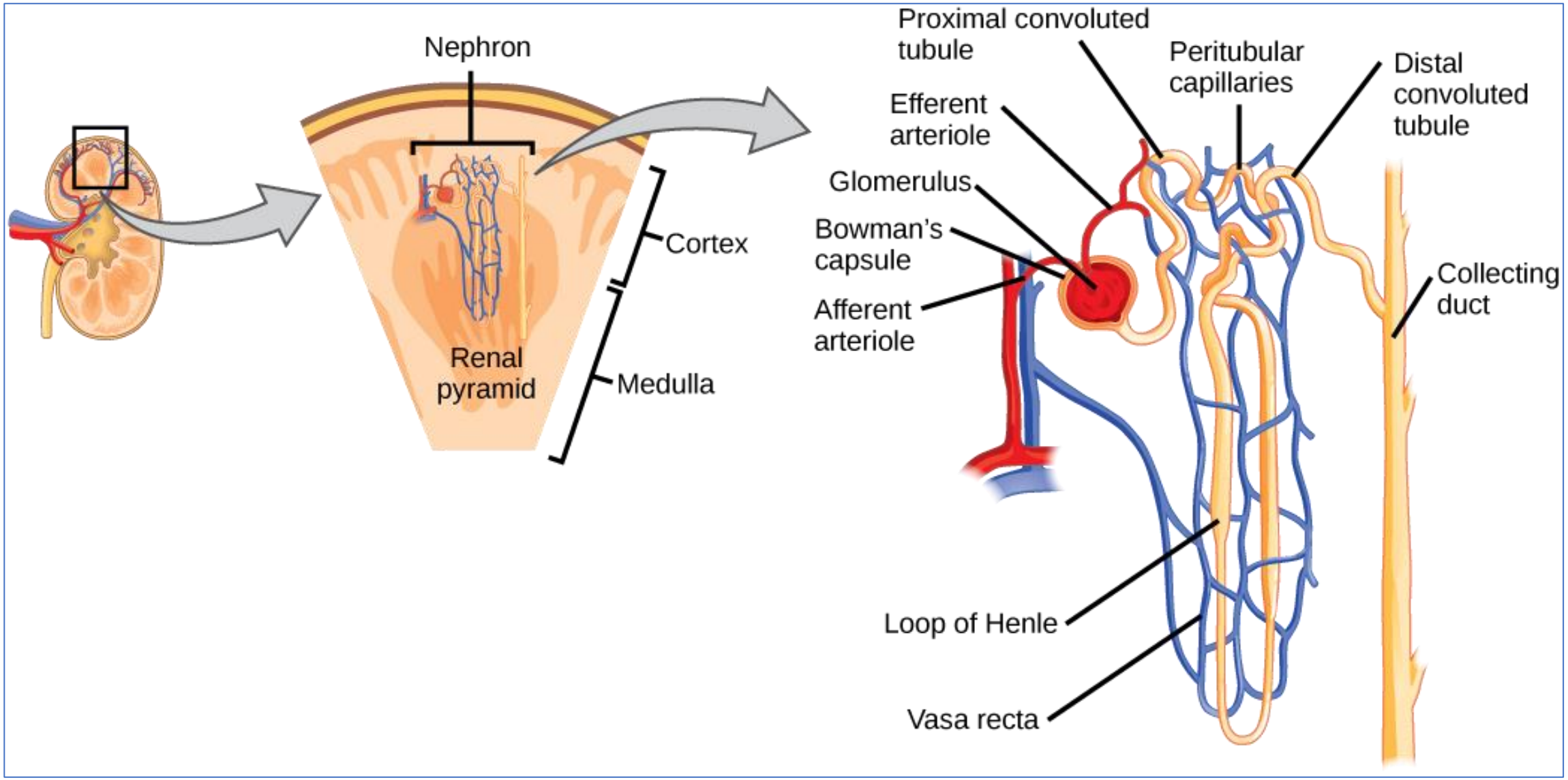
Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 1

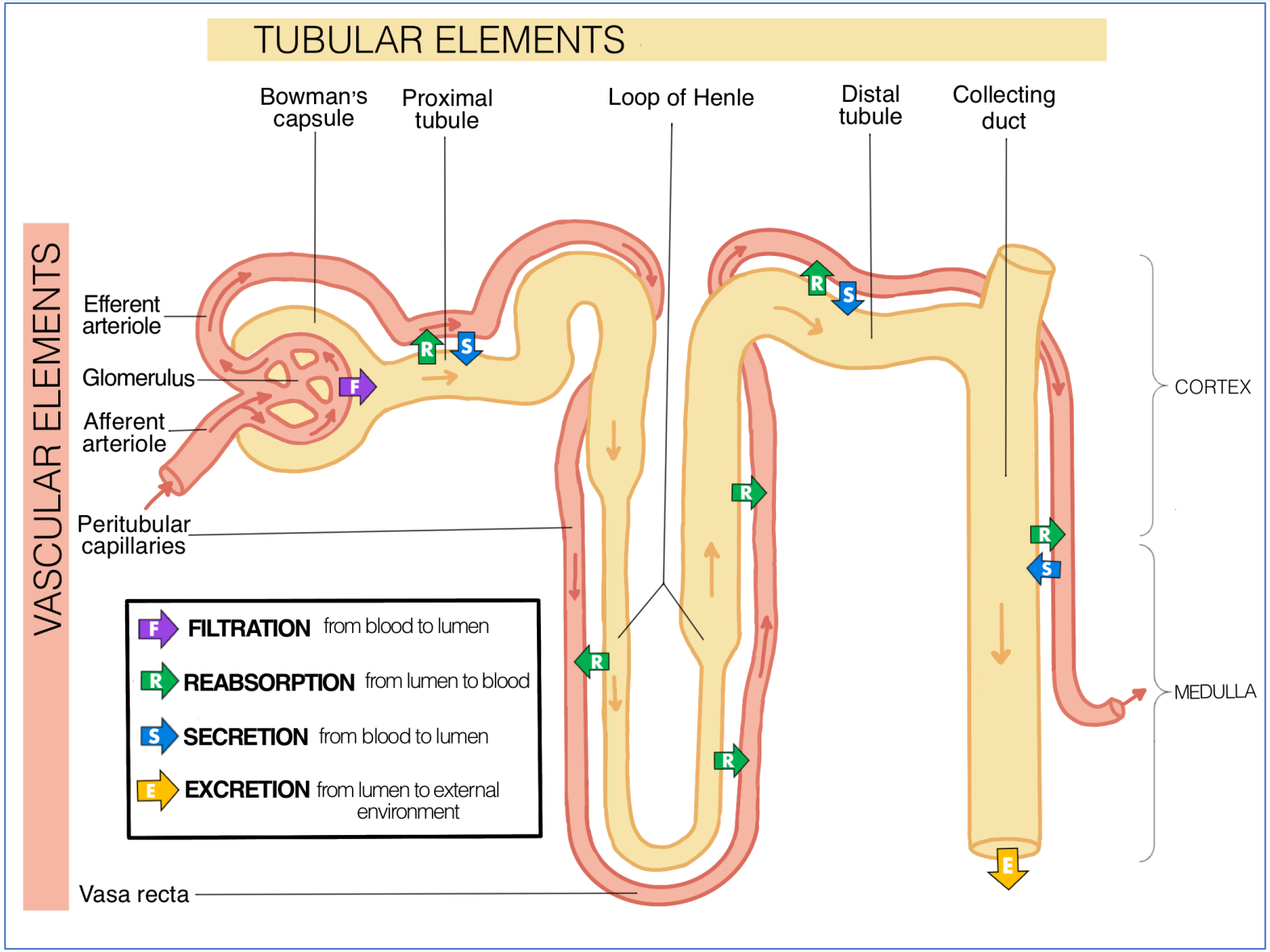
Diuretics

Dr. Qassim A. Zigam

Overview


Nephron
Cortex
Renal pyramid
Medulla
Proximal convoluted tubule
Peritubular capillaries
Distal convoluted tubule
Efferent arteriole
Glomerulus
Bowman's capsule
Afferent arteriole
Collecting duct
Loop of Henle
Vasa recta

Overview


TUBULAR ELEMENTS
Bowman's capsule
Proximal tubule
Loop of Henle
Distal tubule
Collecting duct
VASCULAR ELEMENTS
Efferent arteriole
Glomerulus
Afferent arteriole
Peritubular capillaries
Vasa recta
CORTEX
MEDULLA
F FILTRATION from blood to lumen
R REABSORPTION from lumen to blood
S SECRETION from blood to lumen
E EXCRETION from lumen to external environment

Overview

- Diuretics are drugs that **increase** the **volume of urine excreted**.
- **Most** diuretic agents are **inhibitors** of renal **ion transporters.**
- They **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.

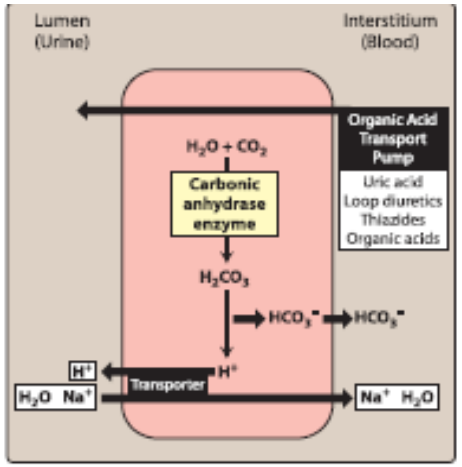


Figure 17.3
Proximal convoluted tubule cell.

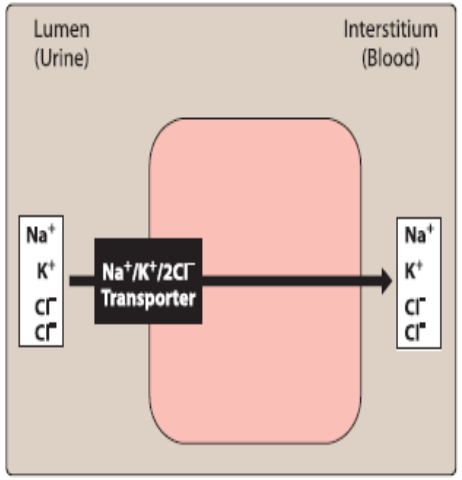


Figure 17.4
Ascending loop of Henle cell.

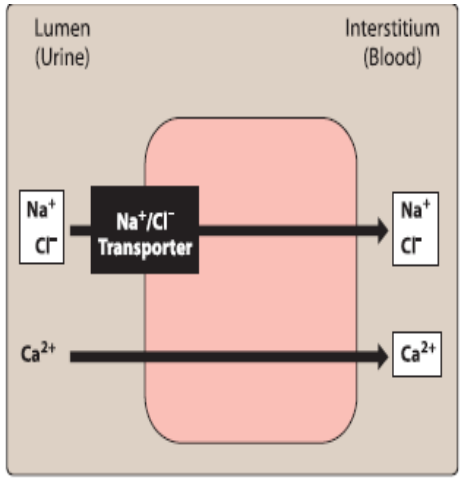


Figure 17.5
Distal convoluted tubule cell.

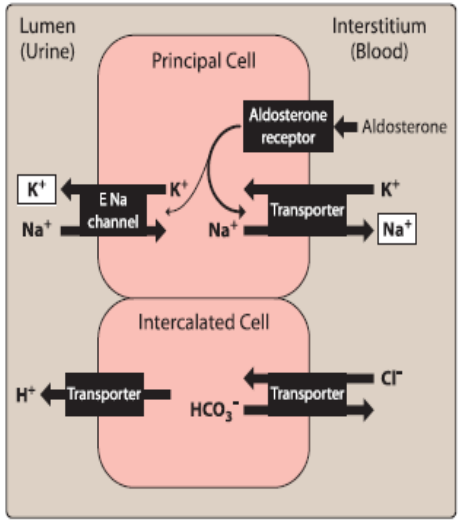
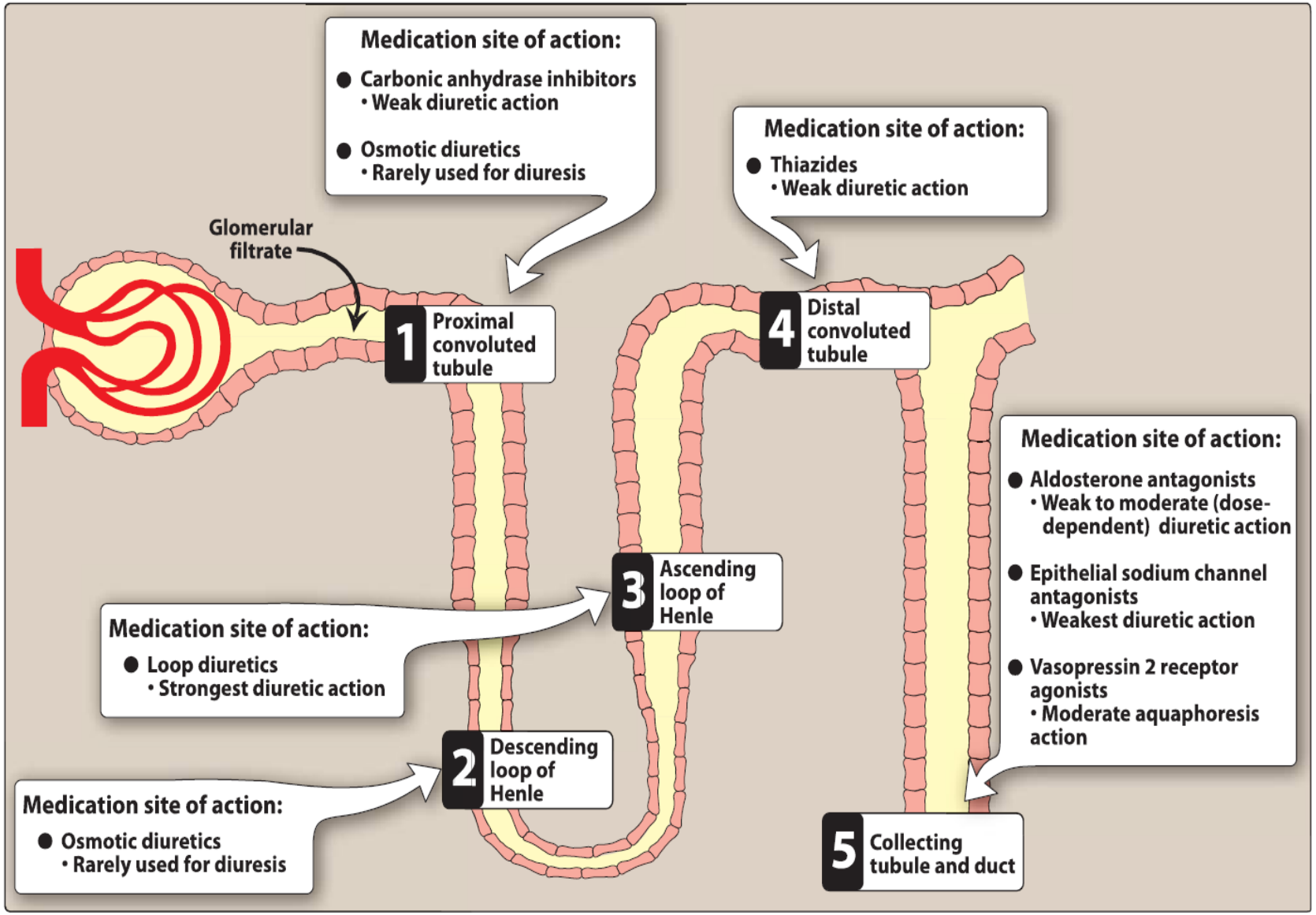


Figure 17.6
Collecting tubule and duct cells. E Na channel = Epithelial sodium channel.

Overview



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

THIAZIDES DIURETICS

- The thiazides are the **most widely used** diuretics **because** of their antihypertensive effects, depending on their **diuretic actions** & reduction effect on the **peripheral vascular resistance** with long-term therapy.
- Despite being **sulfonamide derivatives** but **not** generally cause **hypersensitivity** reactions in patients with allergies to sulfonamide antimicrobials such as sulfamethoxazole.
- **All** thiazides affect the **distal convoluted tubule**.
- **All** have **equal maximum diuretic effects**, **differing** only in **potency**.
- Thiazides are sometimes called **"low ceiling diuretics**:· **because** increasing the dose above normal therapeutic doses does not promote further diuretic response.

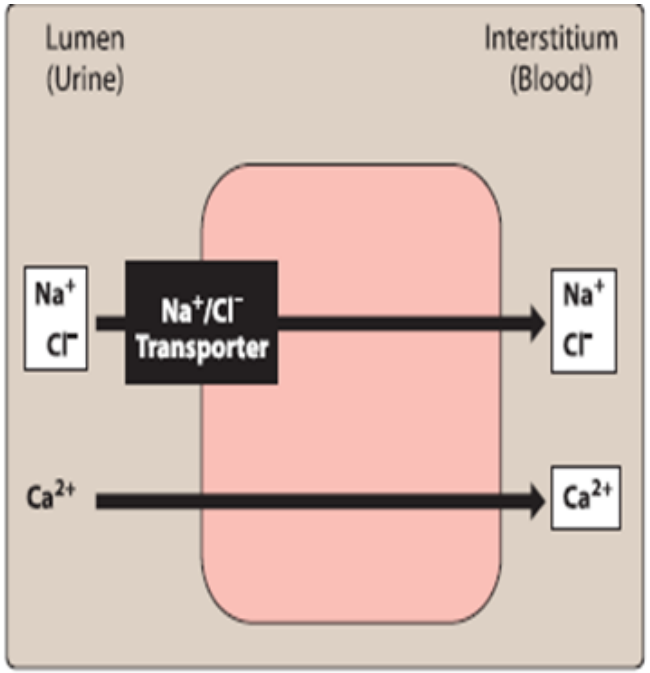


Figure 17.5
Distal convoluted tubule cell.

THIAZIDES DIURETICS

- **Chlorothiazide** was the **first** orally active thiazide.
- **Hydrochlorothiazide** and **chlorthalidone** are now used **more commonly** due to better **bioavailability**.
- **Hydrochlorothiazide** is **more potent**, so the required dose is considerably lower than that of chlorothiazide, but the **efficacy is comparable** to that of the **parent drug**.
- **Chlorthalidone** is approximately **twice as potent** as **hydrochlorothiazide**.
- **Chlorthalidone, indapamide, and metolazone** are referred to as **thiazide-like diuretics**.

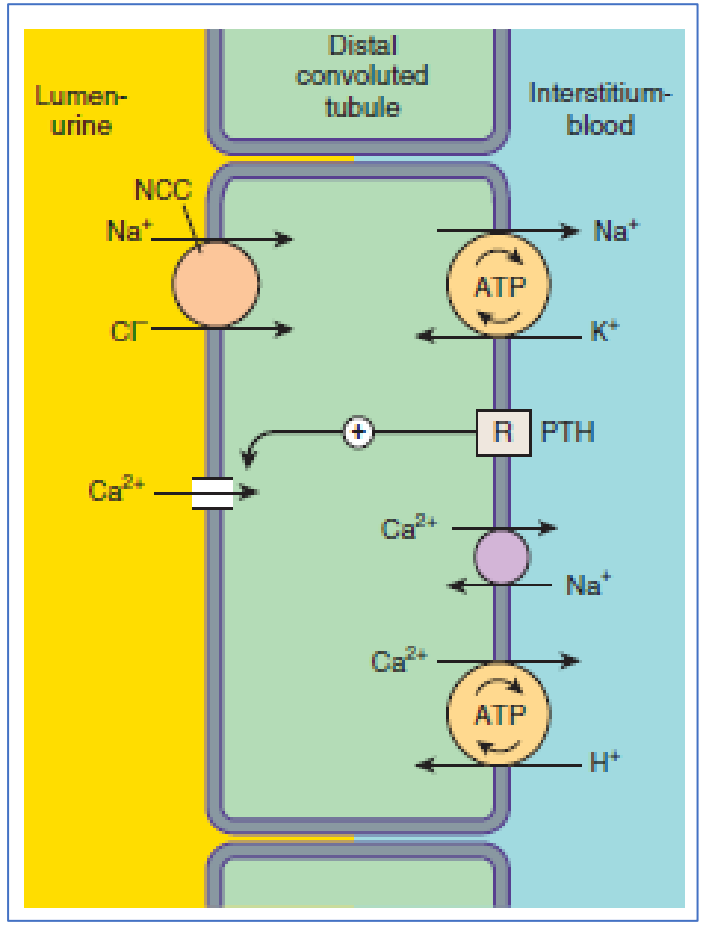
Thiazide Mnemonic Phrase

Cats **H**ate **C**old **I**n **M**y Apartment

THIAZIDES DIURETICS

1. Mechanism of action:

- They act mainly in the **DCT to decrease the reabsorption** of Na by inhibition of a **Na/Cl-cotransporter**.
- As a result, these drugs **increase** the conc. of Na and Cl in the tubular fluid.
- Thiazides must be **excreted** into the tubular lumen at the **PCT to be effective**, Therefore, decreasing renal function reduces the diuretic effects.
- The **antihypertensive** effects of thiazides may **persist** even when the GFR is below **30** .
- The efficacy of thiazides may be diminished with concomitant use of **NSAIDs**, such as indomethacin, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.



THIAZIDES DIURETICS

2. Actions

A. **Increased excretion of Na & Cl:** result in the excretion of **very hyperosmolar** (concentrated) urine (**unique criteria**).

B. **Decreased urinary calcium excretion:** decrease the Ca content of urine by **promoting** the **reabsorption** of Ca in the DCT.

C. **Reduced peripheral vascular resistance:** caused by relaxation of arteriolar smooth muscle

THIAZIDES DIURETICS

3. Therapeutic uses:

A. **Hypertension:** mainstay of antihypertensive treatment, **because** they are inexpensive, convenient to administer, and well tolerated.

B. **Heart failure:** thiazide diuretics may be added in patients resistant to loop diuretics (1.st choice), with careful monitoring for hypokalemia.

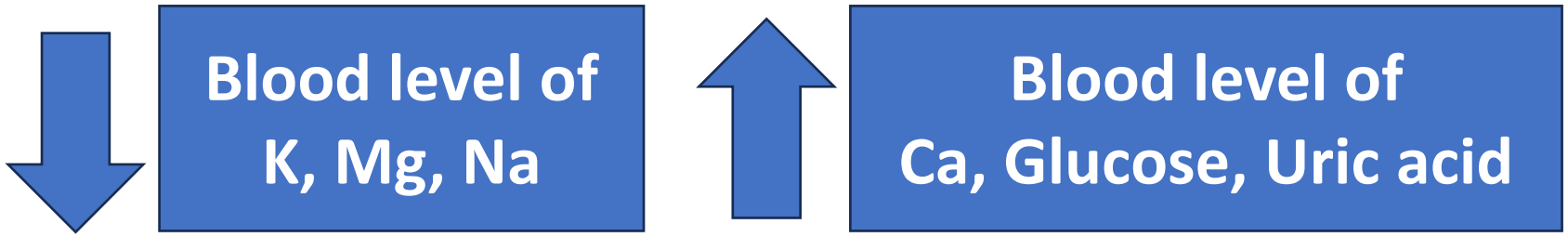
C. **Hypercalciuria:** thiazides can be useful in treating **idiopathic hypercalciuria** and **calcium oxalate stones** in the urinary tract, because they inhibit urinary Ca excretion.

D. **Diabetes insipidus:** thiazides produce a **hyperosmolar** urine, so thiazides can be utilized as a Rx for **nephrogenic** diabetes insipidus (11 to. 3 L/day)

THIAZIDES DIURETICS

4. Adverse effects:

1. **Hypokalemia** (most **frequent** with the thiazide) , **Hypomagnesemia**, **Hyponatremia, Hypovolemia** (this can cause orthostatic hypotension or light-headedness)
2. Hyperuricemia: (may precipitate a **gouty attack** in predisposed individuals, it used with **caution**)
3. **Hypercalcemia**: (inhibit the secretion of Ca)
4. **Hyperglycemia**: (possibly due to **impaired** release of insulin related to **hypokalemia**)



LOOP DIURETICS

- **Bumetanide, furosemide, torsemide and ethacrynic acid "Be Fit To get Elegancy"**
- Have their major diuretic action on the **ascending limb of the loop of Henle.**
- These diuretics have the **highest efficacy** in mobilizing Na and Cl from the body.
- **Furosemide** is the most **commonly** used of these drugs.
- The use of **bumetanide** and **torsemide** is increasing, as these agents **have better bioavailability** and are **more potent** compared to furosemide.
- **Ethacrynic acid** is used **infrequently** due to its adverse effect profile.

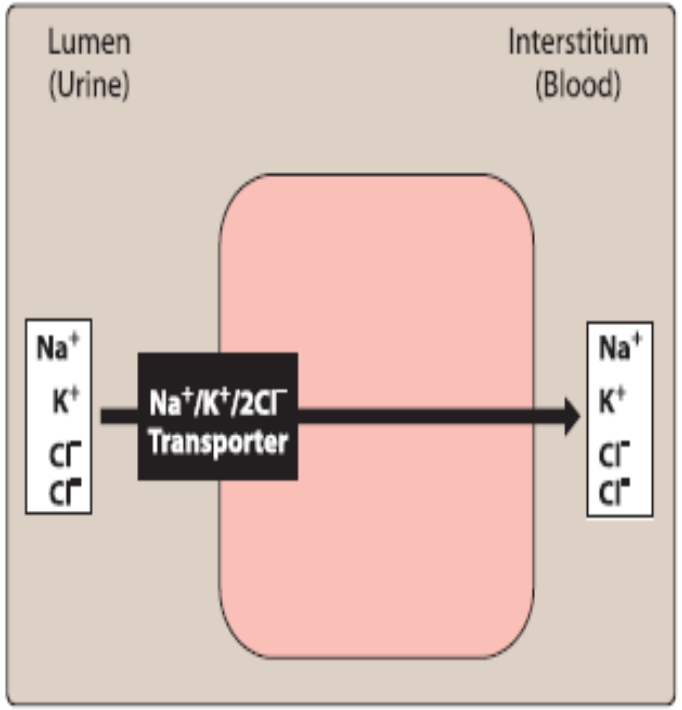
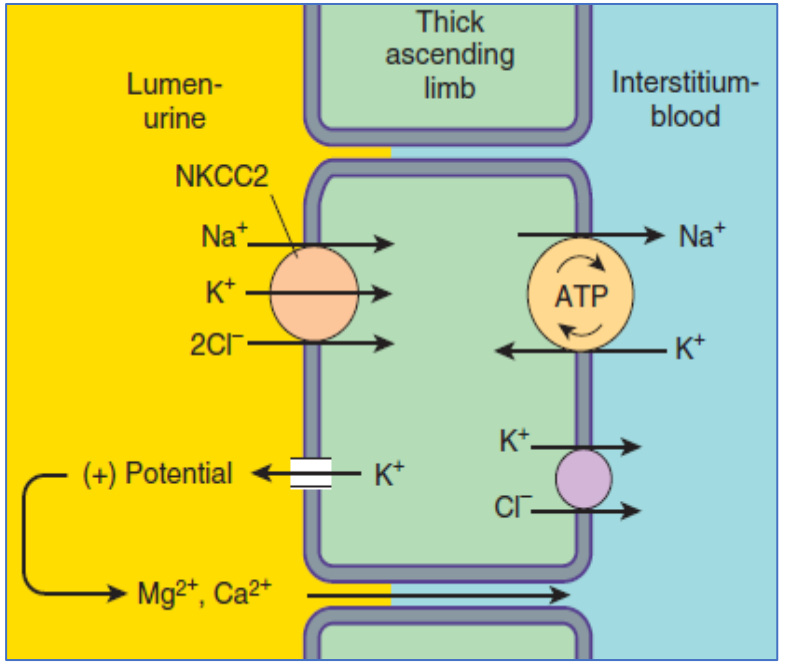


Figure 17.4
Ascending loop of Henle cell.

LOOP DIURETICS

1. 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**.
- These agents have the **greatest diuretic** effect of **all** the diuretics.
- Loop diuretics must be **excreted** into the tubular lumen at the **PCT** to be effective.
- **NSAIDs** inhibit renal prostaglandin synthesis and can **reduce** the diuretic action of loop diuretics.



LOOP DIURETICS

2. Actions:

A. Diuresis:

- Loop diuretics cause diuresis, **even** in patients with **poor renal function** or **lack of response** to other diuretics.

B. Increased urinary calcium excretion:

- Unlike thiazides, loop diuretics increase the Ca content of urine.(**hypocalcemia)**
- In patients with normal serum Ca conc., **hypocalcemia** does **not** result, because Ca is reabsorbed in the **DCT**.

C. Venodilation:

- **Prior** to their diuretic actions, loop diuretics cause **acute venodilation** via **enhanced prostaglandin synthesis**.

LOOP DIURETICS

3. Therapeutic uses

a. Edema:

- Loop diuretics are the **drugs of choice** for treatment of **pulmonary edema** and acute/chronic **peripheral edema** caused from heart failure or renal impairment.

b. Hypercalcemia:

- Loop diuretics (**along with hydration**) are also useful in **hypercalcemia Rx**, because they **stimulate tubular Calcium excretion**.

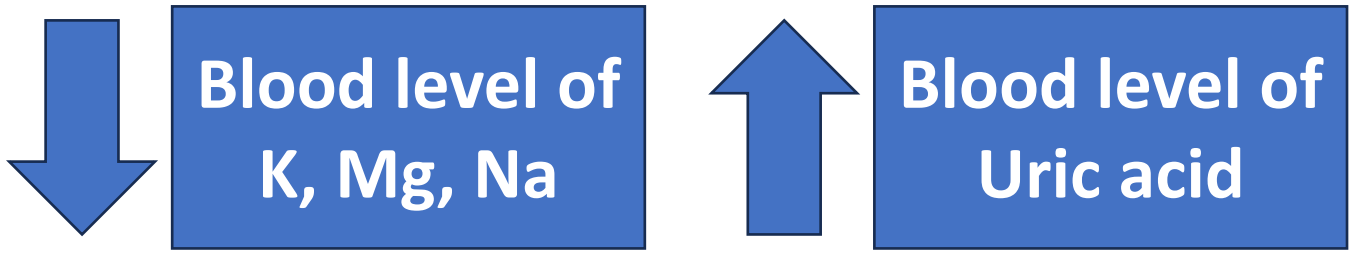
c. Hyperkalemia:

- Loop diuretics can be used with or without replacement intravenous fluid for the of **hyperkalemia Rx**.

LOOP DIURETICS

4. Adverse Effects:

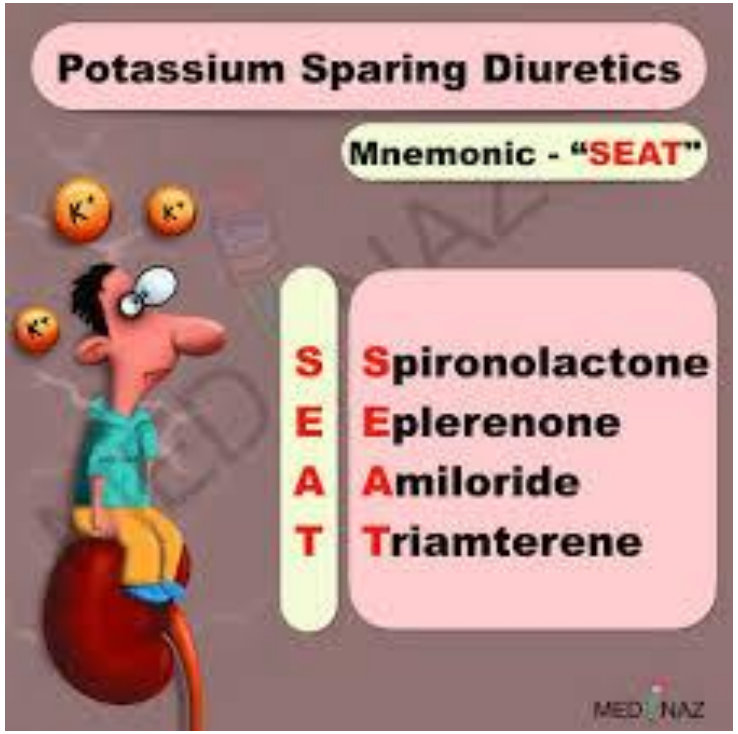
1. **Acute hypovolemia**: can cause a **severe** and **rapid** reduction in blood volume
2. **Hypokalemia:** The loss of K from cells in exchange for H leads to **hypokalemic alkalosis?**.
3. **Hypomagnesemia**
4. **Ototoxicity:** Reversible or permanent hearing loss may occur, **Ethacrynic acid** is the most.
5. **Hyperuricemia:** Loop diuretics **compete** with uric acid for the renal secretory systems.



POTASSIUM-SPARING DIURETICS

- Potassium-sparing diuretics act in the **collecting tubule** to **inhibit Na reabsorption and K excretion**.
- **Potassium levels** must be **monitored** in patients treated with potassium-sparing diuretics.
- These drugs should be used **cautiously in moderate renal dysfunction** and **avoided** in patients with **severe renal dysfunction** because of the increased risk of hyperkalemia.
- Within this class, there are drugs with **two distinct mechanisms of action**:

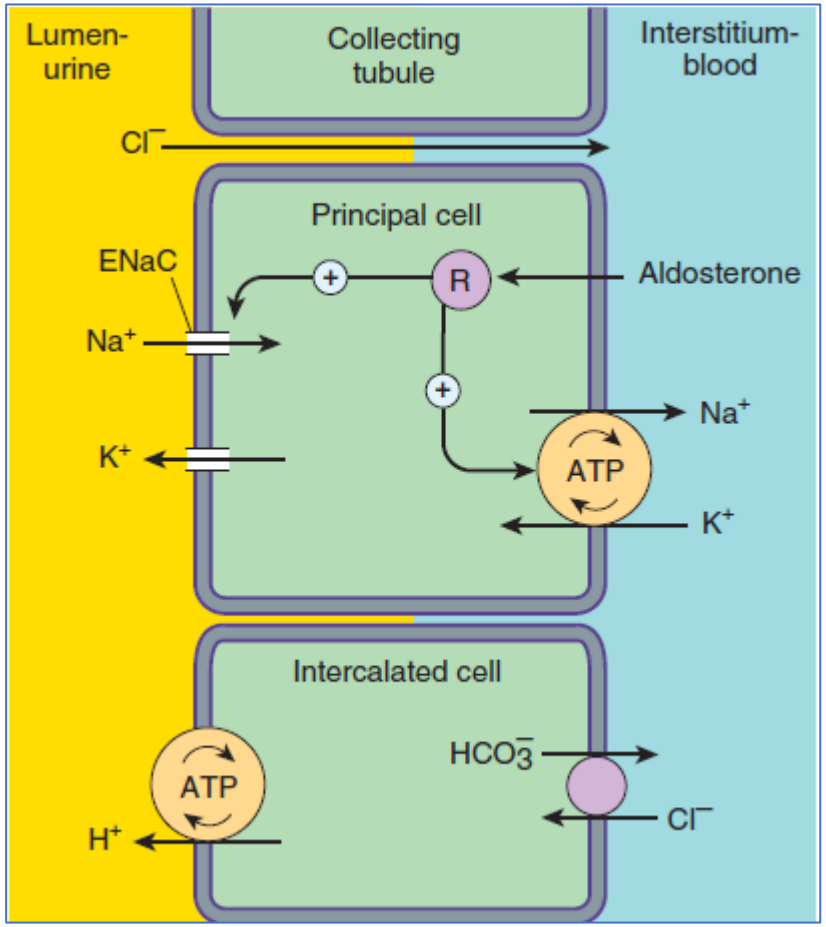
1. **Aldosterone antagonists**
2. **Epithelial sodium channel blockers (ENaC Blockers)**



POTASSIUM-SPARING DIURETICS (Aldosterone antagonists)

1. 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 the **Na/K exchange** sites of the **collecting tubule**.
- Thus, they **prevent Na reabsorption** and, therefore, **K and H secretion**.
- **Eplerenone** is **more selective** for aldosterone receptors and causes **less endocrine effects** (gynecomastia) than spironolactone, which also binds to **progesterone and androgen receptors**.



POTASSIUM-SPARING DIURETICS (Aldosterone antagonists)

3. Therapeutic uses:

a. Edema:

- They are particularly effective diuretics when used in high doses for **edema associated** with **secondary hyperaldosteronism**, such as hepatic cirrhosis and nephrotic syndrome.
- Spironolactone is the **diuretic of choice** in patients with **hepatic cirrhosis** with fluid in the peritoneal cavity (**ascites**).

b. Hypokalemia: they are often given in **conjunction** with **thiazide or loop diuretics?**

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

d. Resistant hypertension:

e. Polycystic ovary syndrome:

- Spironolactone is often used **off-label** for the Rx of PCOS.
- It **blocks androgen receptors** and inhibits steroid synthesis at high doses.

POTASSIUM-SPARING DIURETICS (Aldosterone antagonists)

4. Adverse effects

a. Hyperkalemia:

- The **most common** side effect, hyperkalemia, is **dose-dependent** and **increases** with **renal dysfunction.**

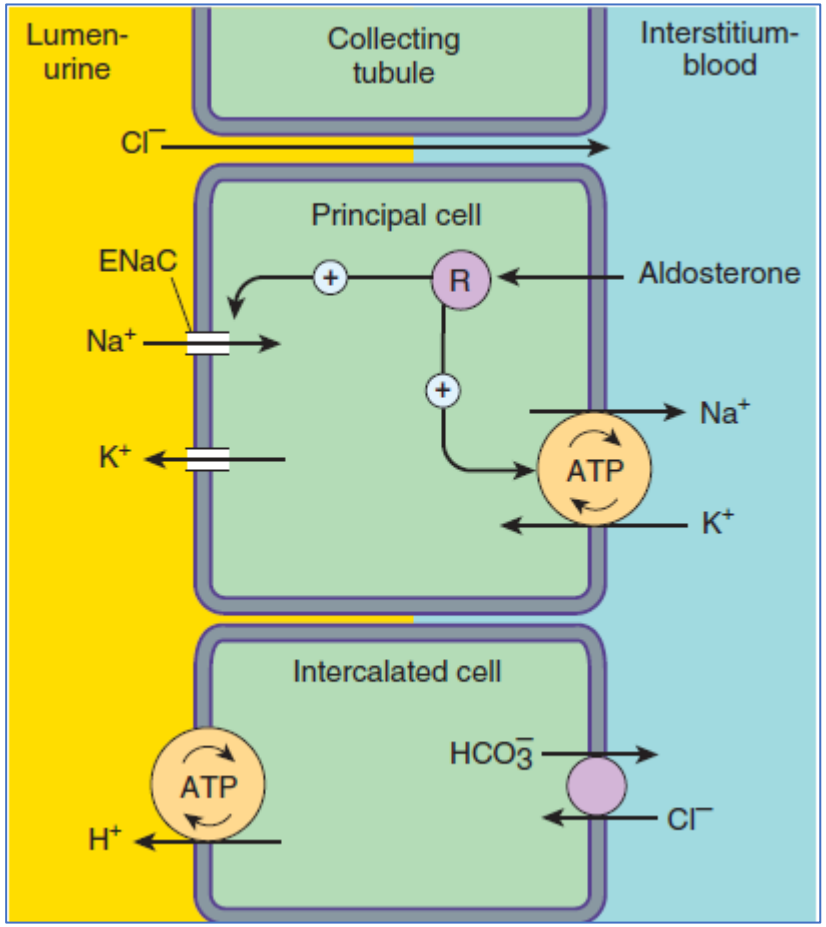
b. Gynecomastia:

- **Spironolactone**, but not eplerenone, may induce **gynecomastia** in approximately **10%** of male patients and **menstrual irregularities** in female patients.

POTASSIUM-SPARING DIURETICS (ENaC Blockers)

B. Triamterene and amiloride

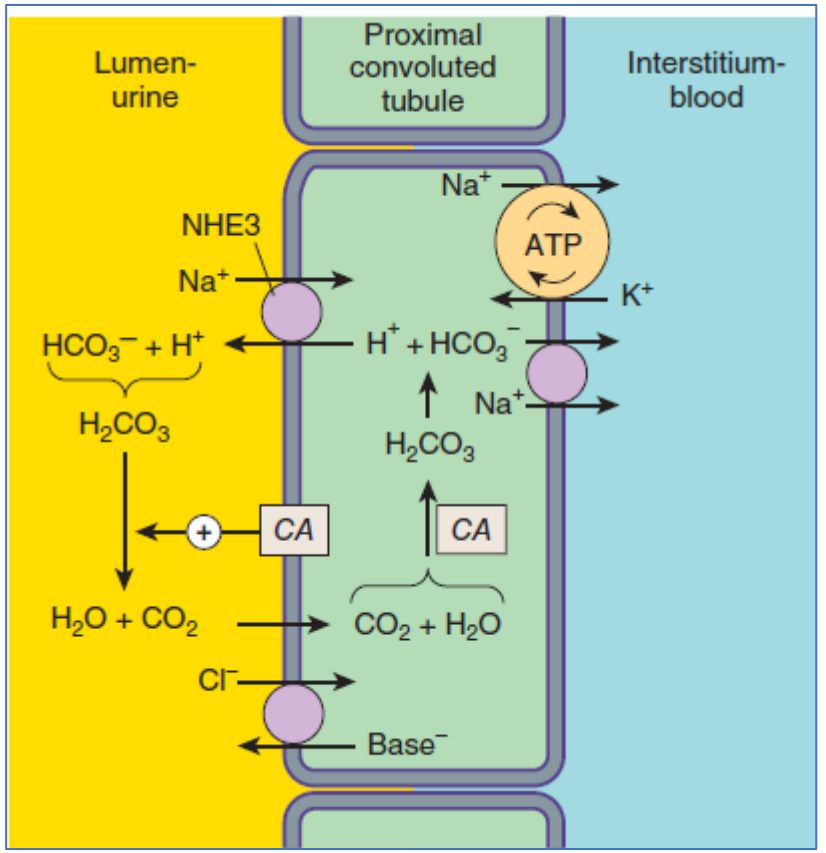
- They **block epithelial sodium channels**, resulting in a **decrease in Na/K exchange**.
- Their action does **not depend on** the presence of aldosterone.
- **Like** the aldosterone antagonists, these agents are **not very efficacious diuretics**.
- They are commonly used in **combination** with other diuretics.



CARBONIC ANHYDRASE INHIBITOR

1. Mechanism of action:

- Acetazolamide inhibits **carbonic anhydrase** located **intracellularly** (cytoplasm) and on the **apical membrane** of the proximal tubular epithelium.
- The **decreased** ability to **exchange Na for H** in the presence of acetazolamide results in a **mild diuresis**.
- Additionally, **$HC0_3^-$** is retained in the **lumen**, with marked **elevation in urinary pH**.
- The **loss of $HC0_3^-$** causes a **metabolic acidosis**.



CARBONIC ANHYDRASE INHIBITOR

2. Therapeutic uses

a. Glaucoma:

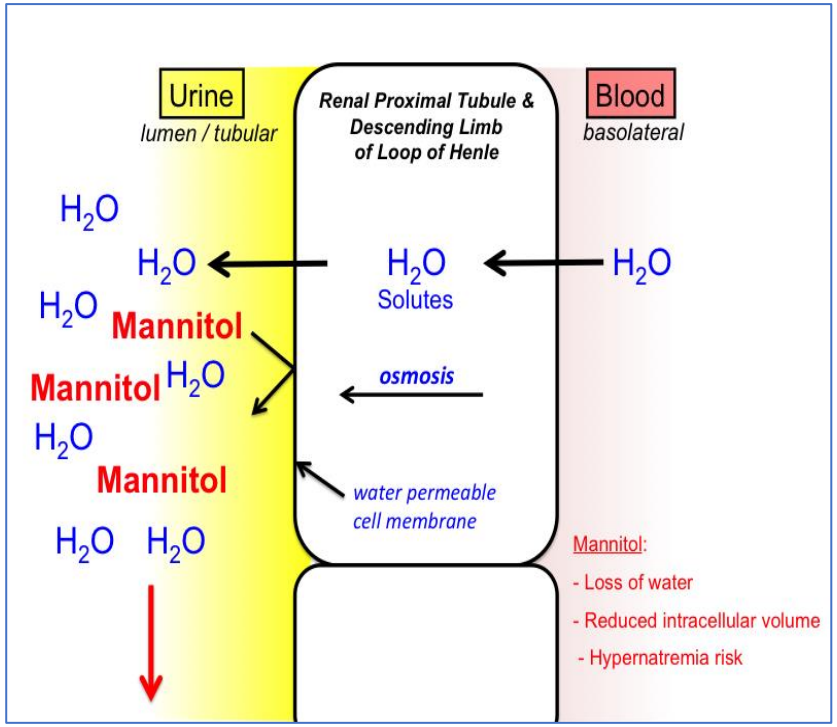
- Oral acetazolamide **decreases** the production of **aqueous humor** and **intraocular pressure** in patients with chronic open-angle glaucoma, probably by **blocking carbonic anhydrase** in the **ciliary body of the eye**.
- **Topical** carbonic anhydrase inhibitors, such as **dorzolamide and brinzolamide**, have the advantage of **not causing systemic effects**.

b. Altitude sickness:

- Acetazolamide can be used in the **prophylaxis of symptoms of altitude sickness**.
- Acetazolamide **prevents** weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

OSMOTIC DIURETICS

- Such as **mannitol** when filtered 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 & PCT**, resulting in **osmotic diuresis** with little additional Na excretion (aquaresis).
- Osmotic diuretics are a **mainstay of Rx** for patients with **increased intracranial** pressure. (not absorbed orally, IV)



OSMOTIC DIURETICS

Adverse effects

- **Dehydration** and **extracellular water expansion** from the osmotic effects in the systemic circulation.
- This **expansion** of extracellular water **extracts water from the cells** and causes **hyponatremia** until diuresis occurs.

THANK YOU