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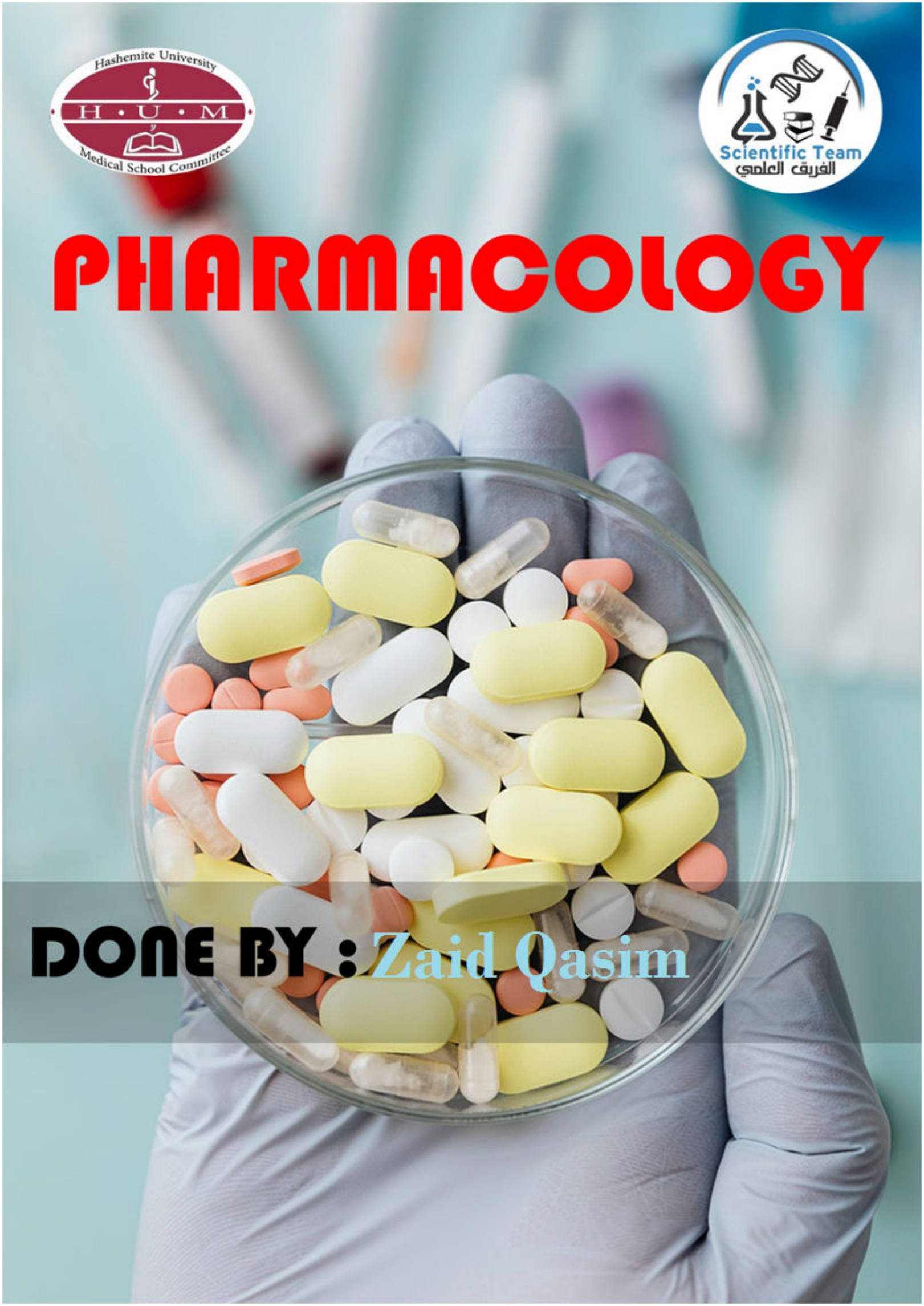
PHARMACOLOGY



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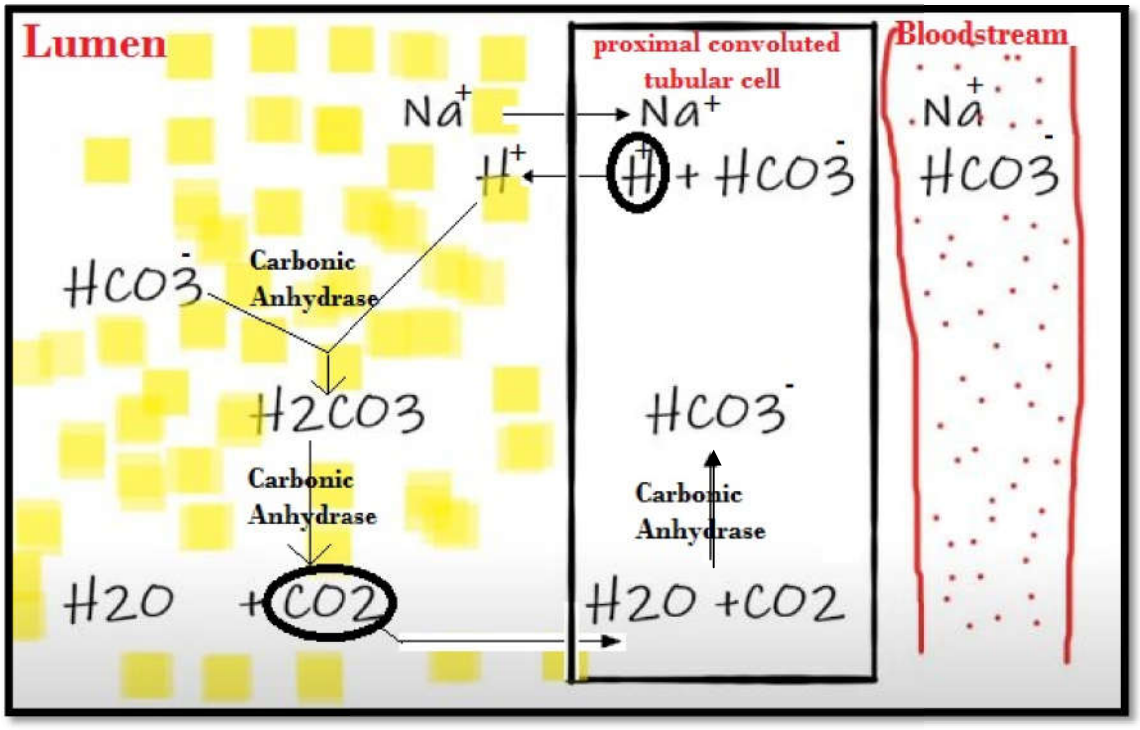
بسم الله الرحمن الرحيم

LECTURE 3 : RENAL DIURETICS (PART 3) – CARBONIC ANHYDRASE INHIBITORS (CAIS) *AND* POTASSIUM (K+) RETAINING DIURETICS

- In this lecture we're going to talk about two different families of renal diuretics. . .

(1) Carbonic Anhydrase inhibitors (CAIs).

- This group of drugs work at luminal side in the proximal convoluted tubule of the nephron (site *2*) where 5% of filtered (Na^+) is normally reabsorbed as ($NaHCO_3$) in exchange with (H^+) under effect of *carbonic anhydrase enzyme*.
- This figure shows you what is normally occurring at these cells . . .



- Na^+ is reabsorbed from the tubular lumen into the proximal convoluted tubular cell then through the basolateral membrane into the blood, in exchange with H^+ which is excreted into the lumen then into the urine.
- The apical membrane of proximal convoluted tubular cell is impermeable for HCO_3^- but it is highly permeable for CO_2. In order to reabsorb HCO_3^-, it must first reacts with H^+ in the tubular lumen by the action of carbonic anhydrase enzyme to form the carbonic acid (H_2CO_3) which will then dissociate into water and carbon dioxide. The latter can enter the

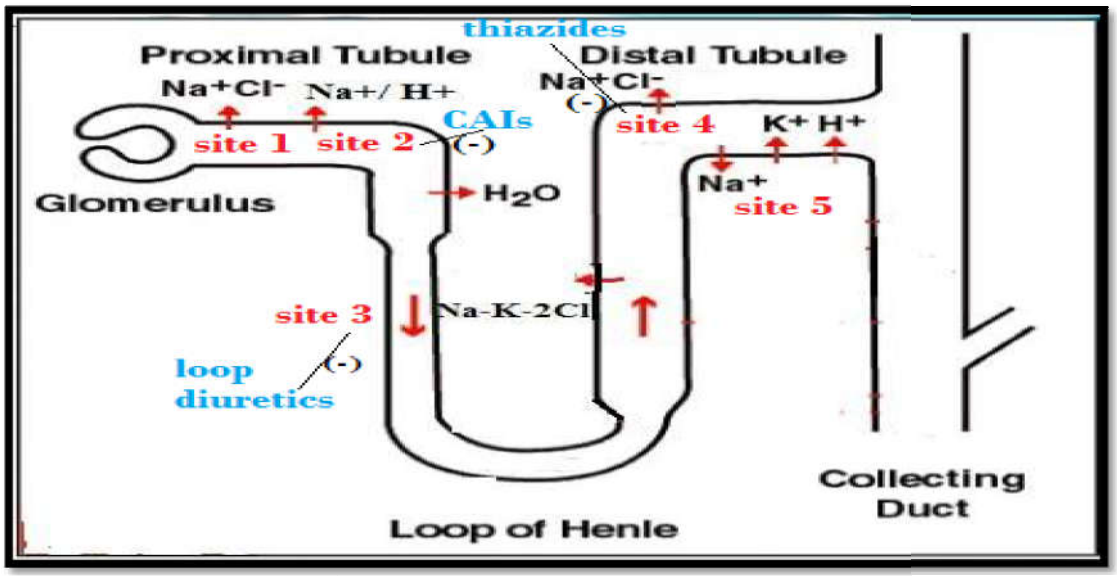
tubular cell and react with water by the action of carbonic anhydrase again forming H_2CO_3 which dissociates into $HCO3^-$ and H^+. The latter is excreted into the lumen again in exchange with Na^+ and the HCO_3^- is reabsorbed into the bloodstream. So, the net result is that the Na^+ and HCO_3^- are reabsorbed into the bloodstream and H^+ is exerted into the tubular lumen.

- Luminal border of the proximal convoluted tubular cell (i.e. the apical membrane) contains a membrane bound carbonic anhydrase. Also, the cytoplasm of this cell contains this enzyme.

- These drugs, as their name indicate, achieve their diuretic effect by inhibition of carbonic anhydrase found in the luminal border of the proximal convoluted tubular cell and inside the cytoplasm of tubular cell resulting in an inhibition of the formation of carbonic acid so that ⟶

a. No CO_2 is formed or reabsorbed into the tubular cell so as a result, the HCO_3^- won't be reabsorbed into the bloodstream.
b. CO_2 which is previously existing in the tubular cell will not react with H_2O so neither H^+ nor HCO_3^- is formed and therefore, Na^+ will not be reabsorbed in exchange with H^+ resulting eventually in $NaHCO_3$ loss in the urine.
c. Passive H_2O reabsorption which usually follows Na^+ reabsorption will also be inhibited.

- Notice that *CAIs* will result in an alkaline urine unlike both *thiazide and loop diuretics* which make an acidic urine and this difference is easily expected if you think about the tubular sites where each of these drug families work. *Thiazides* work by inhibition of the active NaCl reabsorption in the early part of the distal tubule (site 4) and the *loop diuretics* work by blocking the 2 Cl^- / Na^+ / K^+ reabsorption pump in the thick ascending segment of the loop of Henle (site 3). Both drugs will allow the late distal convoluted tubule to reabsorb Na^+ in exchange with H^+ and K^+ so the urine will contain some amounts of H^+ making an acidic urine as well as metabolic alkalosis. However, the *CAIs* inhibit the $NaHCO_3$ reabsorption into the blood and H excretion into the urine (site 2) resulting in an alkaline urine and metabolic acidosis.



	Thiazides	*Loop diuretics*	*CAIs*
SOA	*SITE 4* where 5-10% of filtered Na^+ is reabsorbed	*Site 3* where 20-30 % of filtered Na^+ is reabs	*Site 2 Site 3* where Only 5% of filtered Na^+ is reabsorbed
Urine	Acidic	Acidic	Alkaline
Blood	Metabolic Alkalosis	Metabolic Alkalosis	Metabolic Acidosis
Potency	Moderately powerful	Potent " high ceiling"	Weakest diuretic

- Carbonic anhydrase inhibitors (CAIs) will not only inhibit the carbonic anhydrase enzyme in the renal tubules, they will also inhibit the carbonic anhydrase enzyme found in the brain and eyes leading to decreased cerebrospinal fluid CSF formation and decreased aqueous humor formation (between the cornea and the iris) respectively.

- CAIs are weak diuretic because they inhibit the reabsorption of only a small percentage of filtered Na^+ (5%) allowing the thick ascending segment of the loop of Henle, early and late distal convoluted tubule [sites 3,4 and 5] to reabsorb more Na^+ and H_2O.

- Because they are weak diuretics they are used in the medical practice for medical INDICATIONS other than diuresis including:

1- **H**igh altitude (mountain) sickness with symptoms like weakness, dizziness, insomnia, headache, and nausea in rapid ascend above 3000 m due to respiratory alkalosis resulted from hyperventilation so CAIs are used to correct alkalosis.

2- **H**ydrocephalus in which an accumulation of cerebrospinal fluid (CSF) occurs within the brain so CAIs are used to decrease CSF formation and decrease intracranial tension.

3- **E**pilepsy in which CAIs suppress the irritable focus directly or by inducing acidosis.

4- **E**ye with glaucoma in which CAIs inhibit & decrease the formation of aqueous humor.

-Remember that osmotic diuretics like Mannitol are used in acute congestive glaucoma.
- Closed-angle glaucoma, occurs when the iris bulges forward to narrow or block the drainage angle formed by the cornea and iris. In such condition the intraocular tension is relieved by surgical intervention.

5- **E**xcretion of acidic drugs: in cases of toxicity as salicylates & barbiturates by alkalinization of the urine to make it less favourable for the reabsorption of these drugs. --Remember that Acidic drugs are highly absorbed from the intestine or reabsorbed from the tubular lumen in kidneys when the pH of the medium is low (acidic). Drugs with alkaline nature are highly absorbed or reabsorbed when the pH of the medium is high (alkaline). When an acidic drug is present in an alkaline urine it will be ionized and not reabsorbed.

- ADVERSE REACTIONS OF CAIS

  - Calcium and phosphate start to precipitate and form **stones** in an alkaline urine resulted from CAIs.

  - **Metabolic acidosis** will occur and cause drowsiness and refractoriness (i.e. resistance) to the diuretic effect of CAIs because the body start to preserve $NaHCO_3$ and will not excrete it in the urine to buffer the metabolic acidosis. Due to that CAIs are self-limiting diuretics.

  - Because CAIs are "sulphonamide derivatives" **hypersensitivity** reactions are common.

- PREPARATIONS (-zolamide) :

Rout of administration	drug name	drug name
Orally	Acetazolamide	Methazolamide. Preferred in glaucoma due to less adverse effects.
Topically through eye drops	Brinzolamide	Dorzolamide

- Thiazides, loop diuretics, osmotic diuretics and Carbonic Anhydrase Inhibitors (CAIs) all are types of Potassium-losing diuretics that they cause hypokalemic alkalosis.

- Now we are going to talk about the 2nd major family of the renal diuretics . . .

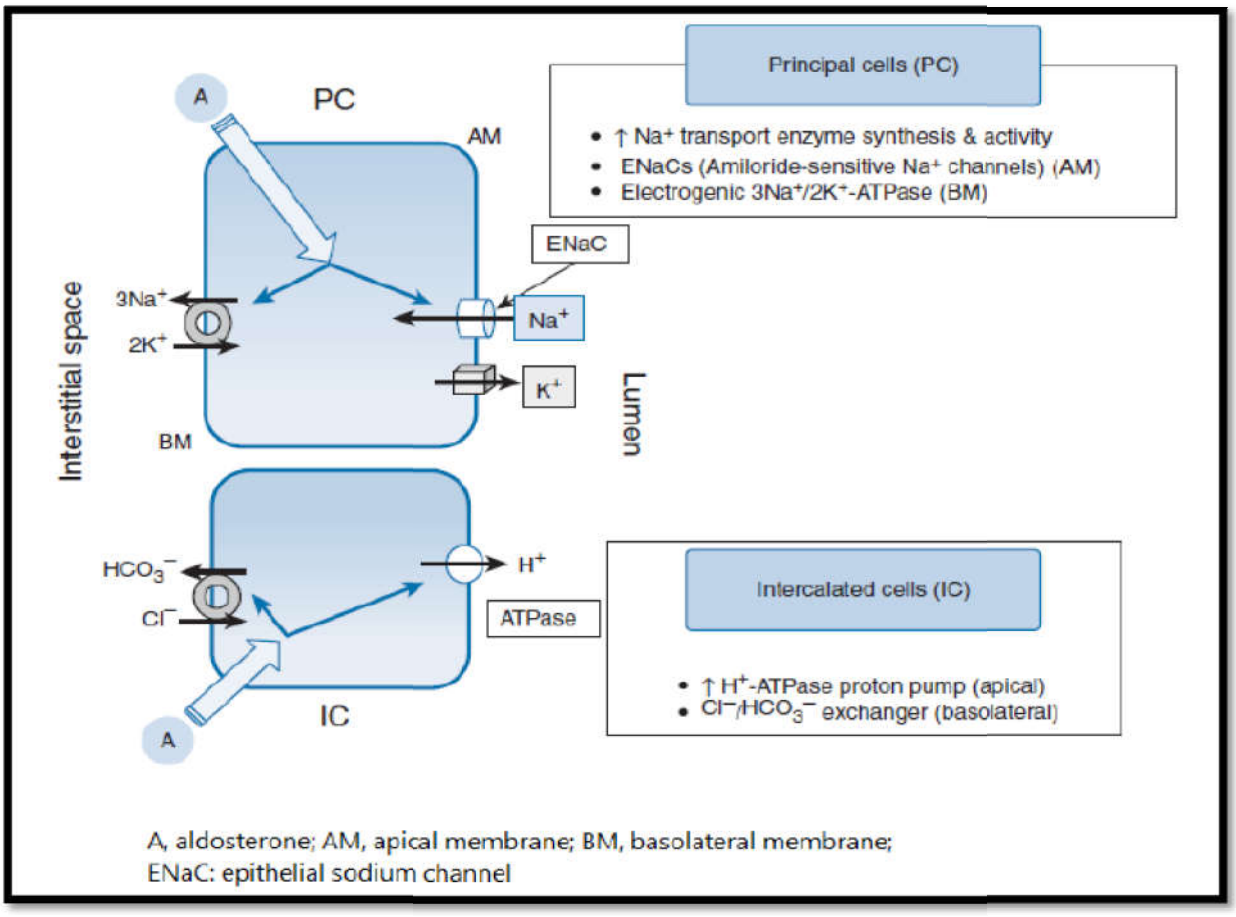
(2) Potassium-Sparing Diuretics.

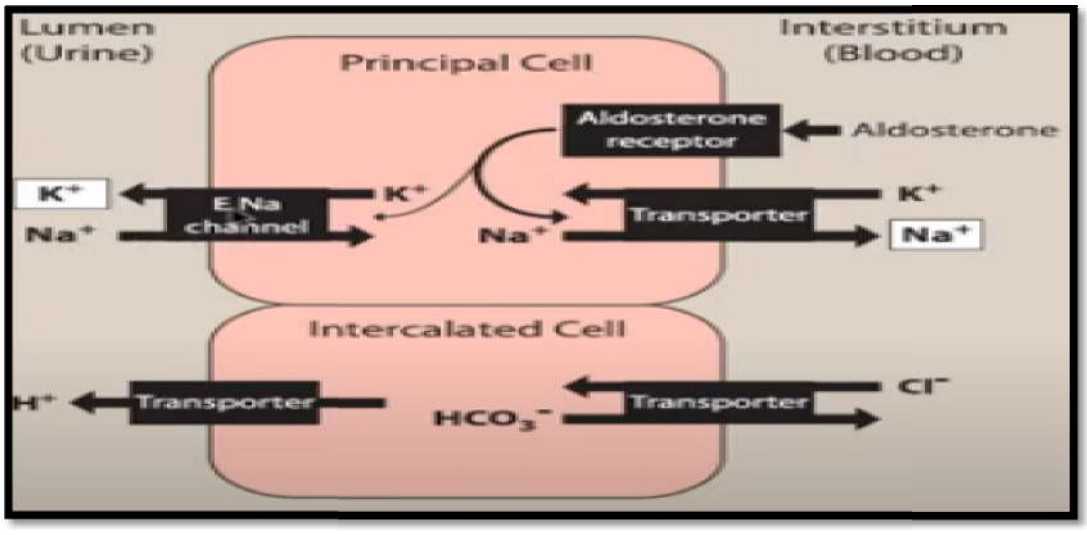
- These drugs work in the late distal convoluted tubule (site 5) where 5% of Na^+ is reabsorbed in exchange with K^+ or H^+ via K^+/ Na^+ / H^+ pump.
- Remember that reabsorption of Na^+ at that site is by aldosterone-dependent and aldosterone-nondependent mechanisms.
- We can remember from the last module that the epithelium of the second half of renal distal tubule and collecting tubule has two types of cells, the **principal** and **intercalated cells**.
- Principal cells (express more aldosterone receptors) are responsible for Na^+ and water reabsorption and secretion of K^+. This function is controlled by *aldosterone* and K^+ *concentration in blood*.

- Aldosterone binds to a cytoplasmic receptor, and the receptor-hormone complex moves to the nucleus where it alters the transcription of mRNAS.

- Aldosterone then increases the reabsorption of Na^+ and increases secretion of K^+ especially by the principal cells of late distal tubules and collecting ducts *by increasing the synthesis of Epithelial sodium channels (E Na^+ channels) at the apical membrane and increasing the synthesis of Na^+ / K^+ –ATPase at the basolateral membrane*. This allows the kidney to conserve Na^+ in the extracellular compartment & expansion of the extracellular fluid volume. Hyperaldosteronism will result in edema.

- Aldosterone also increases the formation of both H^+ –ATPase proton pump at the apical membrane and Cl^- / HCO_3^- exchanger at the basolateral membrane of the intercalated cells.





- These drugs inhibit the $Na^+/ K^+ / H^+$ exchange at the distal tubule by two different mechanisms :

  (1) ***DIRECLTY***: by inhibiting the E Na^+ channels independently of aldosterone. Such as *T*riamterrene and *A*miloride. They have rapid onset of action.

  (2) ***INDIRECTLY*** : by antagonism &blocking of aldosterone receptor-binding and decreasing the synthesis of mRNA responsible for Na^+ pump. Such as *S*pironolactone and *E*plerenone. They have delayed onset of action (3-4 days).

- Potassium-retaining diuretics are weak diuretics because they inhibit the reabsorption of only 5% of filtrated Na^+ from the late distal convoluted tubules (site *5*).

- N.E. CAIs still weaker than this group.

- INDICATIONS

1. Edema of Hyperaldosteronism: (spironolactone is the drug of choice)

a. ***Primary Hyperaldosteronism*** in case of aldosterone-secreting adenoma in the adrenal cortex (*Conn's syndrome*).
b. ***Secondary Hyperaldosteronism*** in case of liver cirrhosis, nephrotic syndrome and congestive heart failure. [Remember that these three conditions will result in renal hypoperfusion and arterial hypovolemia which trigger the activation of the renin-angiotensin system and eventually increase the aldosterone level in the plasma].

- As the edema is resulted from Hyperaldosteronism, other diuretics like thiazides or loop diuretics are of less efficacy in this situation because Na^+ lost by other diuretics is reabsorbed again by excess aldosterone at $Na^+/K^+/H^+$ exchange site in distal tubule. Also, since the problem is due to high aldosterone concentration in the plasma, directly acing potassium-retaining diuretics like triamterrene & amiloride are less effective because aldosterone can still binds with the receptors and therefore enhances Na^+ reabsorption.

2. Hypokalemia and hypomagnesemia: **(amiloride and triamterene are of choice)**

- This drug family inhibit $Na^+/ K^+ / H^+$ exchange so the body conserve the potassium ions so they can be used in hypokalemia. Also they inhibit Mg^{++} excretion so they're used in hypomagnesemia.

- Direct agents like triamterrene & amiloride are preferable to spironolactone in this situation for many reasons :
  A. Rapid onset.
  B. Short acting.
  C. Possibility of daily dosage adjustment.

3. **Heart failure:** (**spironolactone is preferred**)

- In advanced heart failure, myocardial cells start to secrete local amounts of aldosterone which can cause fibrosis and myocardial remodelling. So, spironolactone can be used in such situation to decrease the mortality remodelling in patients with heart failure and decrease the end stage of heart failure which requires hospitalization and increase the survival rate.

4. Combined with loop and thiazide diuretics to :

(1) Synergize their diuretic effects in resistant edema since each one of them work on different site in tubular system.
(2) Decrease the risk of electrolyte imbalance: loop and thiazide diuretics cause hypokalemia whereas K^+ – retaining diuretics cause hyperkalemia.
(3) Decrease the risk of acid-base disturbances: loop and thiazide diuretics cause metabolic alkalosis whereas K^+ – retaining diuretics cause metabolic acidosis.

5. **Spironolactone has antiandrogenic effect** which is useful in treatment of hirsutism and acne in females. This effect is achieved only by spironolactone.

- ADVERSE EFFECTS

1. Hyperkalemia & metabolic acidosis. [Potassium-losing diuretics causes hypokalemia & metabolic alkalosis].

2. Nausea, abdominal pain, drowsiness & mental confusion.

3. Spironolactone antagonizes other steroid hormones:

- Androgens ⟶ Gynecomastia, loss of libido & impotence in MALES.
- Estrogen ⟶ Menstrual irregularities FEMALES.
- Eplerenone ⟶ No antiandrogenic effect but it can't be used in acne or hirsutism in females.

4. Triamterene may precipitate in urine ⟶ stone formation.

	Spironolactone	Triamterene & Amiloride
Structure	Synthetic steroid.	Synthetic non-steroid.
Metabolism	Extensive metabolism in liver.	- Triamterene is metabolized in liver. - Amiloride is excreted unchanged (hydrophilic).
Mechanism	Competitive antagonism with aldosterone at its receptors in DCT.	Direct block of $Na^+/K^+/H^+$ exchange in DCT.
Antiandrogenic effects	Gynecomastia & impotence.	Not present.

THE END ☺