemia**: given in conjunction with thiazide or loop diuretics to prevent K+ excretion that occurs with those diuretics.

3- **Heart failure**: lower doses to prevent myocardial remodeling mediated by aldosterone.

4- **Resistant hypertension**: This effect can be seen in those with or without elevated aldosterone levels.

5- **Polycystic ovary syndrome**: It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.

- **Pharmacokinetics**:
- Both spironolactone and eplerenone are well absorbed after oral administration and extensively metabolized and converted to several active metabolites.

C- Potassium- Sparing Diuretics Cont..

- **Adverse effects**

1. **Hyperkalemia**: dose-dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.
2. **Gynecomastia**: Spironolactone, but not eplerenone, may induce gynecomastia in approximately 10% of male patients and menstrual irregularities in female patients.

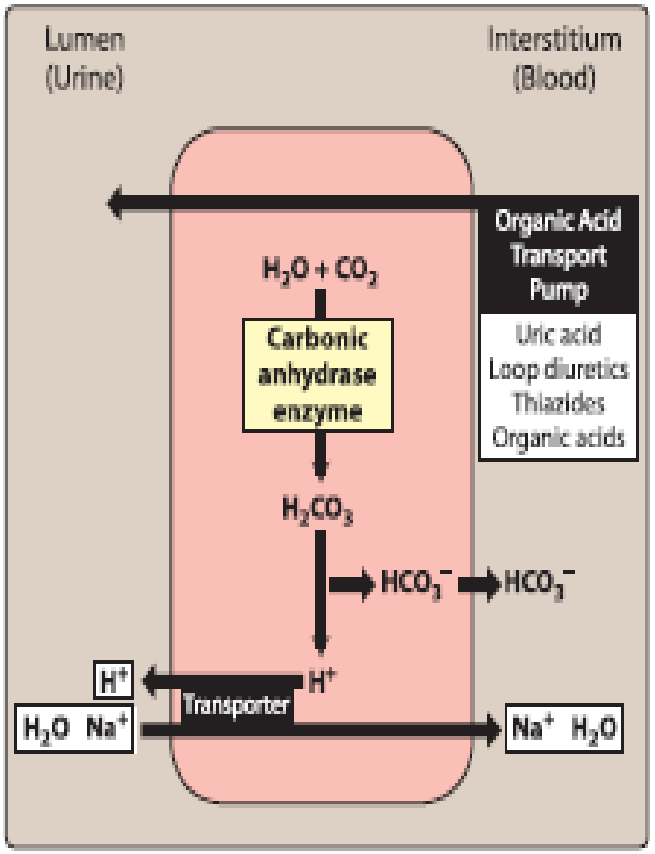
B. Triamterene and amiloride

Triamterene and amiloride block epithelial sodium channels (ENaC), resulting in a decrease in Na+/K+ exchange. Although they have a K+-sparing diuretic action similar to that of the aldosterone antagonists, their ability does not depend on the presence of aldosterone. They are weak diuretics and commonly used in combination with other diuretics, almost solely for their potassium- sparing properties.

D- Carbonic Anhydrase Inhibitors

- Acetazolamide and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than the thiazide or loop diuretics.
- **Mechanism of action:**

Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium. Carbonic anhydrase catalyzes the reaction of C02 and H20, leading to H2C03 , which spontaneously ionizes to H+ and HC03- (bicarbonate). The decreased ability to exchange Na+ for H+ in the presence of acetazolamide results in a mild diuresis. Additionally, HC03- is retained in the lumen, with marked elevation in urinary pH. The loss of HC03- causes a hyperchloremic metabolic acidosis.



D- Carbonic Anhydrase Inhibitors Cont..

- **Therapeutic uses**

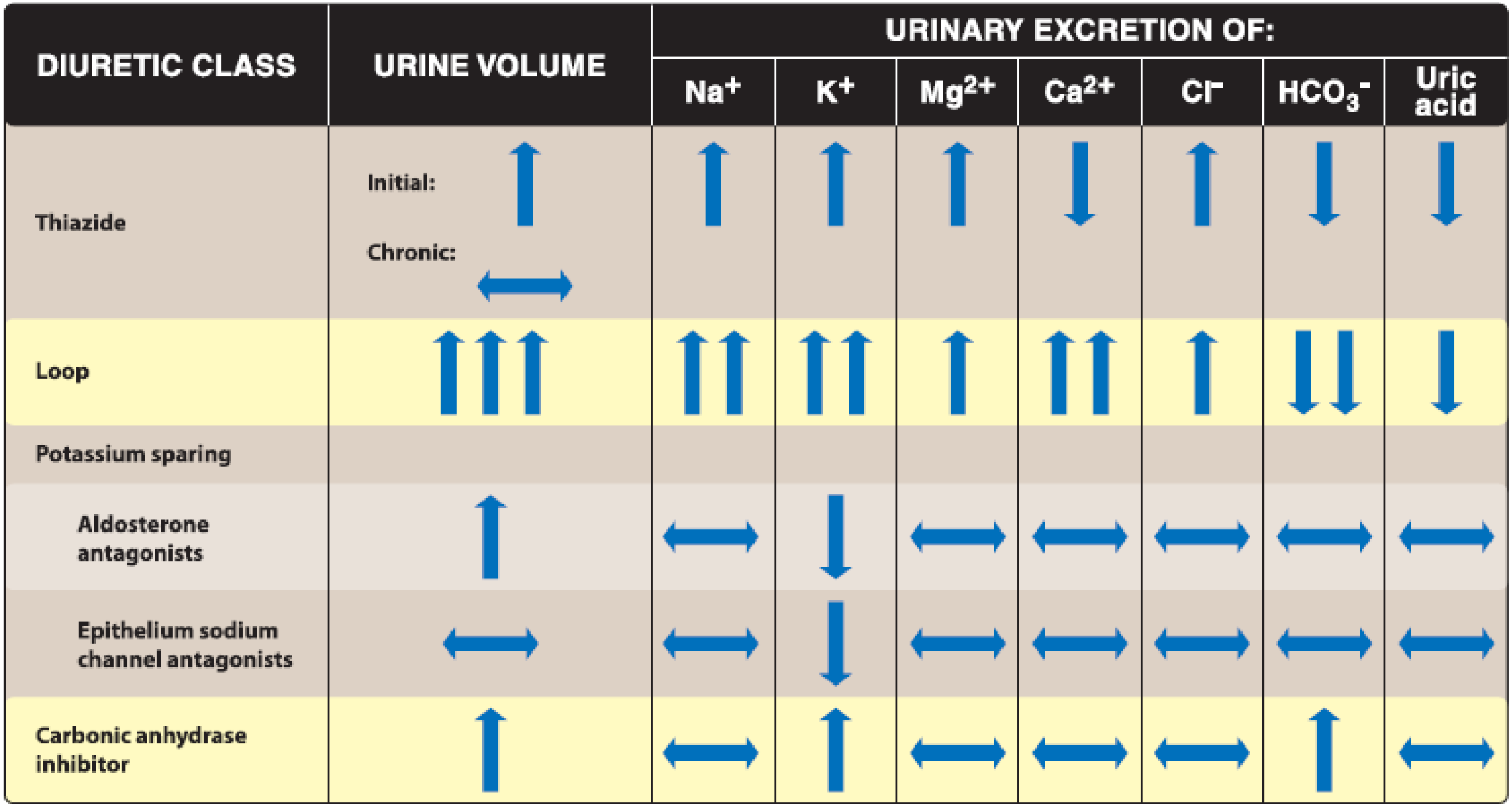
a. **Glaucoma**: Oral acetazolamide decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma, probably by blocking carbonic anhydrase in the ciliary body of the eye. Topical Dorzolamide and Brinzolamide can have the advantage of not causing systemic effects.

b. **Altitude sickness**: Acetazolamide can be used in the prophylaxis of symptoms of altitude sickness by creating a metabolic acidosis in order to mitigate a developing respiratory alkalosis from a decreased inhaled oxygen concentration.

- **Pharmacokinetics**: oral or IV , 90% protein binding , and renally excreted
- **Adverse effects**: Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

E- Osmotic Diuretics

- **Mechanism of action:** Mannitol undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This prevents further water reabsorption at the descending loop of Henle and proximal convoluted tubule, resulting in osmotic diuresis with little additional Na+ excretion (aquaresis).
- **Therapeutic uses:** used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure.
- **Pharmacokinetics**: Mannitol is not absorbed when given orally and should be given intravenously.
- **Adverse effects :** dehydration, extracellular water expansion from the osmotic effects in the systemic circulation and temporary hyponatremia.


DIURETIC CLASS
URINE VOLUME
URINARY EXCRETION OF:
Na+
K+
Mg2+
Ca2+
Cl-
HCO3-
Uric acid
Thiazide
Initial:
Chronic:
Loop
Potassium sparing
Aldosterone antagonists
Epithelium sodium channel antagonists
Carbonic anhydrase inhibitor