YOU KNOW THE SEMESTER HAS REALLY STARTED WHEN...

YOUR PHONE AUTO-CORRECTS "A LOT" TO "AORTA"

PHARMACOLOGY

Diuretics

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify clinical uses for diuretics
2. Explain the mechanism of action of diuretics (carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazides, and potassium sparing) and correlate to underlying pathophysiology
3. Identify the site of action of carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazides, and potassium sparing diuretics
4. State adverse effects and contraindications to carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazides, and potassium sparing diuretics
5. Describe the clinically important drug interactions of carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazides, and potassium sparing diuretics

PHARM MODULATION OF EXTRACELLULAR FLUID

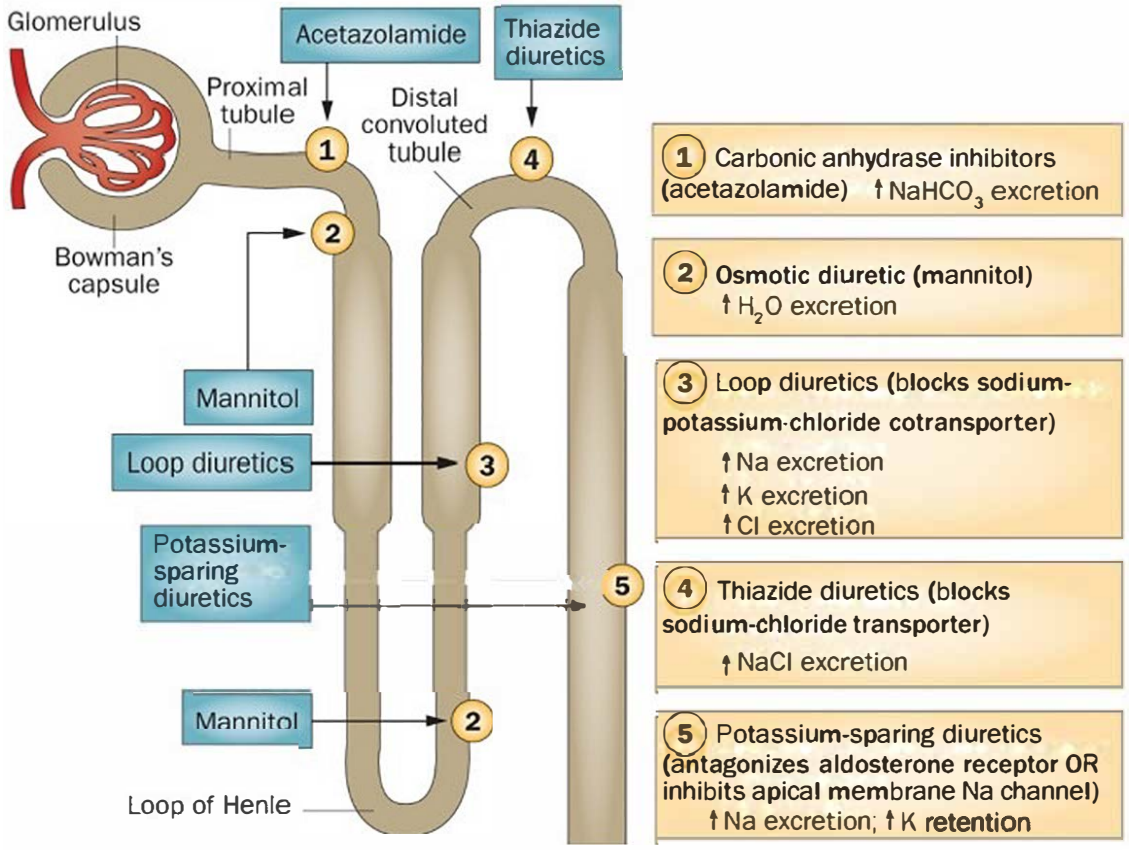
To increase or decrease body fluid volume, the kidneys must increase or decrease renal Na+ reabsorption from the volume of glomerular filtrate

- Accomplished by integrated action of apical and basolateral ion channels and transporters

Pharmacologic modulators of extracellular fluid volume include agents that

1. Modify neurohormonal volume regulators (e.g., ACEIs and ARBs)
2. Act directly on the nephron segments to alter renal Na+ handling

NEPHRON & SITES OF DIURETIC ACTION



Adapted from: Nature Reviews | Cardiology

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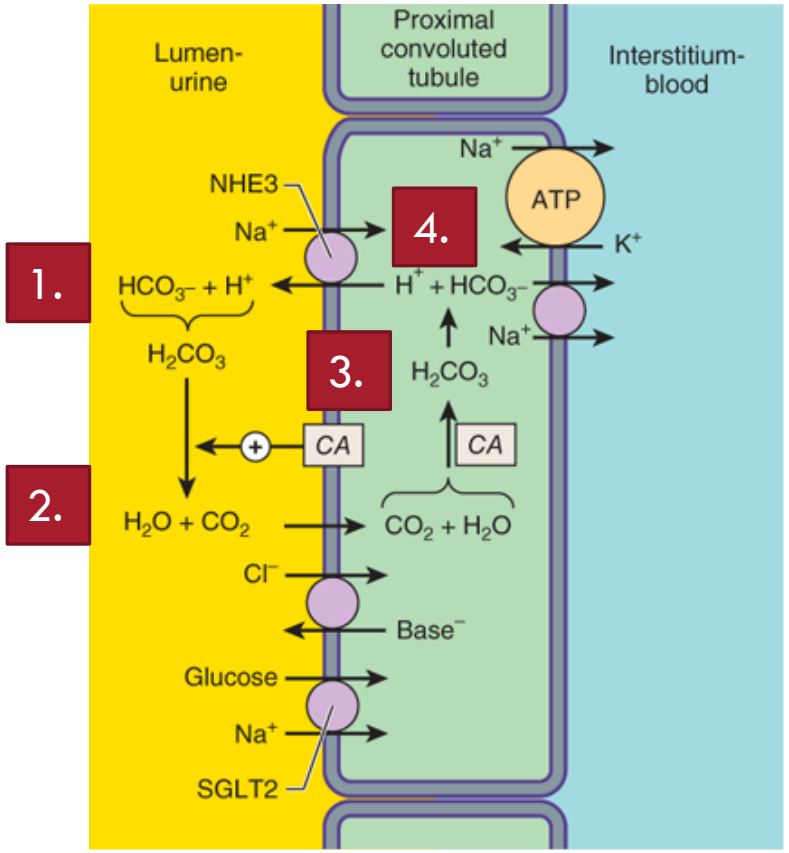
CARBONIC ANHYDRASE INHIBITORS (CAIs)

NA REABSORPTION IN PROXIMAL CONVOLUTED TUBULE

1. Bicarbonate poorly reabsorbed through luminal membrane
2. Conversion of bicarbonate to C02 (via carbonic acid) permits rapid C02 reabsorption
3. Bicarbonate then regenerated from C02 within tubular cell and transported into interstitium
4. Sodium separately reabsorbed from lumen in exchange for H+
5. Carbonic anhydrase (CA), the enzyme required for bicarbonate reabsorption process on the brush border and in the cytoplasm, is the target of carbonic anhydrase inhibitor drugs



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CAI MECHANISM OF ACTION

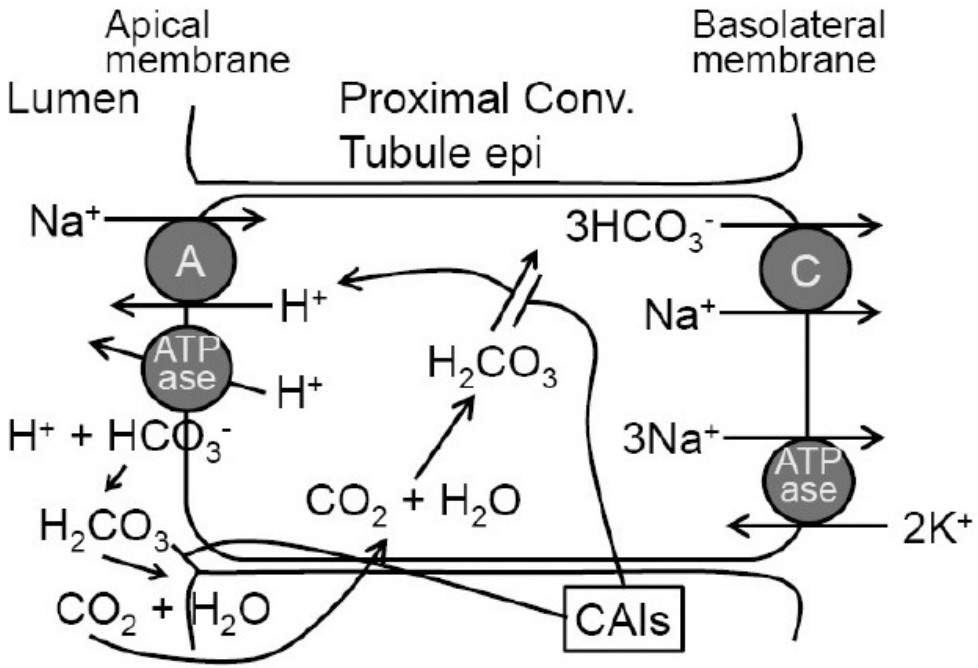
Inhibit Na+ reabsorption by inhibiting proximal tubule cytoplasmic carbonic anhydrase II and luminal carbonic anhydrase IV

- Noncompetitively and reversibly

Leads to increased delivery of Na^+ and $HCO3^-$ to more distal nephron segments

Much sodium bicarbonate initially excreted → acute decrease in plasma volume (diuresis)

- Diuretic effect diminished by compensatory mechanisms resulting in up-regulation of sodium bicarbonate reabsorption and by NaCl reabsorption across more distal nephron segments



ACTIVE LEARNING

Based on the mechanism of action of carbonic anhydrase inhibitors, which of the following adverse effects would you expect from their use? Explain your answer to a classmate.

A. Metabolic acidosis

B. Metabolic alkalosis

C. Respiratory acidosis

D. Respiratory alkalosis

ACTIVE LEARNING

Based on the mechanism of action of carbonic anhydrase inhibitors, which of the following adverse effects would you expect from their use? Explain your answer to a classmate.

A. **Metabolic acidosis**
   - Bicarbonate diuresis (excreted in large amounts) -> body depletion of bicarbonate -> metabolic acidosis

CAIs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Acetazolamide (Diamox)	**COPD (↑ risk of metabolic acidosis)** Avoid in severe renal impairment	**Metabolic acidosis** Proximal renal tubular acidosis Paresthesias **NH3 toxicity** **Sulfa allergy cross-reaction** Hypokalemia Promotes calcium phosphate stone formation	Increased urinary pH increases excretion of organic acid anions and decreases excretion of weak organic bases

CLINICAL USE

Glaucoma (eye drop formulation; reduces formation of aqueous humor and thus lowers intraocular pressure in treating open angle glaucoma)

Metabolic alkalosis

Altitude sickness (by offsetting respiratory alkalosis)

Idiopathic intracranial hypertension

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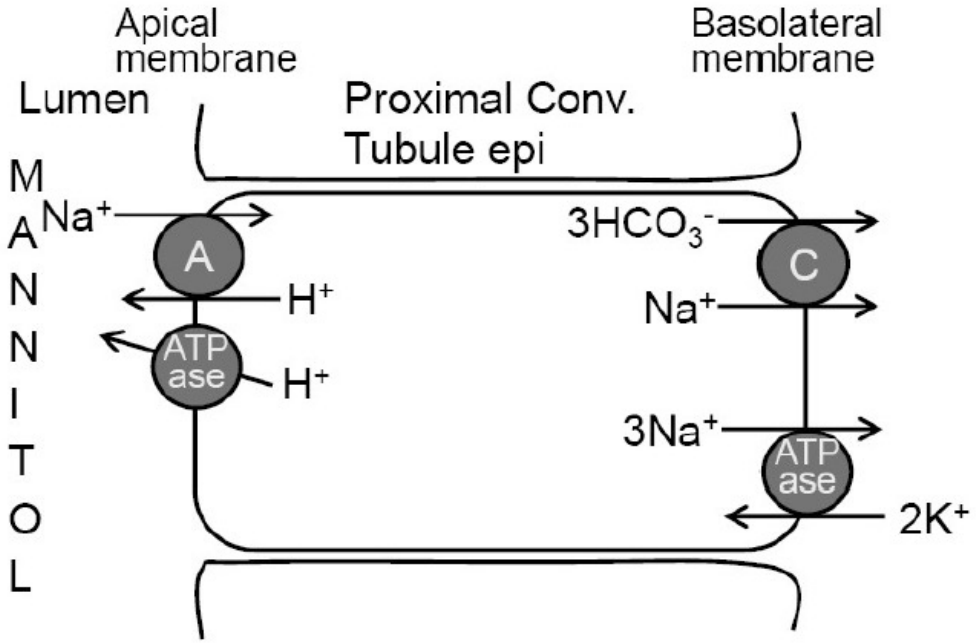
OSMOTIC DIURETICS

OSMOTIC DIURETIC MECHANISM OF ACTION

Small molecules filtered at glomerulus, but not reabsorbed in the nephron

Constitute an intraluminal osmotic force limiting reabsorption of water across water-permeable nephron segments

Effect most pronounced in loop of Henle and proximal tubule where most iso-osmotic water reabsorption takes place



OSMOTIC DIURETICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Mannitol	**Pulmonary congestion** (↑ extracellular volume → pulmonary edema) **Heart failure** (↑ extracellular volume → pulmonary edema) Severe renal disease (↓ GFR cannot dissipate initial ↑ in extracellular volume expansion)	Dehydration Hypo or hypernatremia Pulmonary edema	May increase nephrotoxicity of aminoglycosides

CLINICAL USE

Reduce intracranial pressure in neurological conditions

- ↓ in systemic vascular volume induced by mannitol → ↓ in cerebral intravascular volume
- ↑ in plasma osmolality contributes to movement of fluid from the brain

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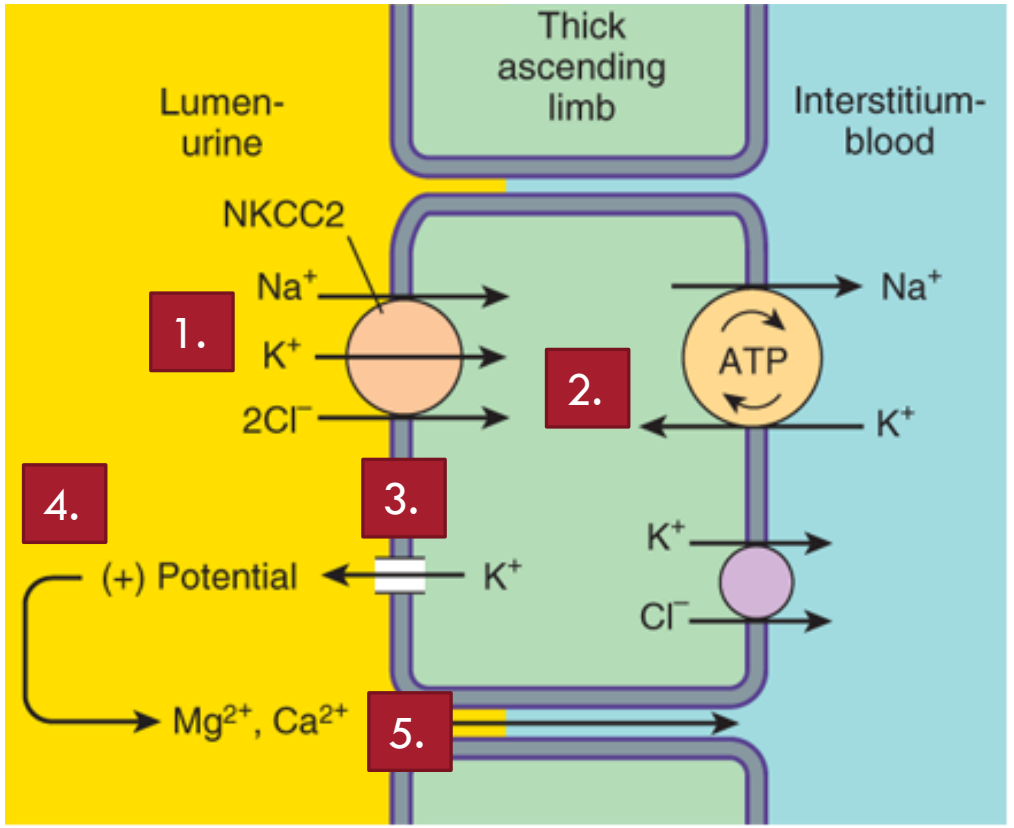
LOOP DIURETICS

NA REABSORPTION IN TAL OF LOOP OF HENLE

1. Na+ is reabsorbed through an apical Na+/K+/2Cl- cotransporter
   - Cotransporter provides part of concentration gradient for countercurrent concentrating mechanism in the kidney
2. K+ pumped into cell from luminal and basal sides
3. K+ escape route provided via potassium-selective channel
4. Because K+ diffusing through these channels is not accompanied by an anion, a net positive charge is set up in the lumen
5. Positive potential facilitates the reabsorption of calcium and magnesium



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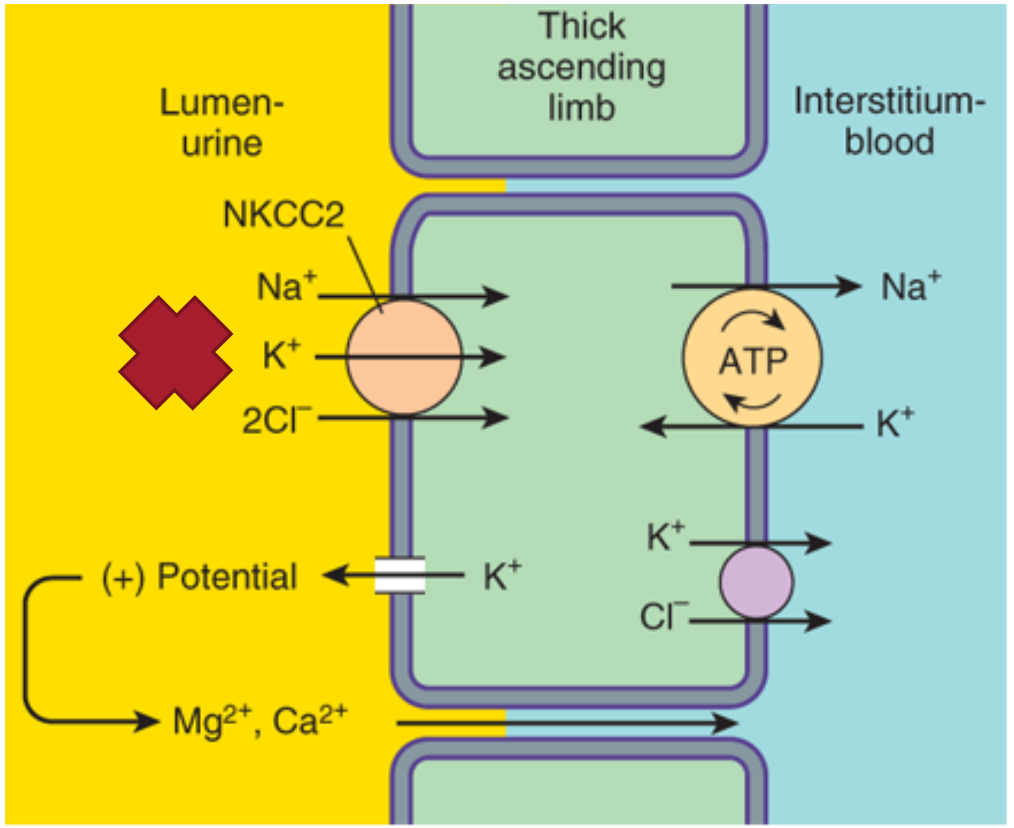
LOOP DIURETIC MECHANISM OF ACTION

Reversibly and competitively inhibit the Na+/K+/2Cl cotransporter → inhibiting Na+ reabsorption

- Compete for Cl- site

Abolishes positive charge (potential) → ↑ excretion of cations, particularly Mg++ and Ca++



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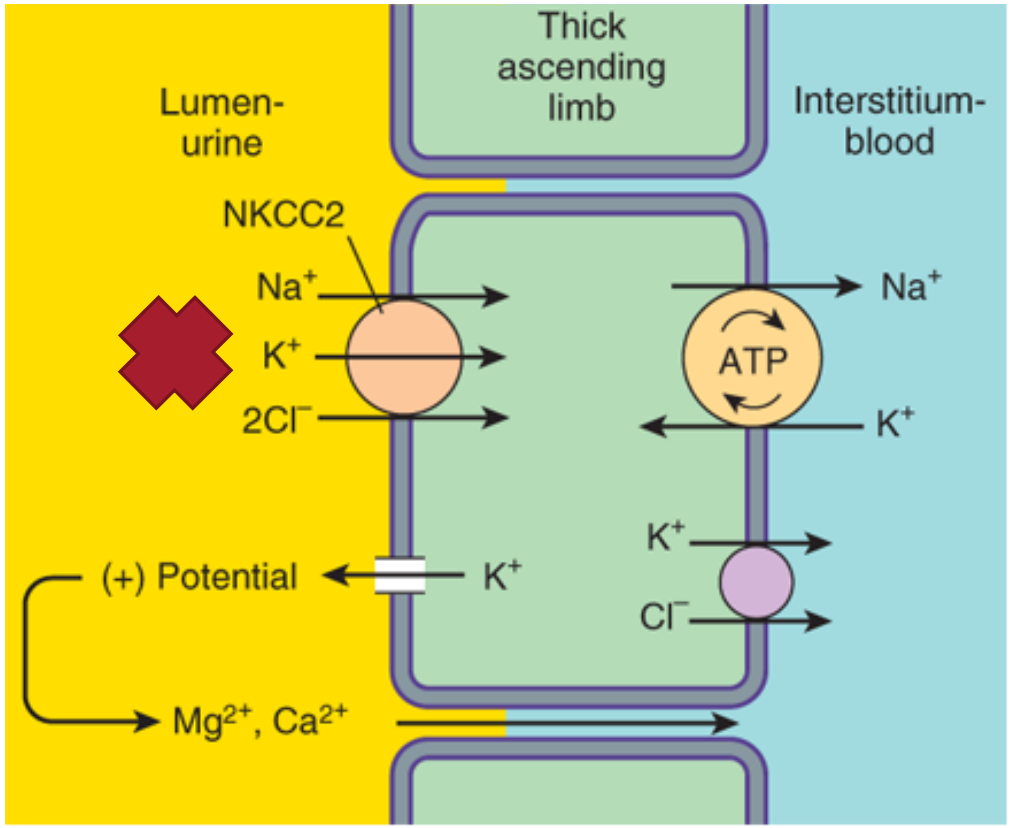
LOOP DIURETIC MECHANISM OF ACTION

Rise in tubular flow → ↑ amount of Na+ entering the distal tubule and collecting duct → ↑ Na+ reabsorption and the lumen negative potential favoring K+ secretion

↑ in Na+ reabsorption stimulates K+ uptake across the basolateral membrane by ↑ activity of the Na+/K+ ATPase → K+ secretion

20% of the filtered Na+ load is reabsorbed by the loop of Henle **and loops are the most effective diuretics**



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LOOP DIURETICS (-IDE)

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Furosemide (Lasix) Bumetanide (Bumex) Torsemide ***-ide***	Patients with hypersensitivity to sulfonamide derivatives	**Ototoxicity** **Hypokalemia** **Hypomagnesemia** **Hypocalcemia** Dehydration **Metabolic alkalosis** Nephritis Gout Decreased glucose tolerance **Sulfa allergy cross-reaction with furosemide**	**Aminoglycosides (synergism of ototoxicity)** NSAIDs can decrease effectiveness of loop diuretics May decrease efficacy of oral hypoglycemics

ACTIVE LEARNING

Create a mnemonic device to help you remember adverse effects of loop diuretics.

CLINICAL USE

Edematous states (heart failure, cirrhosis, nephrotic syndrome, pulmonary edema)

Hypertension

Hypercalcemia

Hyperkalemia caused by potassium-retaining drugs or renal insufficiency with impaired potassium excretion

Hyponatremia

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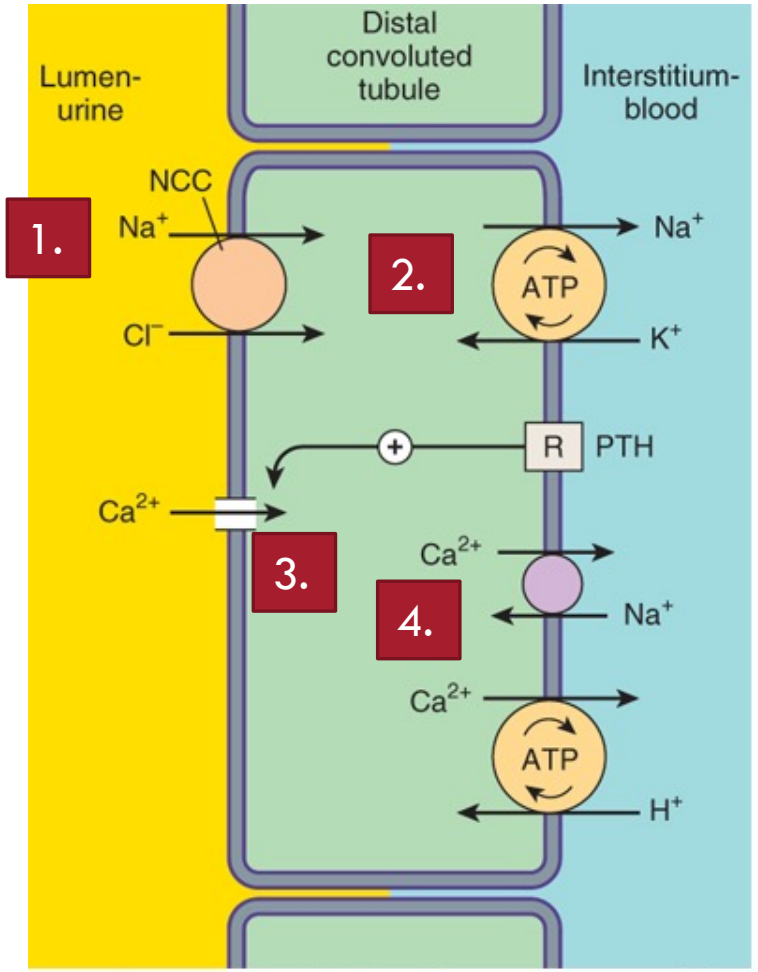
THIAZIDE DIURETICS

NA REABSORPTION IN DISTAL CONVOLUTED TUBULE

1. Na+ enters the epithelial cells via the Na+/Cl- cotransporter (NCC).
2. Basolateral exit of Na+ is mediated by Na+/K+ ATPase. Basolateral exit of Cl- occurs via Cl- channels.
3. Ca++ and Mg++ reabsorption occurs through channels in the apical membrane (only Ca++ channel shown)
4. Ions cross basolateral membrane via specific exchangers (only Ca++/Na+ exchanger shown) and by ATPases



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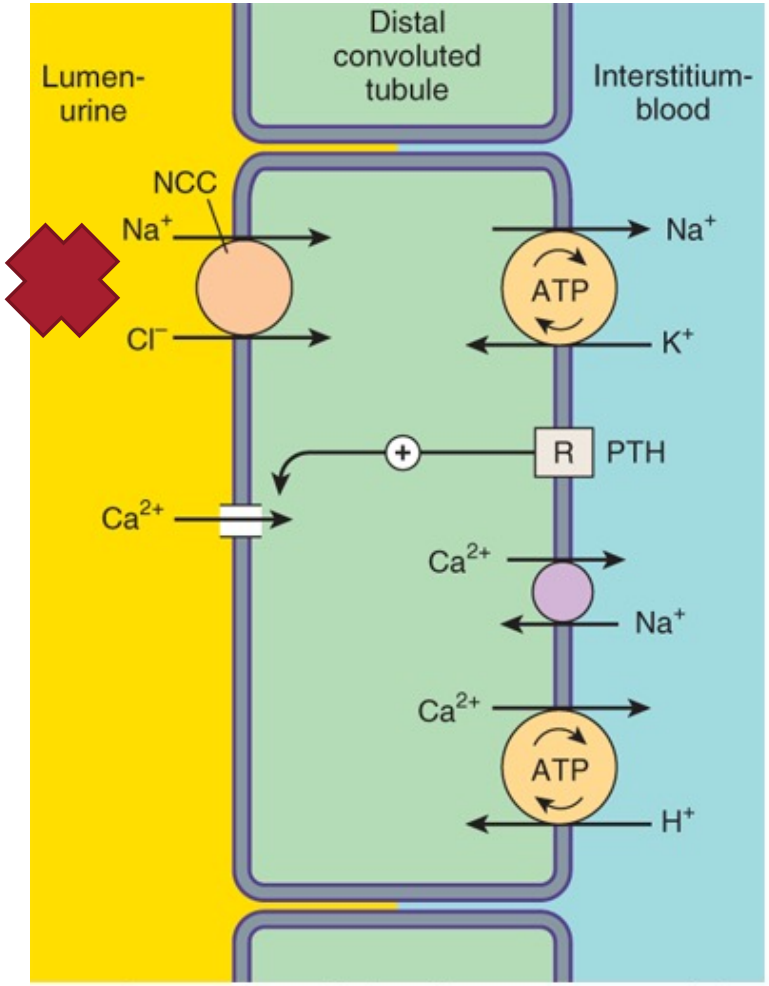
THIAZIDE DIURETIC MECHANISM OF ACTION

Competitive antagonists of the Na+/Cl- cotransporter

Promote transcellular reabsorption of calcium (may be due to increased expression of Ca++ channels and the Ca++/Na+ exchanger)



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ACTIVE LEARNING

Based on the mechanism of action of thiazide diuretics, how would you expect them to impact serum:

- Sodium
- Potassium
- Calcium

ACTIVE LEARNING

Based on the mechanism of action of thiazide diuretics, how would you expect chronic use to impact serum:

- Sodium
  - Inhibit NaCl reabsorption → hyponatremia
- Potassium
  - Potassium wasting → hypokalemia
    - Increased Na load presented to collecting tubules and cortical collecting tubules compensate by reabsorbing Na and excreting potassium
- Calcium
  - Increase transcellular reabsorption of calcium → hypercalcemia

THIAZIDE DIURETICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Hydrochlorothiazide (HCTZ) Chlorthalidone Metolazone	Hypersensitivity to sulfonamide derivatives Anuria	**Hypokalemic metabolic alkalosis** Hyponatremia **Hyperglycemia** Hyperlipidemia **Hyperuricemia** Hypercalcemia **Sulfa allergy cross-reaction**	Oral hypoglycemics (decreased effect of oral hypoglycemics) NSAIDs (decrease the efficacy of thiazides) Loop diuretics (synergistic effect when combined with a thiazide diuretic)

CLINICAL USE

Hypertension

Heart failure (in combination with loop diuretics)

Diminish hypercalciuria in patients at risk for nephrolithiasis

Nephrogenic diabetes

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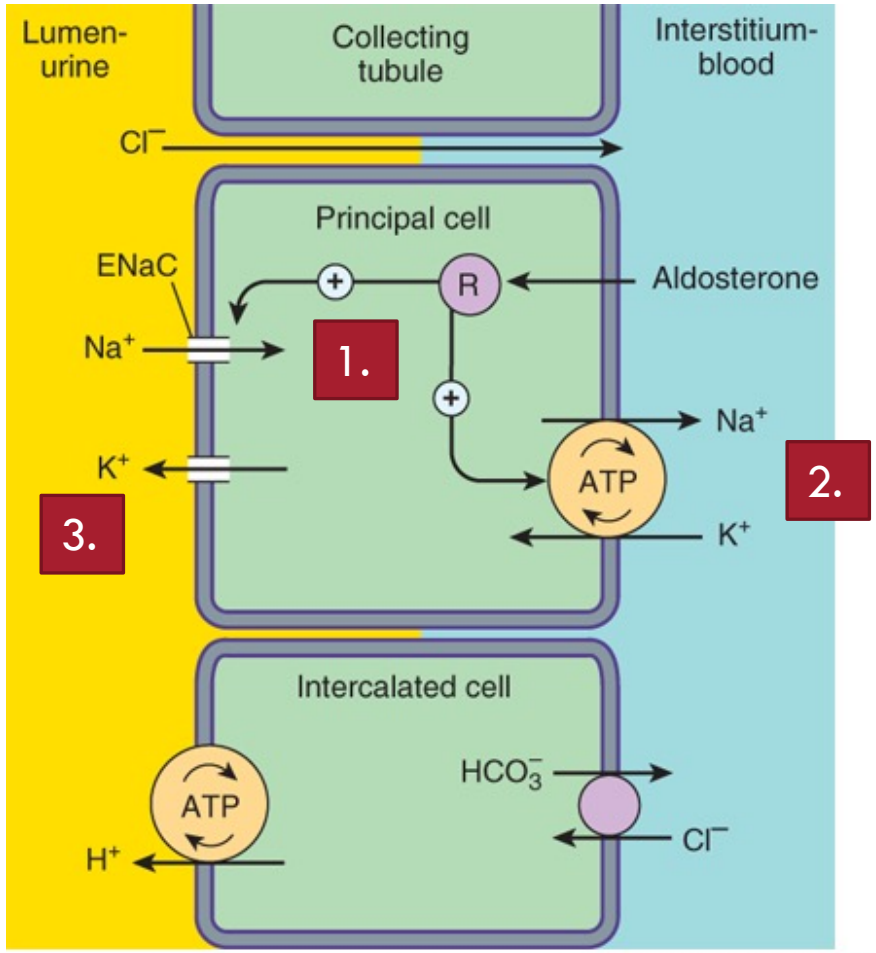
POTASSIUM-SPARING DIURETICS

NA REABSORPTION IN COLLECTING DUCT

1. Luminal Na+ enters the principal cell via a Na+ channel
2. Na+ exits the basolateral membrane via a Na+/K+ ATPase
3. Collecting duct cells express apical K+ channels that allow K+ to exit into the lumen

Expression of Na+ channels and Na+/K+ ATPase is **modulated by aldosterone**



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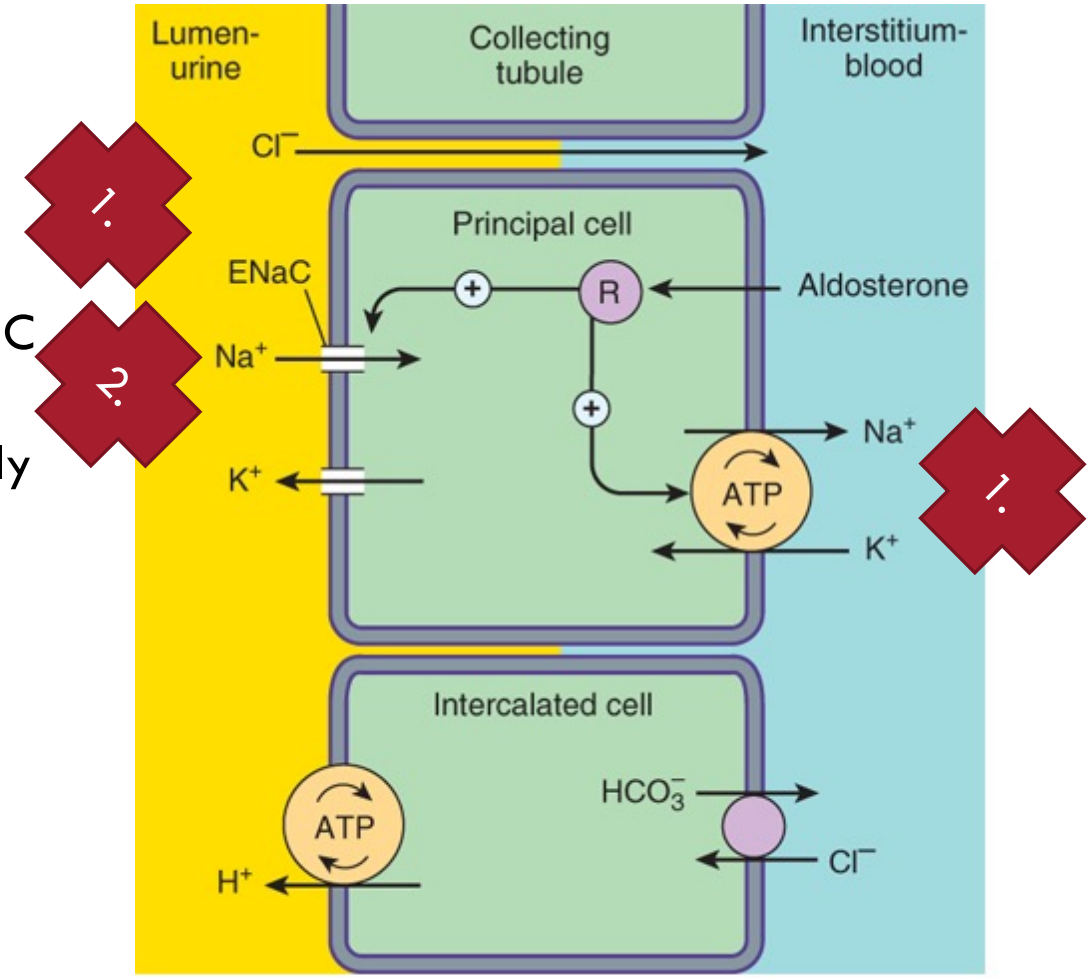
POTASSIUM-SPARING DIURETIC MECH OF ACTION

1. **Spironolactone and eplerenone** antagonists of aldosterone in collecting tubules
   1. Antagonizing aldosterone → ↓ expression of genes that code for ENaC and Na+/K+ ATPase
2. **Amiloride and triamterene** competitively inhibit apical membrane Na+ channel

Potassium-sparing diuretics decrease K+ excretion by decreasing the lumen negative potential and thus decreasing the driving force for K+

Proton secretion also diminished by the decrease in Na+ uptake



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POTASSIUM-SPARING DIURETICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Amiloride Triamterene	Anuria Hyperkalemia Concurrent use of potassium-sparing drugs, potassium supplements, ARBs, or ACEIs	**Hyperkalemia** **Metabolic acidosis**	Concurrent use of these drugs with other potassium-sparing diuretics, potassium supplements, ARBs, or ACEIs can increase the risk of hyperkalemia NSAIDs can decrease effectiveness
Spironolactone Eplerenone (***Aldosterone antagonists)*** ***-one***		Same as above PLUS **Endocrine effects (gynecomastia, antiandrogen effects, impotence)**	

Boxed warning for amiloride and triamterene: potentially fatal elevation of potassium

ACTIVE LEARNING

How might the potassium-sparing effects of potassium-sparing diuretics be useful in combination with other diuretics?

CLINICAL USE

Potentiate action of more proximally acting diuretics

Potassium depletion (counteracts K+ wasting of thiazide and loop diuretics)

Spironolactone/eplerenone
- Hypertension
- Hyperaldosteronism
- Heart failure
- Ascites/edema associated with impaired protein biosynthesis secondary to hepatic failure
- Hypokalemic alkalosis

Amiloride
- Hypertension
- Lithium-induced nephrogenic diabetes insipidus

Triamterene
- Edema

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RELATIVE EFFICACY OF DIURETICS

Diuretics

ACTION SITE & RELATIVE EFFICACY OF DIURETICS

Diuretic Class	Site of Action	% Na+ Reabsorbed	Relative Efficacy *(higher = more efficacious)*
Carbonic anhydrase inhibitors	Proximal tubule	65%	2
Loop	Thick ascending limb of Loop of Henle	25 - 35%	15
Thiazide	Distal tubule	2 - 10%	5
Potassium-sparing	Collecting duct	1 - 5%	1

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SUMMARY OF CLINICAL USES

Diuretics

MANAGEMENT OF EDEMA

Clinical Situation	Abbreviated Cause	Diuretics Used
Nephrotic syndrome	Primary cause is glomerular dysfunction Enhanced Na+ retention	Spironolactone Loop Thiazide
Heart failure	Increased aldosterone synthesis/secretion Increased collecting duct Na+ reabsorption	Spironolactone Loop (acute setting to reduce extent of pulmonary edema)
Cirrhosis	Ascites → ↓ intravascular volume → ↓ cardiac output → ↑ Na+ retention	Spironolactone Loop Thiazide

NON-DIURETIC USES

CAIs	Osmotic	Loop	Thiazide	Potassium-Sparing
▪ Acute mountain sickness ▪ Glaucoma ▪ Restore acid-base balance in heart failure patients with metabolic alkalosis caused by loop diuretics	▪ Reduce intracranial pressure in neurological conditions	▪ Hypercalcemia ▪ Hyponatremia (administered with hypertonic saline) ▪ Counteract hyperkalemia caused by potassium-retaining drugs or renal insufficiency with impaired K+ excretion	▪ Hypertension ▪ Nephrolithiasis ▪ Nephrogenic diabetes insipidus ▪ Counteract hyperkalemia caused by potassium-retaining drugs or renal insufficiency with impaired K+ excretion	▪ Lithium-induced nephrogenic diabetes insipidus (amiloride) ▪ Counteract the potassium wasting of thiazide and loop diuretics

ELECTROLYTE CHANGES WITH DIURETICS

Diuretic	Amount in Urine			Body pH
	NaCl	NaHCO3	K+	
CAIs	↑[a]	↑[a]	↑[a]	Acidosis[b]
Loop	↑↑↑↑	↑↑↑↑	↑	Alkalosis
Thiazide	↑↑	↑↑	↑	Alkalosis
K+-sparing	↑	↑	↓	Acidosis

[a] self-limited (2-3 days)
[b] not self-limited

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ANY QUESTIONS?