Diuretics agents I

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Objectives

1. List major types of diuretics and relate them to their sites of action.
2. List the major applications, toxicities, and the efficacy of thiazides, loop diuretics and potassium-sparing diuretics.
3. Describe drugs that reduce potassium loss during diuresis

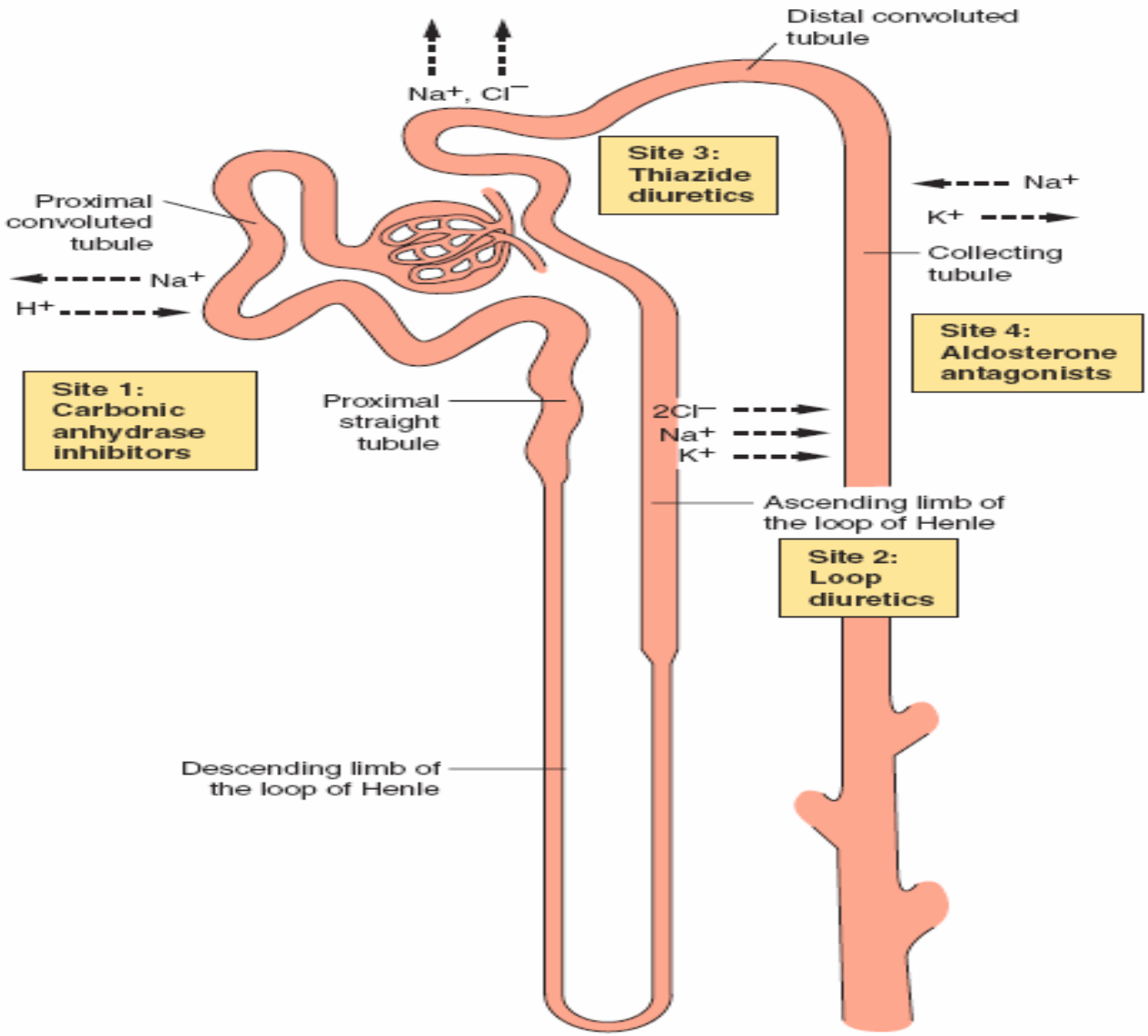
Introduction

- Diuretics increase urine production by acting on the kidney
- **Most** agents affect water balance indirectly by altering electrolyte reabsorption or secretion.
- Osmotic agents affect water balance directly.
- **Natriuretic diuretics produce diuresis, associated with increased sodium (Na)** excretion, which results in a concomitant loss of water and a reduction in extracellular volume.

Introduction

- **Therapeutic uses.**

1. ***used for the management of edema,***
2. hypertension,
3. **congestive heart failure (CHF),**
4. **abnormalities in body fluid distribution.**

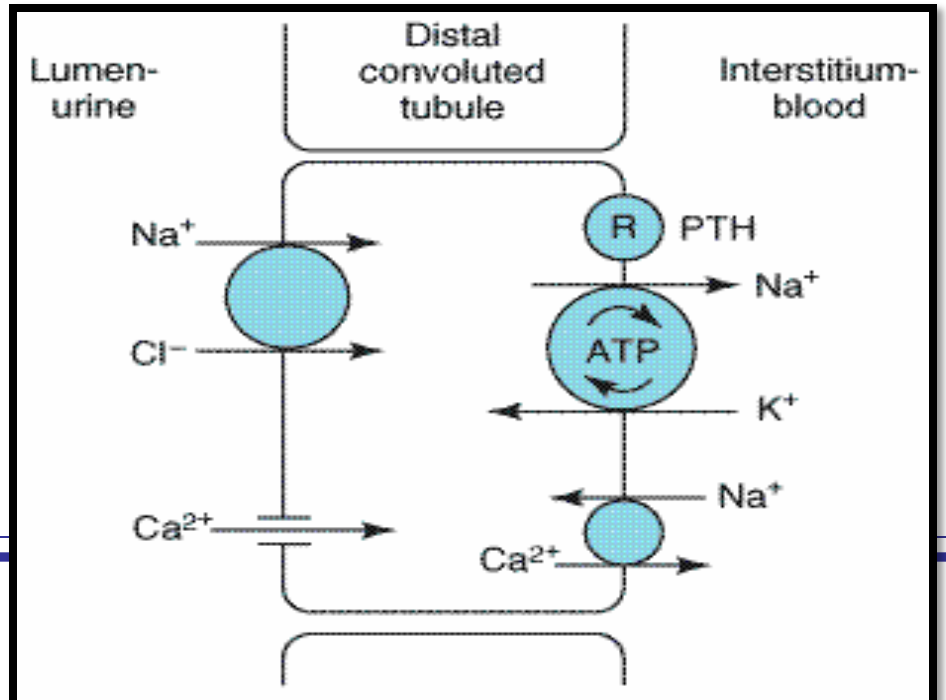

Distal convoluted tubule
Na^+, Cl^-
Site 3: Thiazide diuretics
Na^+
K^+
Collecting tubule
Proximal convoluted tubule
Na^+
H^+
Site 4: Aldosterone antagonists
Site 1: Carbonic anhydrase inhibitors
Proximal straight tubule
$2Cl^-$
Na^+
K^+
Ascending limb of the loop of Henle
Site 2: Loop diuretics
Descending limb of the loop of Henle

Diuretics:

1. Thiazides: Chlorothiazide, Hydrochlorothiazide, chlorthalidone
2. Loop diuretics: Furosemide, Bumetanide
3. K+ sparing: Spironolactone, Triamterene And Amiloride
4. Carbonic anhydrase inhibitors: Acetazolamide
5. Osmotic Diuretics (mannitol)

Thiazide diuretics

- Only about 10% of the filtered NaCl is reabsorbed in the distal convoluted tubule.
- The mechanism of NaCl transport in the distal convoluted tubule is electrically neutral Na+ and Cl- cotransport
- This NaCl transporter is blocked by diuretics of the thiazide class.



Thiazide diuretics

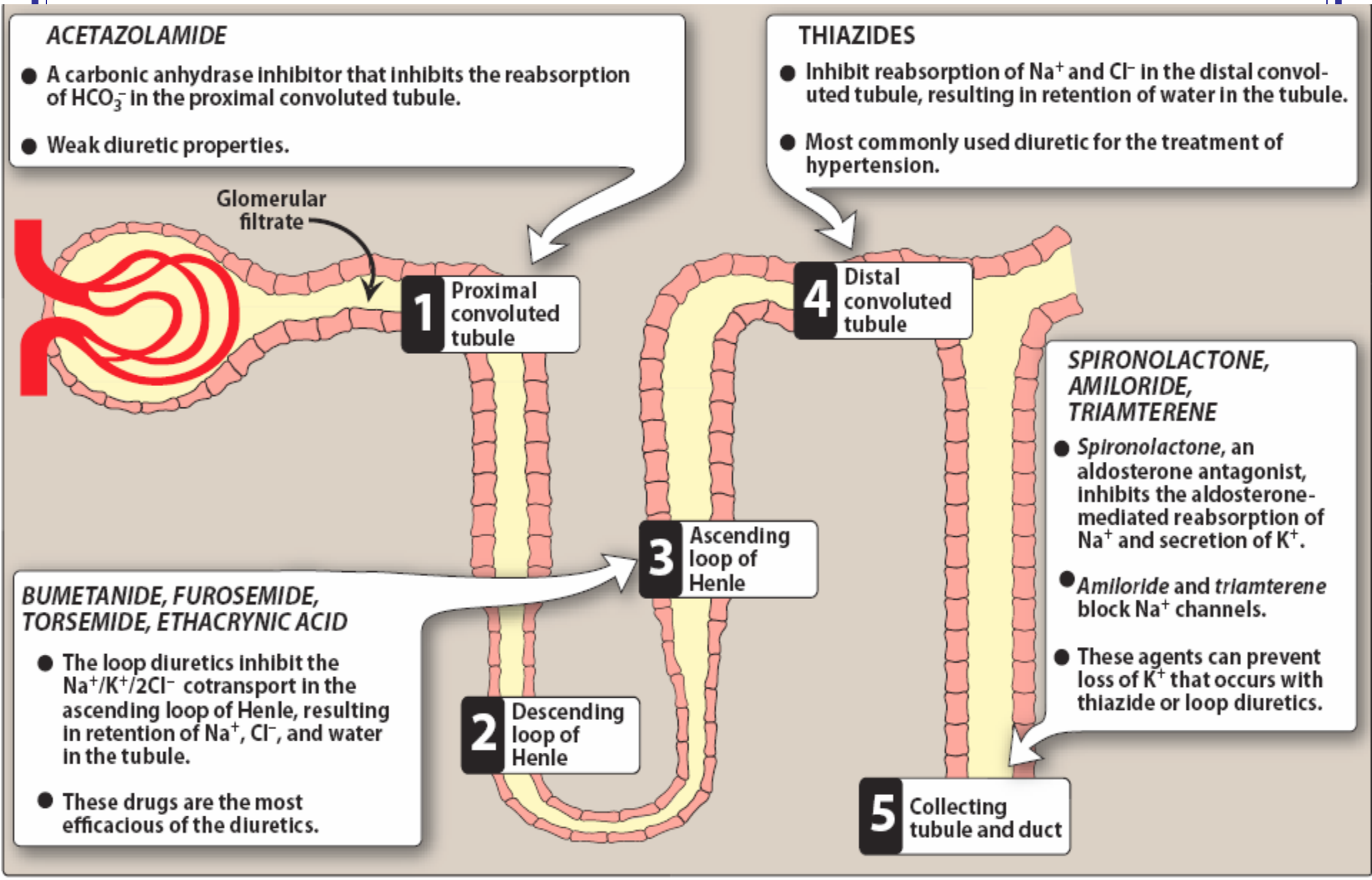
- MOA:

a. These agents inhibit active reabsorption of sodium chloride (NaCl) in the distal convoluted tubule by interfering with Na/Cl cotransporter (**NCC),** resulting in the net excretion of Na and an accompanying volume of water.

(1) **These agents increase excretion of Cl, Na, potassium (K), and, at high doses HCO3**

(2) **They reduce excretion of calcium (Ca+2).**

MOA: Diuretics



Thiazides:Specific agents

- **Prototype true thiazides**
  - **chlorothiazide and hydrochlorothiazide**. **methyclothiazide.**
  - Chlorothiazide is the only thiazide available for parenteral use.
- **Thiazide-like drugs**
  - **metolazone, chlorthalidone, and indapamide**
  - Unlike thiazides, these agents may be effective in the presence of some renal impairment.

Thiazides: Therapeutic uses

1. **Thiazide diuretics are the preferred class of diuretic for the treatment of essential hypertension when renal function is normal;**
   - **they are often used in combination with** other antihypertensive agents to enhance their blood pressure-lowering effects.
   - They reduce plasma volume and total peripheral resistance.
2. **These agents reduce the formation of new calcium stones in idiopathic hypercalciuria.**
3. **Thiazide diuretics may be useful in patients with diabetes insipidus that is not** responsive to antidiuretic hormone (ADH).
4. **These agents are often used in combination with a potassium-sparing diuretic to** manage **mild cardiac edema, cirrhotic or nephrotic edema, and edema produced by hormone imbalances.**
5. **They are frequently used in the treatment of Ménière disease**

Thiazides:contraindications

- ***Thiazide diuretics should be used cautiously in the*** presence of: **renal or hepatic diseases such as cirrhosis**, and they should be used only as an ancillary treatment in nephrotic syndrome.

Thiazides: Adverse effects

1. **Electrolyte imbalances** such as **hypokalemia, hyponatremia, Hypomagnesemia** and **hypochloremic alkalosis.**
2. These imbalances are often accompanied: by central nervous system (CNS) disturbances, including **dizziness, confusion, and irritability;**
3. Hypokalaemia – **muscle weakness; fatigue and cardiac arrhythmias**;
   - by decreasing plasma K, **increased sensitivity to digitalis.**
   - **Diets low in Na and high in K are recommended;**
   - **K supplementation** may be required.

Thiazides: Adverse effects

4. **Gout-like symptoms may appear**: **elevate serum urate, presumably as a result of competition for the** organic anion carriers (which also eliminates uric acid)
5. **Hyperglycemia**: Inhibition of insulin release due to K+ depletion (decrease proinsulin to insulin) – precipitation of diabetes **(especially in patients with diabetes)**
6. **hypertriglyceridemia, hypercholesterolemia** rise in total LDL level – risk of stroke
7. **hypercalcemia**
8. **hypersensitivity reactions (sulfa groups).**
   - All the above metabolic side effects – higher doses (50 – 100 mg per day)
   - But, its observed that these adverse effects are minimal with low doses (12.5 to 25 mg)

Thiazides

- **Thiazide diuretics are absorbed from the gastrointestinal (GI) tract and**

Drug	Chemical Class	Potency	Half-Life (h)
Chlorothiazide	Benzothiadiazide	0.1	2
Hydrochlorothiazide	Benzothiadiazide	1.0	3
Metolazone	Quinazoline	5	5
Chlorthalidone	Quinazoline	10	26
Indapamide	Indoline	20	16

Loop diuretics

- **Prototype drugs include:**
  - **Furosemide, Bumetanide, Ethacrynic Acid and Torsemide**.
- They are administered either orally or parenterally.
- Diuresis occurs within 5 minutes of intravenous (IV) administration and within 30 minutes of oral administration

Table 15–2. Loop Diuretics: Dosages.

Drug	Daily Oral Dose[1]
Bumetanide	0.5–2 mg
Ethacrynic acid	50–200 mg
Furosemide	20–80 mg
Torsemide	2.5–20 mg

[1] As single dose or in two divided doses.

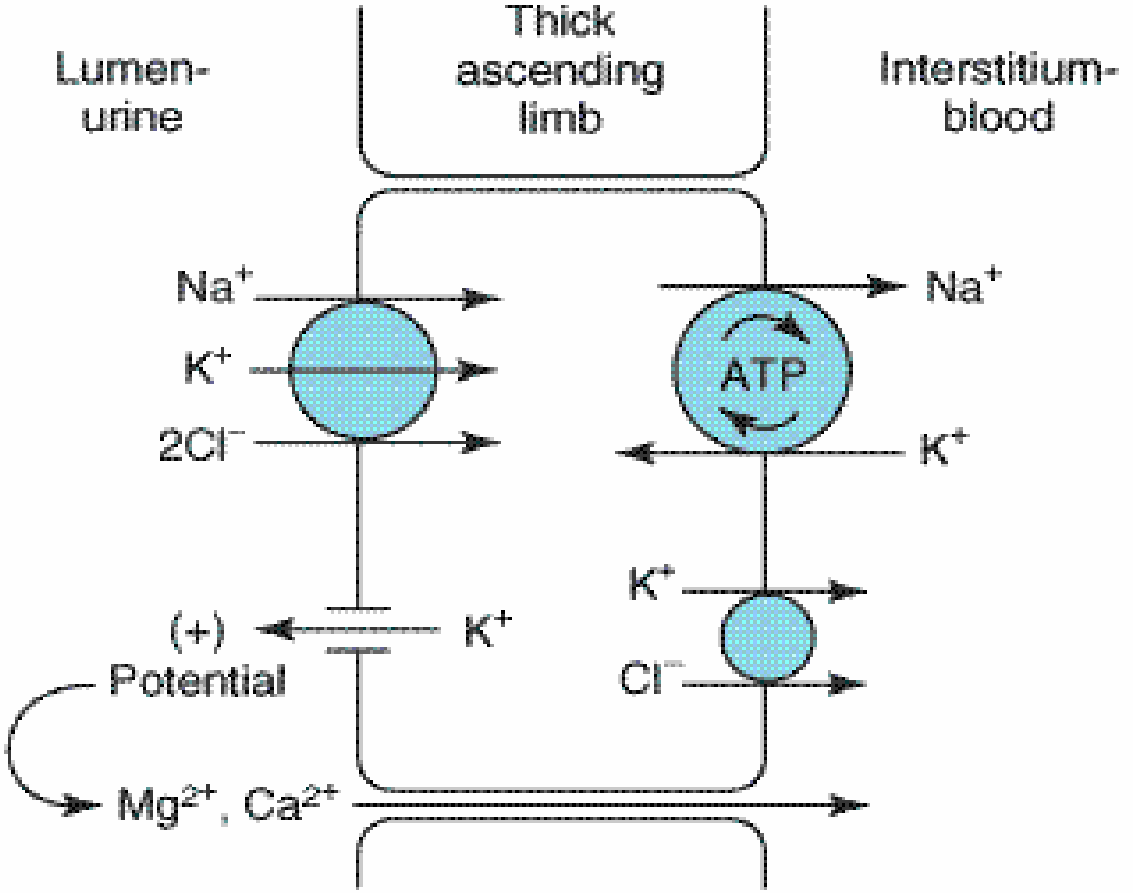
Loop diuretics

- **Mechanism.**

a. **Loop diuretics inhibit active Na/K/Cl reabsorption in the thick ascending limb of the loop** of Henle by inhibiting **specific** Na+/K+/2Cl- **co-transporter.**

- This results in back diffusion of K+ into the tubular lumen and development of a lumen-positive electrical potential
- This electrical potential provides the driving force for reabsorption of cations—including Mg2+ and Ca2+
- **Because of** the high capacity for Na/Cl reabsorption in this segment, agents active at this site markedly increase water and electrolyte excretion and are referred to as **high-ceiling diuretics.**
- The loop diuretics are the most efficacious diuretic drugs. Reduce reaborption by 25%.

Loop diuretics



Loop diuretics

- **Mechanism.**

b. Loop diuretics cause increased renal prostaglandin production, which accounts for some of their activity. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the effectiveness of loop diuretics.

c. Net effects: These agents reduce reabsorption of Cl- and Na+; they increase Ca+2 excretion and magnesium (Mg).

Loop diuretics: Therapeutic uses

1. Loop diuretics are used in the treatment of **CHF** by reducing **acute pulmonary edema**
2. They are synergistic with thiazide diuretics when coadministered.
3. These agents are used to treat **hypertension**, especially in individuals with **diminished renal function**. They reduce the plasma volume and also the total peripheral resistance.
4. They are also used to treat **acute hypercalcemia**

Loop diuretics: Therapeutic uses

5. Hyperkalemia: loop diuretics can significantly enhance urinary excretion of K+.

6. Acute Renal Failure

- Loop agents can increase the rate of urine flow and enhance K+ excretion in acute renal failure.

7. **halide poisoning**

- Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide.

Loop diuretics: Adverse effects

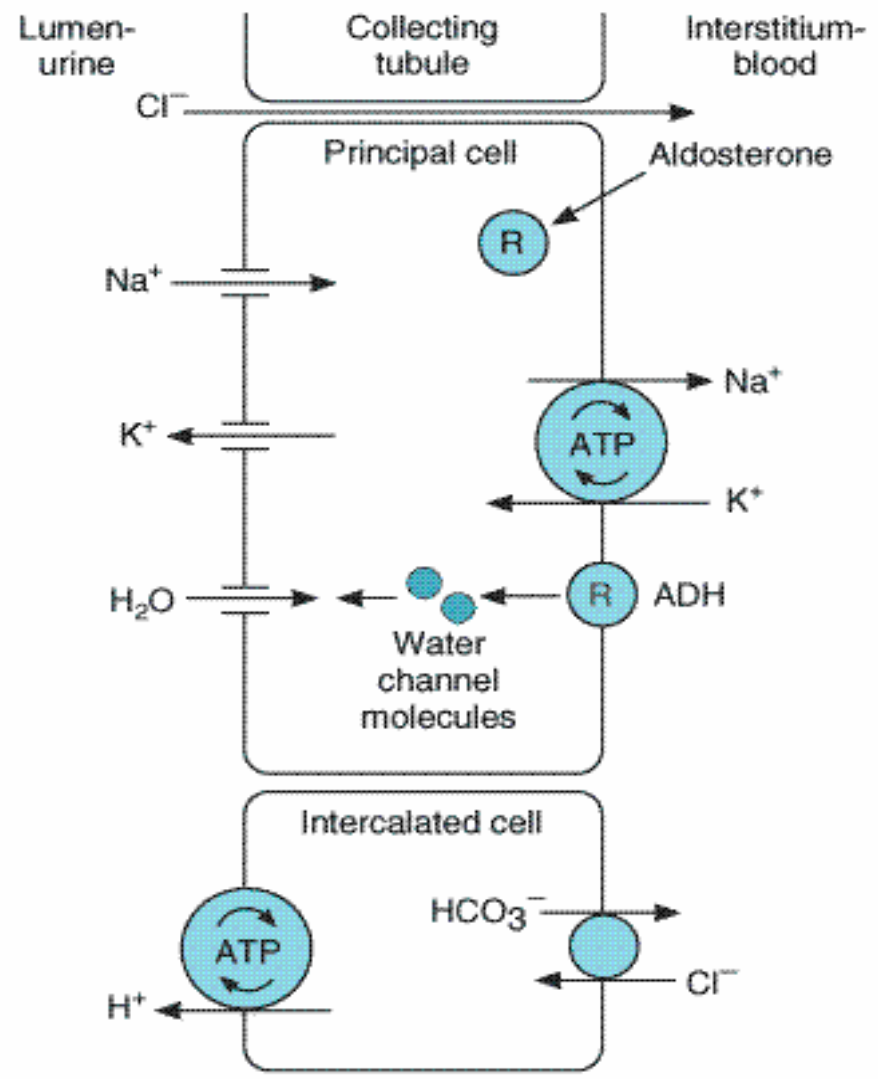
- **Hyponatremia**
- **Hypotension and volume depletion,**
- **Hypokalemia**
- They may also produce **alkalosis due to** enhanced H+ secretion.
- **Hypocalcemia**
- **Hypomagnesemia:**

Loop diuretics: Adverse effects

- **Loop diuretics can cause dose-related ototoxicity, more often in individuals with renal impairment.** These effects are more pronounced with **ethacrynic acid** than with furosemide.
- These agents should be administered cautiously in the presence of renal disease or with the use of other **ototoxic agents** such as **aminoglycosides.**
- **These agents can cause hypersensitivity reactions.**
- **Ethacrynic acid produces GI** disturbances

Potassium-sparing diuretics

- The mechanism of NaCl reabsorption in the collecting tubule is distinct from the mechanisms found in other tubule segments.
- The **principal cells are the major sites of Na+, K+, and H2O transport and** the **intercalated cells are the primary sites of proton secretion**
- **Mechanism:**
  - **reduce Na+ reabsorption and reduce K+ secretion in the** distal part of the nephron (collecting tubule).
- **These are not potent diuretics when used alone; they are primarily used in combination** with other diuretics


Lumen-
urine
Collecting
tubule
Interstitium-
blood
Cl⁻
Principal cell
Aldosterone
R
Na⁺
Na⁺
K⁺
ATP
K⁺
H₂O
R
ADH
Water
channel
molecules
Intercalated cell
HCO₃⁻
ATP
Cl⁻
H⁺

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor include**
    1. **Eplerenone, which** is highly receptor selective,
    2. **Spironolactone, which binds to other nuclear receptors** such as the androgen receptor

- **MOA*:* These agents inhibit the action of aldosterone by competitively binding** to the mineralocorticoid receptor and preventing subsequent cellular events that regulate K and H secretion and Na reabsorption.
- **These agents are active only when endogenous mineralocorticoid is present;** the effects are enhanced when hormone levels are elevated.
- **These agents are absorbed from the GI tract and are metabolized in the liver**
- therapeutic effects are achieved only after several days

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor**

Therapeutic uses.

- ***These drugs are generally used in combination with a thiazide*** or loop diuretic to treat **hypertension, CHF, and refractory edema.**
- **They are also** used to induce diuresis in clinical situations associated with **hyperaldosteronism,** such as in **adrenal hyperplasia and in the presence of aldosterone-producing adenomas when surgery is not feasible**

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor:**

Adverse effects

- **hyperkalemia, hyperchloremic metabolic acidosis, and arrhythmias**.
- **Spironolactone** is associated with **gynecomastia and can also** cause menstrual abnormalities in women.

- **These drugs are contraindicated in :**
  - **renal insufficiency, especially in diabetic** patients.
  - They must be used cautiously in the presence of **liver disease**
  - They are contraindicated in the presence of other potassium-sparing diuretics and should be used with extreme **caution in individuals taking an ACEI (e.g., captopril)**

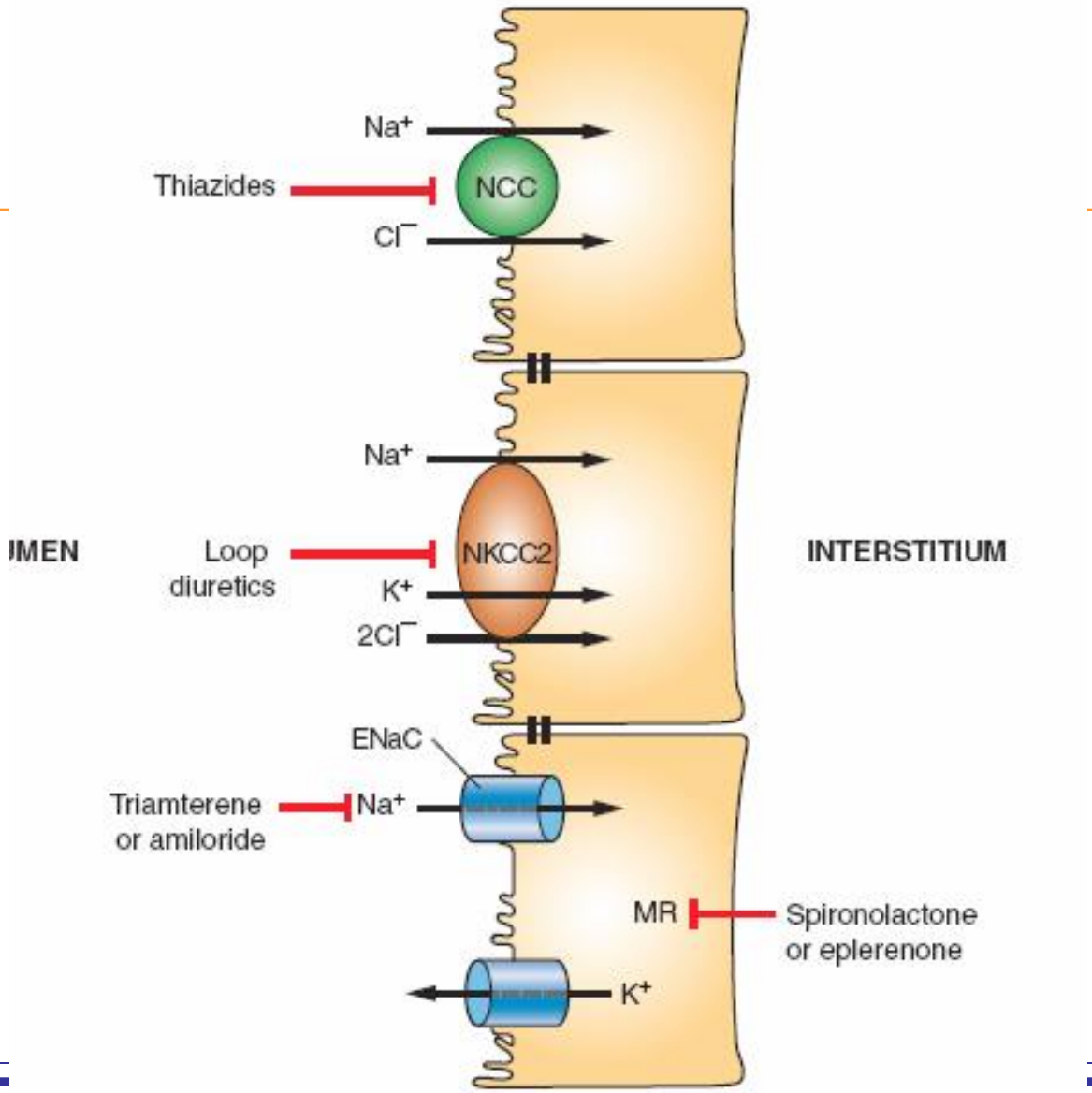
Potassium-sparing diuretics

2. Amiloride and triamterene

- **Mechanism.**
- **Amiloride and triamterene bind to and block Na channel and thereby** decrease absorption of Na and excretion of K in the cortical collecting tubule, independent of the presence of mineralocorticoids.
- **These drugs produce diuretic effects 2–4 hours after oral administration**
- **Triamterene increases urinary excretion of Mg but amiloride does not;**
- **Triamterene and amiloride** are metabolized in the liver.

Potassium-sparing diuretics

- **Therapeutic uses.**
  - These agents are used to manage **CHF, cirrhosis, and edema**
  - They are available in combination products containing thiazide or loop diuretics (e.g., triamterene/hydrochlorothiazide, amiloride/hydrochlorothiazide) to treat **hypertension**.
- **Adverse effects and contraindications.**
  - hyperkalemia,
  - ventricular arrhythmias.
  - Dietary potassium intake should be reduced.
  - Minor adverse effects include nausea and vomiting.
- **The use of these drugs is contraindicated in the presence of diminished renal function**.


Na+
Thiazides
NCC
Cl−
Na+
IMEN
Loop
diuretics
NKCC2
INTERSTITIUM
K+
2Cl−
ENaC
Triamterene
or amiloride
Na+
MR
Spironolactone
or eplerenone
K+