GENITOURINARY SYSTEM

SUBJECT : Pharmacology

LEC NO. : 1

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وقل رب زدني علماً

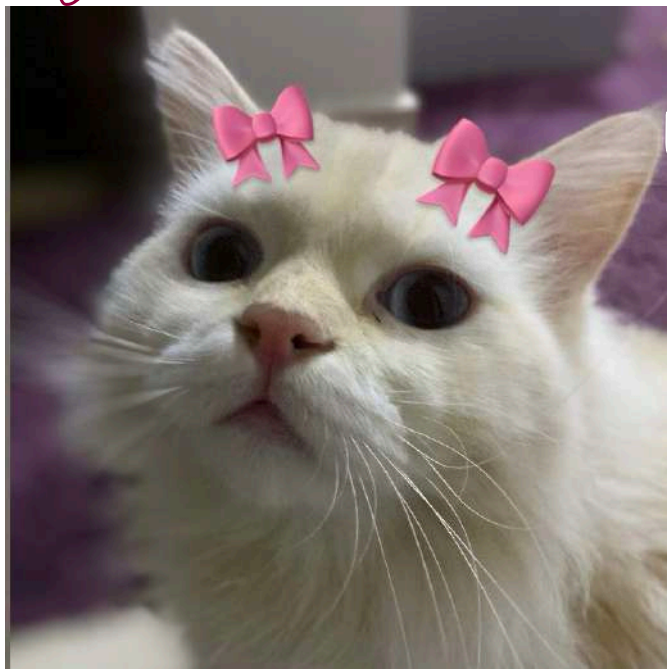
Genitourinary System Module

Pharmacology

Diuretics (1)

Faculty of Medicine
The Hashemite University

Say Hi to Snowy :-) !



Intro

Diuretics are drugs that increase H_2O + Na^+ excretion in urine.

→ so eventually the urine amount or volume increases & their concentration in blood decreases.

Diuretics: Overview

- Diuretics promotes excretion of water and electrolytes by the kidneys
- Increase the rate of urine flow and the 24h-urine volume
- Most diuretic acts 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.
- They often change urine pH and ionic composition of urine and blood
- Indications: edema, hypertension, glaucoma, heart failure.

MOA:

Result:

→ acid-base imbalance

↳ Leads to edema either

Diseases to treat:

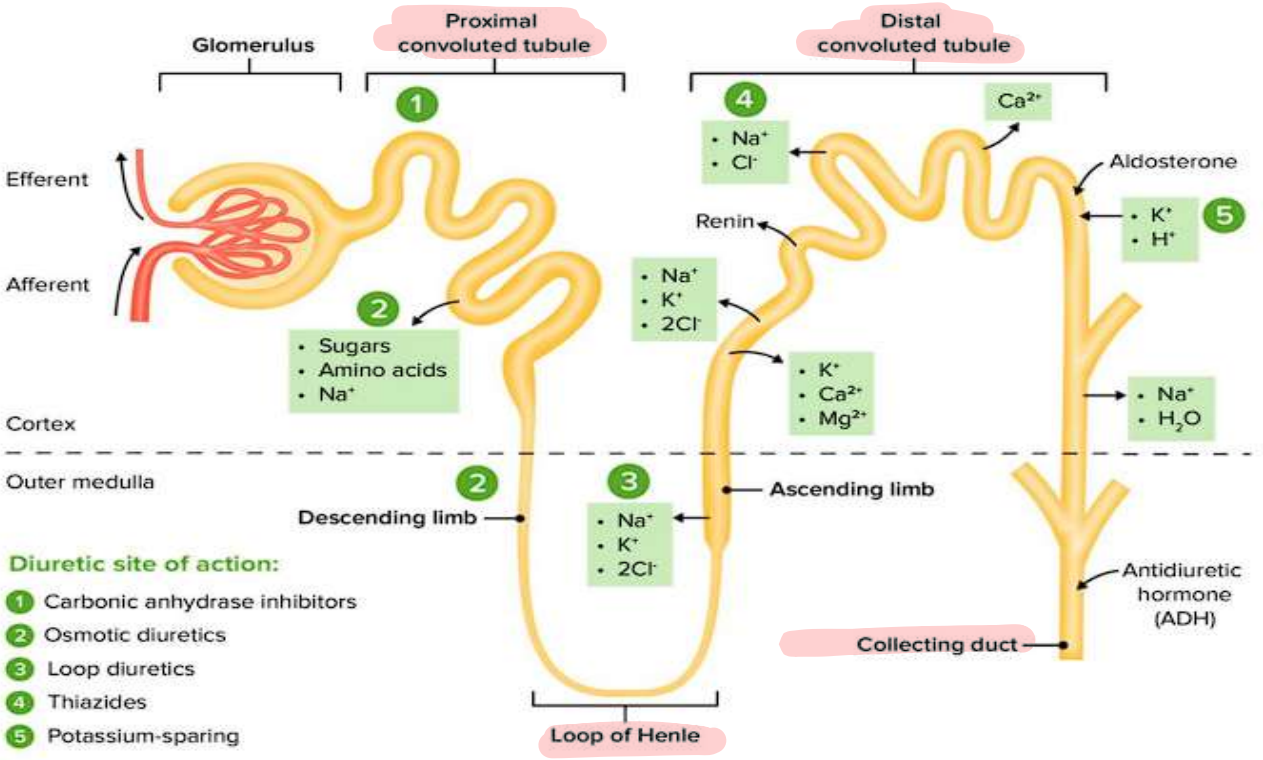
MOAs:

Diuretics: Classes

- Thiazides → inhibits Na^+/Cl^- cotransporter / Distal convoluted tubule
- Loop diuretics → Reduces $Na^+ + Cl^-$ Reabsorption in the thick ascending limb – Loop of Henle.
- Potassium sparing diuretics → 2 MOA → Interfering with Na^+/K^+ exchange / DCT
  → Antagonising the Aldosterone receptor
- Carbonic anhydrase inhibitors → Inhibiting the Carbonic Anhydrase enzyme
- Mannitol (Osmotic Diuretics) → inhibit H_2O Reabsorption

- (***will be discussed according to the frequency of their use***)

Site of action



16% to 20% of the blood plasma entering the kidneys is filtered into Bowman's capsule. The filtrate, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na + , K+ , and Cl− . The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water

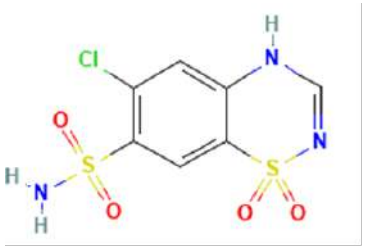
Thiazides

- Thiazides are the most widely used diuretics because of their antihypertensive effects.
- They are sulfonamide related organic acids that do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials

imp

Thiazides:

- Chlorothiazides
- Hydrochlorothiazide



Chlorothiazides

Thiazide-like diuretics:

- Chlorthalidone
- Indapamide
- Metolazone

Mechanism

PCT

➢ **Secreted into the proximal tubule by an organic secretory mechanism**. (Thiazides compete for the same secretory process by which uric acid is secreted into the proximal tubule). Receptor competetion between both

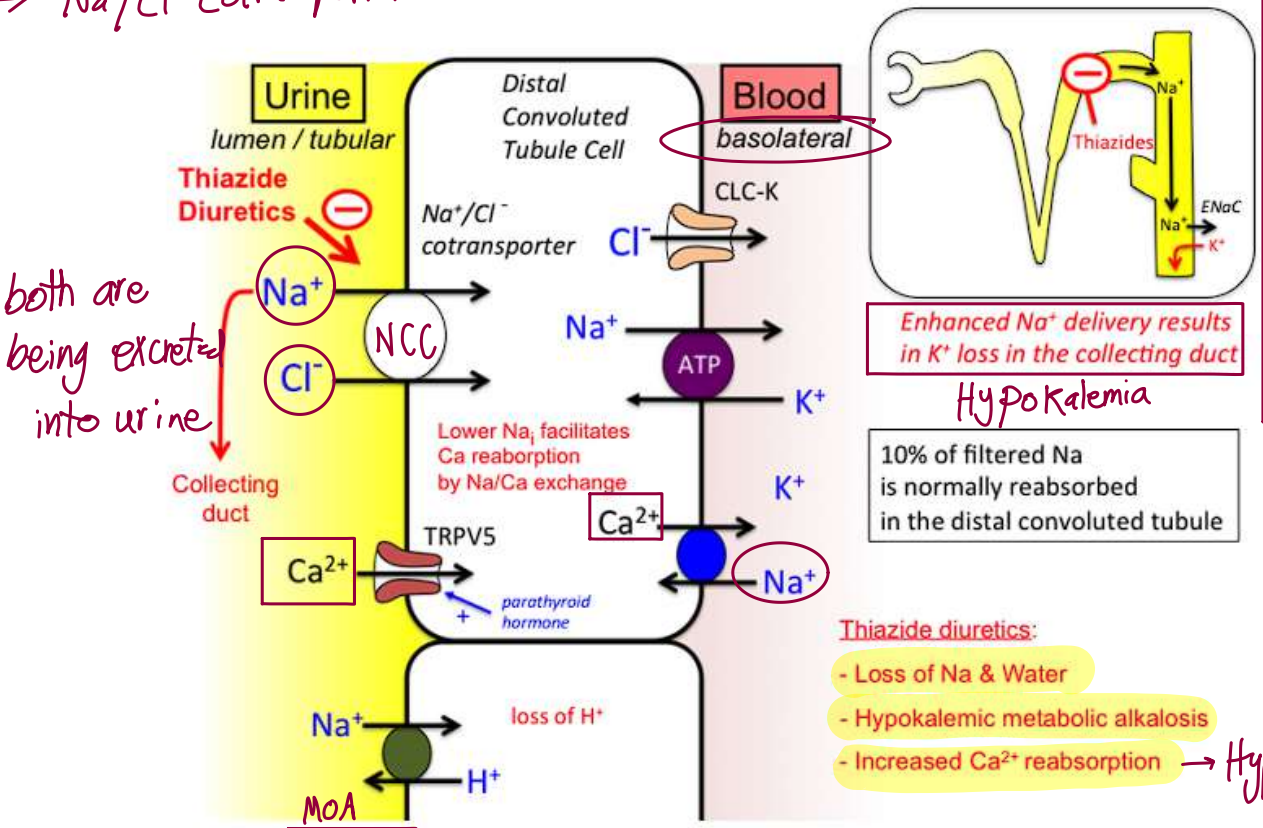
MOA → ➢ They block the sodium-chloride (Na/Cl) channel expressed in the proximal segment of the distal convoluted tubule (DCT), resulting in increased excretion of Na,Cl ions. ← Result

➢ Thiazides enhance Ca2+ reabsorption in the distal convoluted tubule, by increasing Na+/Ca2+ exchange. Thiazide diuretics also reduce the urinary excretion of Ca2+.

➢ Natriuresis (excretion of sodium in the urine) may be accompanied by some loss of potassium and H+.

while the nephron [DCT] is eliminating the Na/Cl it'll be reabsorbing Ca^{+2} ⟶ So: increased Ca^{+2} levels in blood (Hypercalcemia) + increased Na^{+}/Cl^{-} in urine (decreased circulating Na^{+})

NCC → Na^+/Cl^- cotransporter



both are being excreted into urine

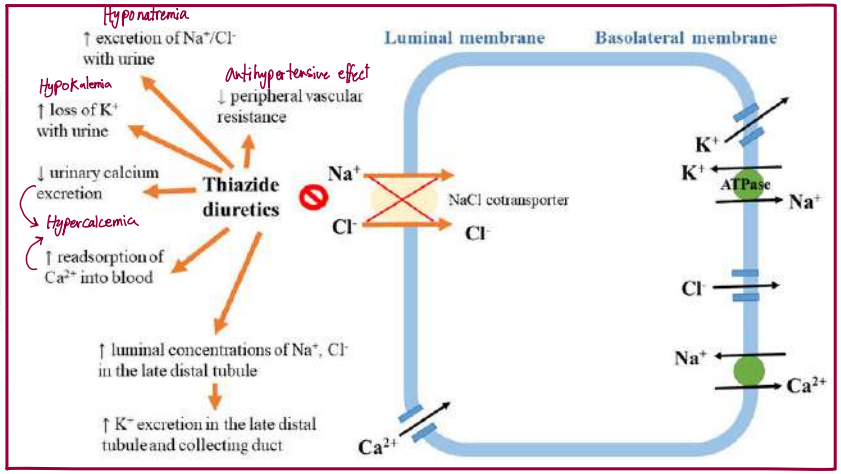
Enhanced Na^+ delivery results in K^+ loss in the collecting duct

Hypokalemia

10% of filtered Na is normally reabsorbed in the distal convoluted tubule

Thiazide diuretics:

- Loss of Na & Water
- Hypokalemic metabolic alkalosis
- Increased Ca^{2+} reabsorption → Hypercalcemia



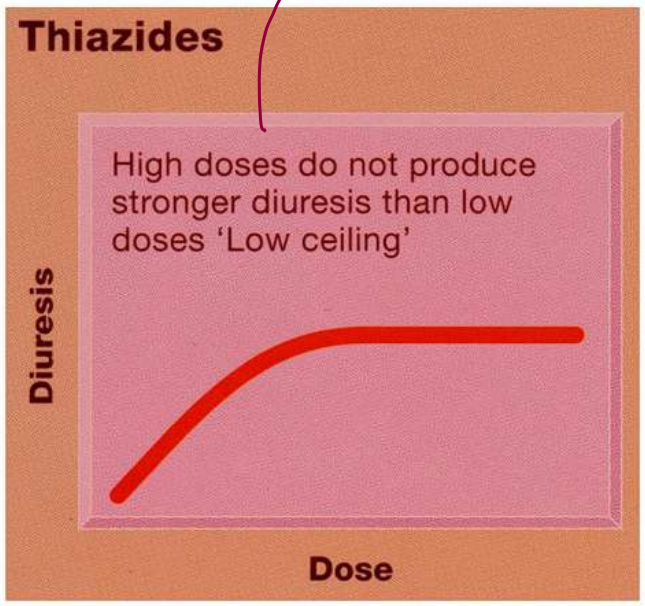
Thiazide diuretics compete for the chloride binding site on the Na/Cl cotransporter that is selectively expressed in the distal convoluted tubule, inhibiting its ability to transport ions. Inhibition of this cotransporter lowers intracellular Na, which in turn results in a lowering of intracellular calcium mediated by Na/Ca exchange expressed on the basolateral membrane. This facilitates the diffusion of calcium through calcium ion channels expressed on the lumen membrane. The inhibition of Na transport in this segment results in greater delivery of sodium to the collecting duct, where enhanced Na influx through epithelial Na channels stimulates potassium efflux, which can result in the development of Hypokalemia + Hypomagnesemia

Thiazides are ‘low ceiling diuretics’

Which means that Thiazides reach the peak response/plateau at low or high doses it bring the same effect.

Thiazides have moderate efficacy as diuretics, as 90% of glomerular filtrate has already been reabsorbed.

The dose-response curve flatten rapidly



Pharmacokinetics

- Thiazides are effective orally with bioavailability of 60%–70%, (except for chlorothiazide is given IV due its low bioavailability (15-30%)

- Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure it takes time for it's antihypertensive effect to appear.

- exhibit a prolonged half-life (approximately 10 to 15 hours).

جطلع متل ما دخل

- Excretion: unmodified in the urine ((except indapamide it undergoes hepatic metabolism and is excreted in both urine and bile))

Therapeutic uses

1. Hypertension: 1st line drugs for uncomplicated hypertension. They have low cost and well tolerated

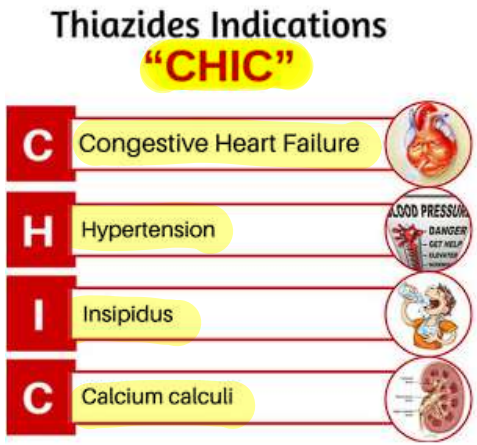
An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, blood volume returns to baseline. However, antihypertensive effects continue, resulting from reduced total peripheral vascular resistance (unclear mechanism).

2. Heart failure: Loop diuretics are the diuretics of choice for reducing extracellular volume in heart failure. However, thiazide diuretics can be added to patients with resistance to loop diuretics. It requires careful monitoring of hypokalemia.

Therapeutic uses

1. Hypercalciuria: used in idiopathic hypercalciuria and calcium oxalate stones in the urinary tract, because they inhibit urinary Ca 2+ excretion. → Result in Hypercalcemia

2. Nephrogenic Diabetes insipidus: caused by the collecting ducts not responding to ADH. Patients present with polyuria (increased urination rate)and polydipsia (increased thirst). The paradoxical effect of diuretics in reducing urine output is not clear. The urine volume of such individuals may drop from 11 to about 3 L/d when treated with thiazides.



Side effects

- Hypokalemia: the most frequent problem with the thiazide diuretics. serum K+ should be measured periodically (more frequently at the beginning of therapy). Potassium supplementation or combination with a potassium-sparing diuretic may be required. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.
- Hypomagnesemia
- Hyponatremia
- Hypovolemia: This can cause orthostatic hypotension or light-headedness.

Recent pt on Thiazides should be more monitored than old ones.

while continuing Thiazides

they trap K^+ in blood resulting in Hyperkalemia

↓ blood Mg^{+2} / ↑ urine Mg^{+2}

↓ blood Na^+ / ↑ urine Na^+

Low Blood pressure

dizzines

Side effects

monitoring is imp.

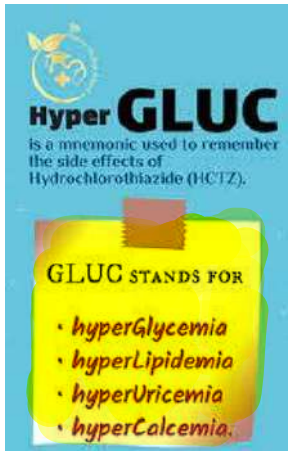
- Hyperglycemia possibly due to impaired release of insulin related to hypokalemia. Patients with diabetes still benefit from thiazide therapy, but should monitor glucose to assess the need for an adjustment in diabetes therapy if thiazides are initiated.

- Hyperlipidemia: Dyslipidemia can by produced by high doses of thiazides (not typically used).

- Hyperuricemia (Why?) uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

→ Bcuz Thiazides competes with uric acid in the same secretory process.

- Hypercalcemia ↑ blood Ca^{+2}



Thiazide efficacy

- Drug and diseases that affects thiazides efficacy:

1-Renal failure and heart failure: results in decreased renal blood flow, which reduces the diuretic effects as thiazides must be secreted into the proximal tubule to be effective.

PG's function: dilation of Afferent a. to Glomeruli so GFR increases

2-Concomitant use of NSAIDs inhibits the production of prostaglandins, which (eventually) inhibits renal blood flow.

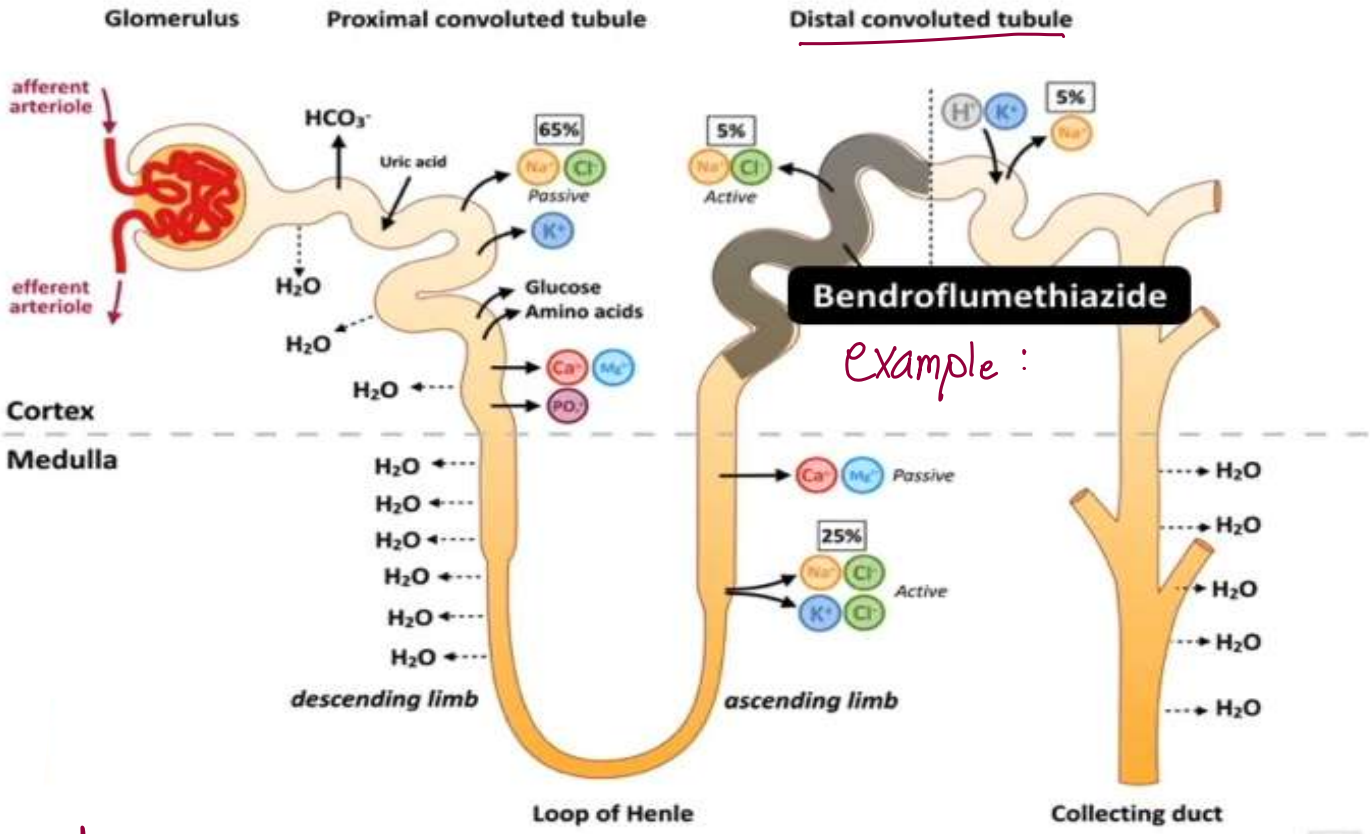
Both depended on RBF so if those diseases affected it there won't be a good/normal Thiazides effects.

- Lithium: thiazide reduces renal clearance of lithium and can cause rapid increase in lithium serum level.

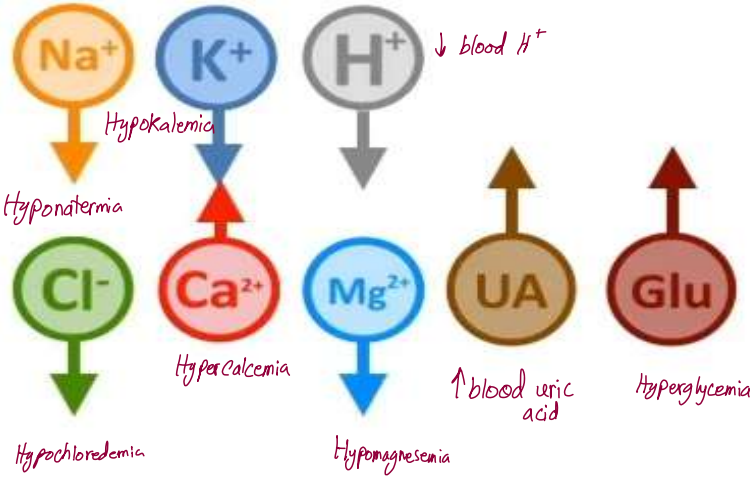
Lithium is a poison which is excreted Renally, since Thiazides are working in the kidney it'll lower it's excretion.

Summary

DCT

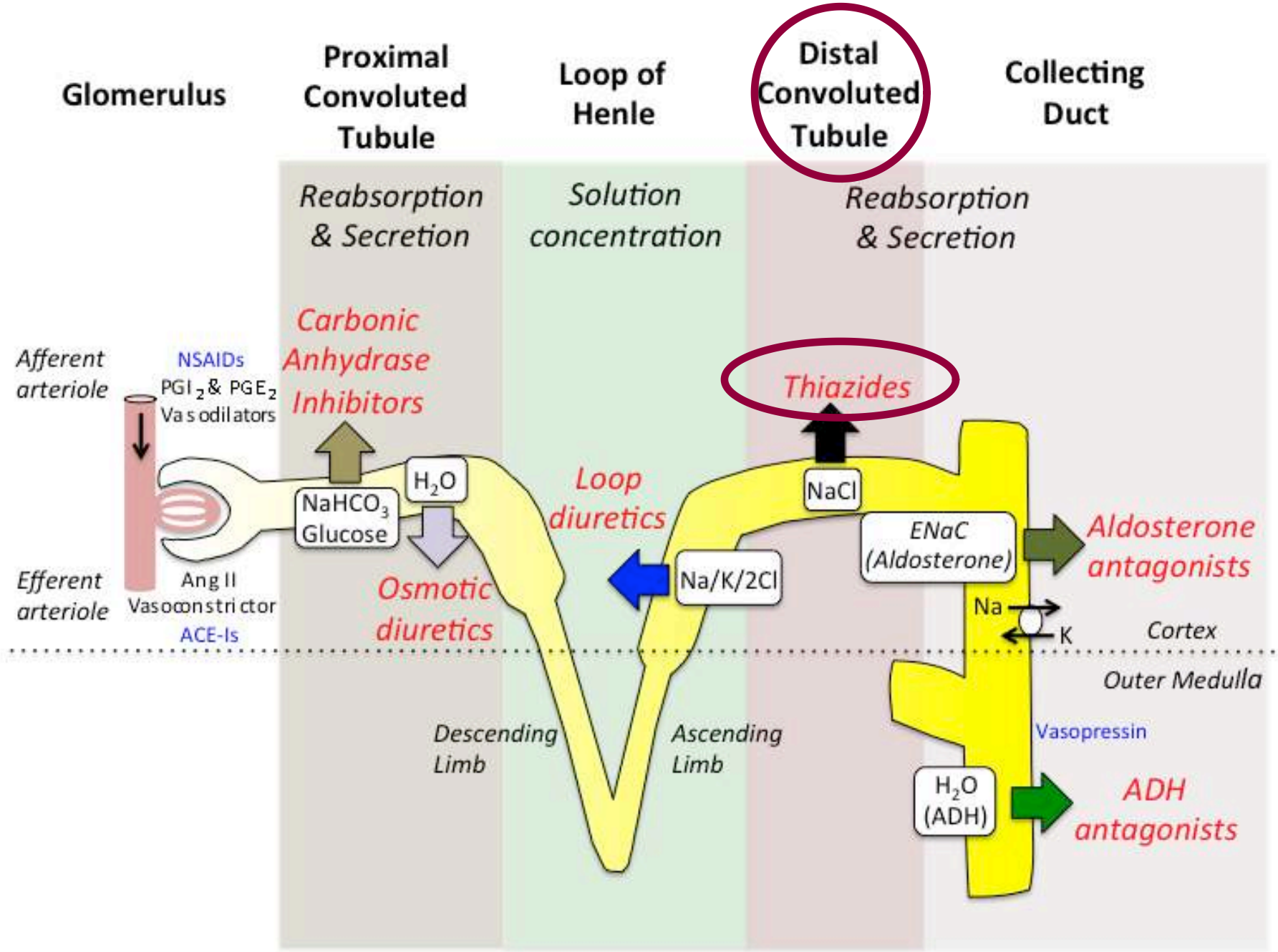


adverse effects in blood.



Note I know we haven't taken "Loop Diuretics" yet but you can revise & differentiate Thiazides here.

	Loop diuretics	Thiazides
Mechanism of action	Inhibit NaK_2Cl cotransporter in asc.LOH	Inhibit NaCl symport in DCT
Efficacy	More	Less
Renal failure	Used	Not used
Effect on calcium	Hypocalcaemia	Hypercalcemia (preferred in osteoporosis)
Ototoxicity	Present	Absent
Nephrogenic diabetes insipidus	Not used	Used


Glomerulus
Proximal Convoluted Tubule
Loop of Henle
Distal Convoluted Tubule
Collecting Duct
Reabsorption & Secretion
Solution concentration
Reabsorption & Secretion
Carbonic Anhydrase Inhibitors
Thiazides
Afferent arteriole
NSAIDs
PGI2 & PGE2
Vasodilators
NaHCO3
Glucose
H2O
Loop diuretics
NaCl
ENaC (Aldosterone)
Aldosterone antagonists
Na/K/2Cl
Efferent arteriole
Ang II
Vasoconstrictor
ACE-Is
Osmotic diuretics
Na
K
Cortex
Outer Medulla
Descending Limb
Ascending Limb
Vasopressin
H2O (ADH)
ADH antagonists

Lippincott

NOT all Lippincott material put here are required, only for you to check them if needed :3

III. THIAZIDES

The thiazides are the most widely used diuretics because of their antihypertensive effects. However, the efficacy of thiazides for hypertension is not entirely dependent on their diuretic actions. These agents also reduce peripheral vascular resistance with long-term therapy. Despite being sulfonamide derivatives, thiazides do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials such as *sulfamethoxazole*. All thiazides affect the distal convoluted tubule (Figure 17.2), and 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.

A. Thiazides

Chlorothiazide [klor-oh-THYE-ah-zide] was the first orally active thiazide, although *hydrochlorothiazide* [hye-dro-klor-oh-THYE-ah-zide] and *chlorthalidone* [klor-THAL-i-done] 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. In all other aspects, *hydrochlorothiazide* resembles *chlorothiazide*. *Chlorthalidone* is approximately twice as potent as *hydrochlorothiazide*. *Chlorthalidone*, *indapamide* [in-DAP-a-mide], and *metolazone* [me-TOL-ah-zone] are referred to as thiazide-like diuretics because they lack the characteristic benzothiadiazine chemical structure; however, their mechanism of action, indications, and adverse effects are similar to those of *hydrochlorothiazide*.

1. **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 (Figure 17.5). 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 (Figure 17.3). Therefore, decreasing renal function reduces the diuretic effects. The antihypertensive effects of thiazides may persist even when the glomerular filtration rate is below 30 mL/min/1.73 m^2. However, hypertension at this level of renal dysfunction is often exacerbated by hypervolemia, requiring a change to loop diuretics for volume status and, therefore, blood pressure control. The efficacy of thiazides may be diminished with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as *indomethacin*, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

2. **Actions**

   a. **Increased excretion of Na^+ and Cl^-:** Thiazide and thiazide-like diuretics cause diuresis with increased Na^+ and Cl^- excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to produce a hyperosmolar urine. Figure 17.7 outlines relative changes in the ionic composition of the urine with thiazide and thiazide-like diuretics.

   b. **Decreased urinary calcium excretion:** Thiazide and thiazide-like diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+} in the distal convoluted tubule where parathyroid hormone regulates reabsorption.

   c. **Reduced peripheral vascular resistance:** An initial reduction in blood pressure results from a decrease in blood volume and,

causing the retention of K^+. These agents are often given in conjunction with thiazide or loop diuretics to prevent K^+ excretion that occurs with those diuretics.

c. **Heart failure:** Aldosterone antagonists are employed at lower doses to prevent myocardial remodeling mediated by aldosterone. Use of these agents has been shown to decrease mortality associated with heart failure, particularly in those with reduced ejection fraction.

d. **Resistant hypertension:** Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.

e. **Polycystic ovary syndrome:** *Spironolactone* is often used off-label for the treatment of 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.

4. **Pharmacokinetics:** Both *spironolactone* and *eplerenone* are well absorbed after oral administration. S*pironolactone* is extensively metabolized and converted to several active metabolites, which contribute to the therapeutic effects. *Eplerenone* is metabolized by cytochrome P450 3A4.

5. **Adverse effects**

a. **Hyperkalemia:** The most common side effect, hyperkalemia, is dose-dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.

b. **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 [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block epithelial sodium channels, 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 to block the Na^+/K^+-exchange site in the collecting tubule does not depend on the presence of aldosterone. Like the aldosterone antagonists, these agents are not very efficacious diuretics. Both *triamterene* and *amiloride* are commonly used in combination with other diuretics, almost solely for their potassium-sparing properties.

Lippincott Qs

Study Questions

Choose the ONE best answer.

17.1 An elderly patient with a history of heart disease has difficulty breathing and is diagnosed with acute pulmonary edema. Which treatment is indicated?

A. Acetazolamide
B. Chlorthalidone
C. Furosemide
D. Spironolactone

Correct answer = C. This is a potentially fatal situation. It is important to administer a diuretic that reduces fluid accumulation in the lungs and improves oxygenation and heart function. The loop diuretics are most effective in removing large fluid volumes from the body and are the treatment of choice in this situation. In this situation, furosemide should be administered intravenously. The other choices are inappropriate.

17.2 A group of college students is planning a mountain climbing trip to the Andes. Which is most appropriate for them to take to prevent altitude sickness?

A. A thiazide diuretic such as hydrochlorothiazide
B. An anticholinergic such as atropine
C. A carbonic anhydrase inhibitor such as acetazolamide
D. A loop diuretic such as furosemide

Correct answer = C. Acetazolamide is used prophylactically for several days before an ascent above 10,000 feet. This treatment prevents the cerebral and pulmonary problems associated with altitude sickness as well as other difficulties, such as nausea.

17.3 An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, which should be prescribed?

A. Acetazolamide
B. Chlorthalidone
C. Furosemide
D. Spironolactone

Correct answer = D. Spironolactone is very effective in the treatment of hepatic edema. These patients are frequently resistant to the diuretic action of loop diuretics, although a combination with spironolactone may be beneficial. The other agents are not indicated.

17.4 A 55-year-old male with kidney stones needs a medication to decrease urinary calcium excretion. Which diuretic is best for this indication?

A. Torsemide
B. Hydrochlorothiazide
C. Spironolactone
D. Triamterene

Correct answer = B. Hydrochlorothiazide is effective in increasing calcium reabsorption, thus decreasing the amount of calcium excreted, and decreasing the formation of kidney stones that contain calcium phosphate or calcium oxalate. Furosemide increases the excretion of calcium, whereas the K^+-sparing diuretics, spironolactone, and triamterene do not have an effect.

17.5 A 75-year-old woman with hypertension and glaucoma is being treated with chlorthalidone, amlodipine, lisinopril, and acetazolamide. In clinic today, she complains of acute joint pain and redness in her great toe, which is diagnosed as gout. Which medication is most likely to have caused the gout attack?

A. Amlodipine
B. Acetazolamide
C. Chlorthalidone
D. Lisinopril

Correct answer = C. Thiazides such as chlorthalidone compete with uric acid for secretion into the lumen of the nephron at the proximal convoluted tubule. This competition decreases uric acid secretion, raising the serum concentration and increasing the risk of a gout attack. Loop diuretics have the same risk.

17.6 Which is contraindicated in a patient with hyperkalemia?

A. Acetazolamide
B. Chlorothiazide
C. Ethacrynic acid
D. Eplerenone

Correct answer = D. Eplerenone acts in the collecting tubule via aldosterone antagonism to inhibit Na^+ reabsorption and K^+ excretion. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is initiated. The other drugs promote the excretion of potassium.

17.7 A 59-year-old male patient in the intensive care unit has a metabolic alkalosis. Which therapy will treat this condition?

A. Amiloride
B. Hydrochlorothiazide
C. Mannitol
D. Acetazolamide

Correct answer = D. Acetazolamide causes an increase in the urinary excretion of bicarbonate, lowering the pH of the blood.

17.8 A male patient is placed on a new medication and notes that his breasts have become enlarged and tender to the touch. Which medication is the most likely taking?

A. Furosemide
B. Hydrochlorothiazide
C. Spironolactone
D. Triamterene

Correct answer = C. An adverse drug reaction to spironolactone is gynecomastia due to its effects on androgens and progesterone in the body. Eplerenone may be a suitable alternative if the patient is in need of an aldosterone antagonist but has a history of gynecomastia.

17.9 A patient with heart failure with reduced ejection fraction researched his medications on the Internet and found he was taking two "diuretics," bumetanide and spironolactone. He asks if this is a mistake with his therapy. What is the best response?

A. Spironolactone is used to prevent hyponatremia.
B. Spironolactone is used to reduce heart structure changes and decrease the risk of death.
C. Bumetanide is used to decrease the potassium lost from spironolactone therapy.
D. This is a duplication error and one diuretic should be stopped.

Correct answer = B. Aldosterone antagonists are used at non-diuretic doses in heart failure to prevent myocardial remodeling and decrease mortality. Bumetanide is used as a diuretic to treat edema from heart failure. Both are appropriate to use together because of the unique indications. Spironolactone reduces the potassium lost from diuresis with bumetanide.

17.10 Which diuretic has been shown to improve blood pressure in resistant hypertension or those already treated with three blood pressure medications including a thiazide or thiazide-like medication?

A. Indapamide
B. Furosemide
C. Mannitol
D. Spironolactone

Correct answer = D. Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.