



Artery Academy

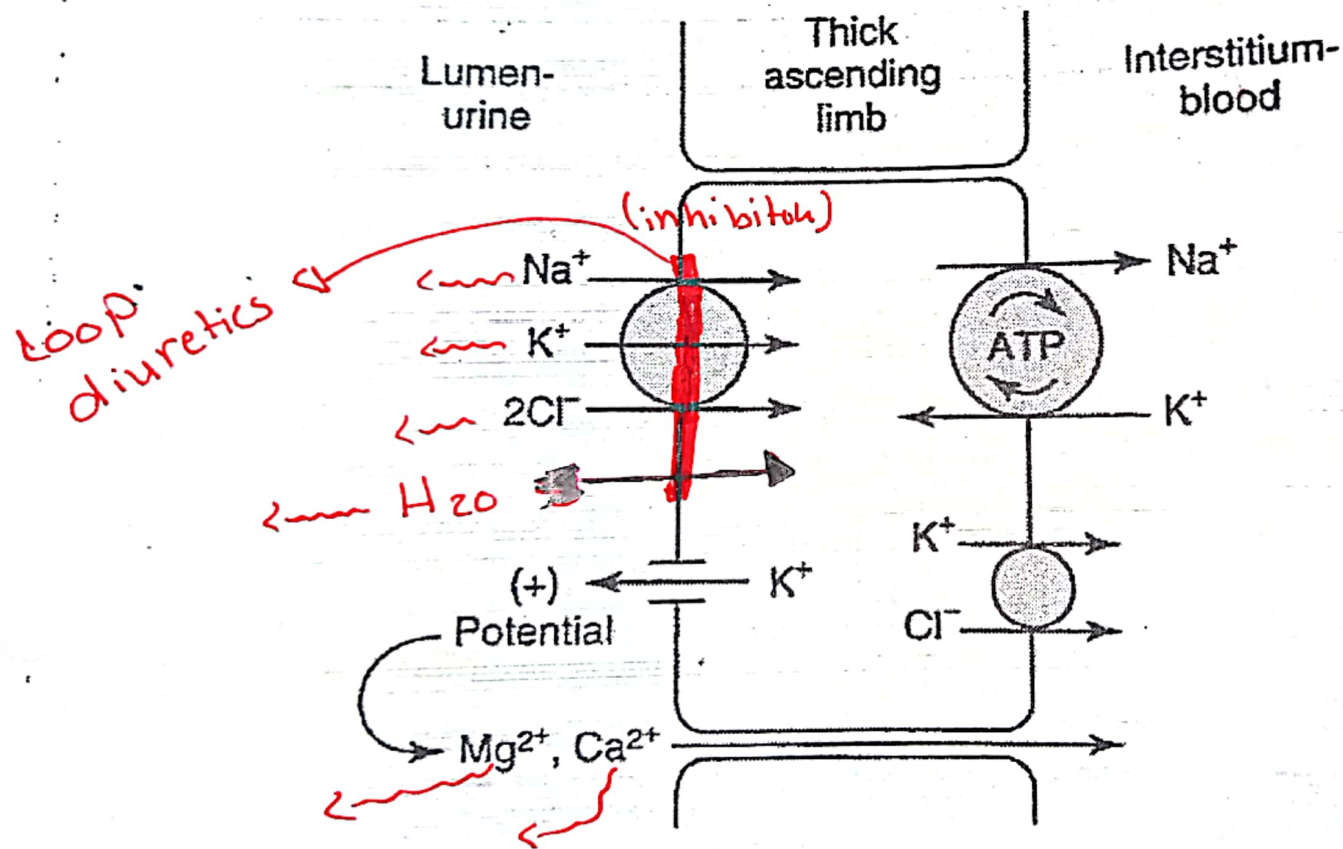
Ayah Rabba'

Loop Diuretics (mainly act on $\text{Na}^+/\text{K}^+/\text{Cl}^-$ pumps)

- ▶ **Mechanism of action**
- ▶ Loop diuretics inhibit the cotransport of $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased.
- ▶ The loop diuretics are the most efficacious of the diuretic drugs.
- ▶ Like thiazides these agents must be secreted into the tubular fluid by proximal tubule cells.

← الأنسجة التي عندهم Renal failure ما يفرزها سيقتضوه لأنه لازم يفرزها proximal tubule

Loop diuretics



* نیز دار Na^+ / K^+ / 2Cl^- نیز دار H_2O excretion

Loop Diuretics

- ▶ Loop diuretics inhibit the luminal $\text{Na}^+ / \text{K}^+ / 2\text{Cl}^-$ transporter in the TAL of Henle's loop.
- ▶ By inhibiting this transporter, the loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential that comes from K^+ recycling.
- ▶ This positive potential normally drives divalent cation reabsorption in the TAL and by reducing this potential, loop diuretics cause an increase in Mg^{2+} and Ca^{2+} excretion.

× بسبب فقدان كميات كبيرة من K^+ هناك يؤدي إلى زيادة إفراز الكبد من
هرمون الغنثاد فيزداد إخراج Ca^{2+} ، Mg^{2+} من الجسم لموازنة فرق
الجهد بين المرفقين .

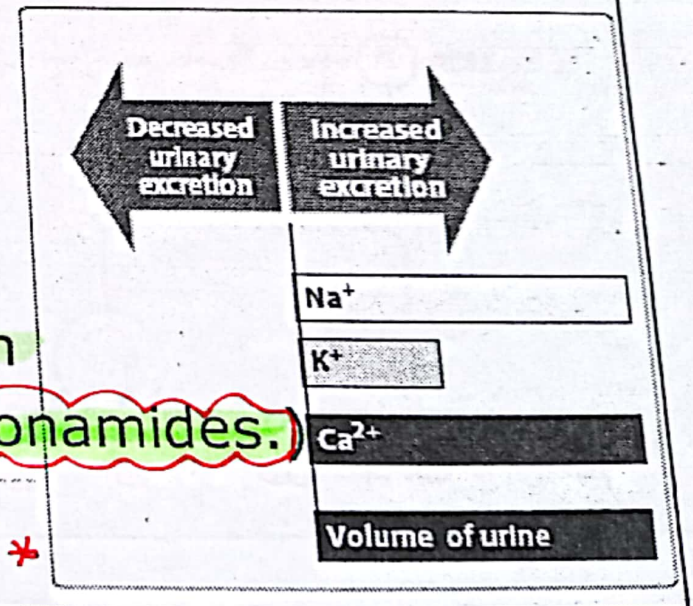
Loop Diuretics

Actions:

- ▶ Increase Na^+ , Cl^- , K^+ and Ca^{++} excretion
- ▶ Decrease renal vascular resistance and increase renal blood flow (via prostaglandin actions on kidney vasculature)

Side effects:

- ▶ Ototoxicity, reversible (esp. with aminoglycoside antibiotics) خفوف → Problems of hearing caused by drug.
- ▶ Hyperuricemia
- ▶ Acute hypovolemia (severe and rapid reduction in blood volume)
- ▶ Hypokalemia
- ▶ Hypomagnesemia
- ▶ Allergic reaction (All loop diuretics, with the exception of ethacrynic acid, are sulfonamides.)



↳ 1. sulfonamides are loop diuretics
↳ ethacrynic acid.

Loop Diuretics

Therapeutic uses:

- ▶ CHF → Congestive Heart Failure.
- ▶ HTN
- ▶ Acute renal failure
- ▶ Pulmonary edema
- ▶ Hypercalcemia (along with hydration)
- ▶ Hyperkalemia (along with hydration) → with fluid to prevent dehydration.
- ▶ Anion overdose
 - Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the TAL (thick ascending limb of Henle's loop).

Loop Diuretics

- ▶ Specific agents:
 - ▶ Bumetanide
 - ▶ Furosemide (most commonly used)
 - ▶ Torsemide
 - ▶ Ethacrynic acid

TABLE 15-4 Typical dosages of loop diuretics.

Drug	Total Daily Oral Dose ¹
Bumetanide	0.5–2 mg
Ethacrynic acid	50–200 mg
Furosemide	20–80 mg
Torsemide	5–20 mg

¹As single dose or in two divided doses.

طويلة
* بنصفهم قبل النوم بفترة ~~معتدلة~~ عشان نقلل من التبول أثناء النوم.

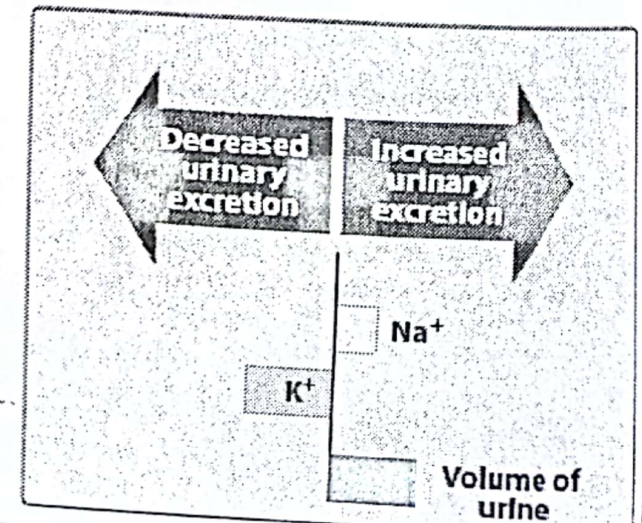
د ادویه قانظ عام ترکیب Ka^+ داخل الجسم و تمنع إخراجہ من الجسم

Potassium-sparing Diuretics

- ▶ There are two types of potassium sparing diuretics:
 - 1) Renal epithelial Na^+ channel inhibitors - **amiloride, triamterene.**
 - 2) Aldosterone Antagonists - **spironolactone, eplerenone.**
- ▶ They are not very efficacious diuretics. They commonly used in combination with other diuretics, for their potassium-sparing properties.

* used specially with patients ~~suffer~~ suffer from hypokalemia.

* used with monitoring of Ka^+ levels.



* ارتباط اسمها مع تأثيرها الجانبي (بتخزين K^+ منه يتعمل Hyperkalemia)

(مدرات البول الموفرة للبوتاسيوم)

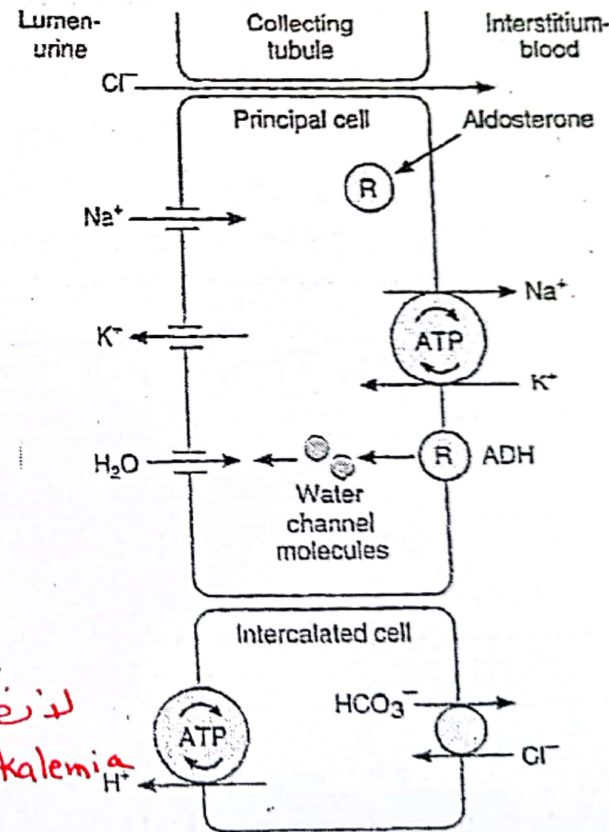
Potassium-sparing Diuretics

1) Na^+ channel inhibitors -
amiloride, triamterene.

Side effects:

- The most obvious side effect is an extension of the therapeutic action of these drugs, that is hyperkalemia.

These drugs are contraindicated in situations in which hyperkalemia could occur such as in renal failure, treatment with ACEIs (angiotensin converting enzyme inhibitors).



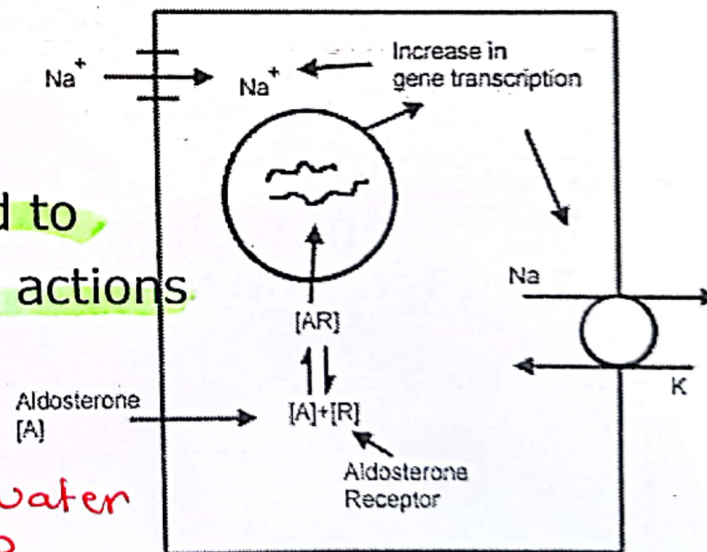
Potassium-sparing Diuretics

2) Aldosterone Antagonists - **spironolactone, eplerenone**.

- ▶ Aldosterone acts as a typical steroid hormone. Aldosterone binds to a cytoplasmic receptor that is transported to the nucleus. The aldosterone-receptor [AR] complex binds to DNA elements to enhance the synthesis of a Na^+ , K^+ -ATPase and a Na^+ channel involved in a Na^+ and K^+ transport in the distal tubule and collecting ducts.

▶ Net aldosterone effect:

- ▶ Na^+ reabsorption
- ▶ K^+ secretion
- ▶ Spironolactone and eplerenone bind to the intracellular receptor blocking the actions of aldosterone on gene expression.



Aldosterone increase Na^+ and water reabsorption, thus increase the B.P.

* These drugs inhibit the effect of aldosterone by binding on its receptors in intracellular and lead to decreased B.P.

Potassium-sparing Diuretics

2) Aldosterone Antagonists - spironolactone, eplerenone.

Side effects:

- ▶ Toxicities and cautions are similar to Na^+ channel inhibitors.
- ▶ Due to its steroid structure, spironolactone can cause antiandrogen effects such as gynecomastia in men.

Therefore, the drug should not be given at high doses on a chronic basis.

- ▶ Eplerenone has little affinity for androgen or progesterone receptors. Therefore it is void of the unpleasant steroid hormone-like effects.

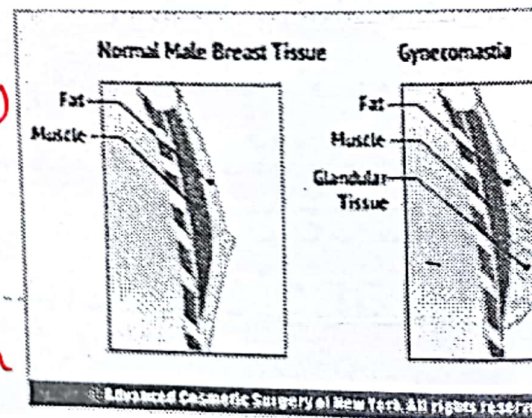
Suppression the action of male sex hormones, such as testosterone in the body.

يفسر

غير المرغوبة

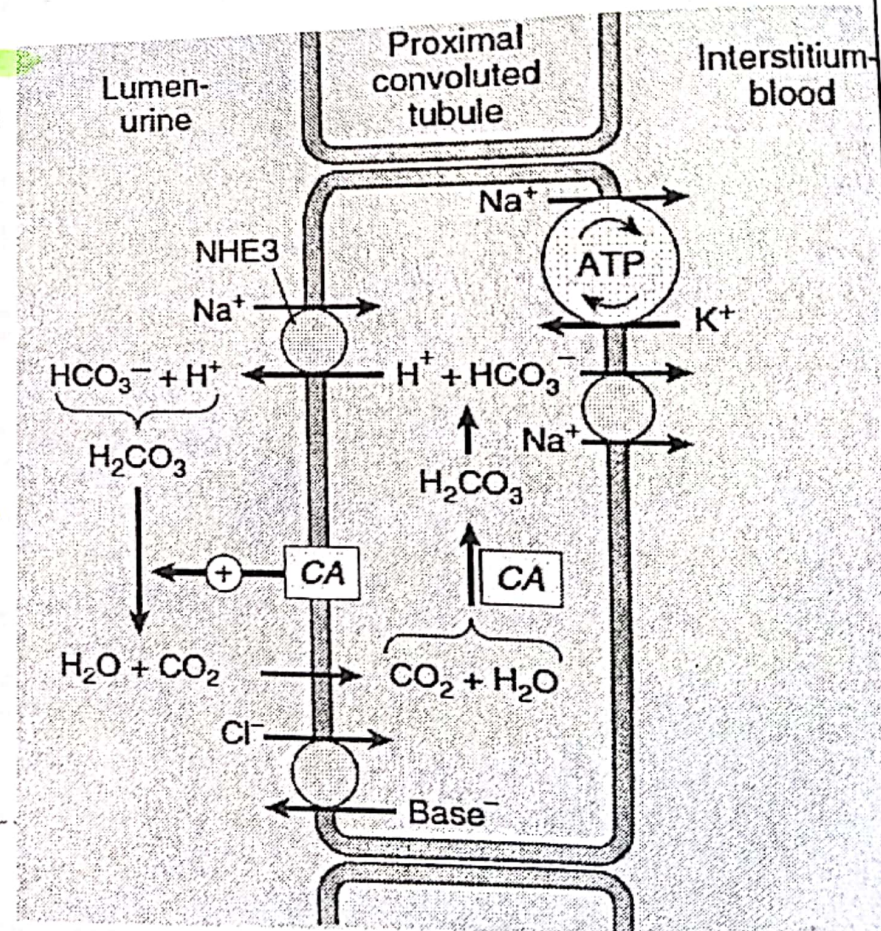
* gynecomastia : increase in the amount of breast glands tissue in men (زيادة الهرمون الذكري لدى الذكر)

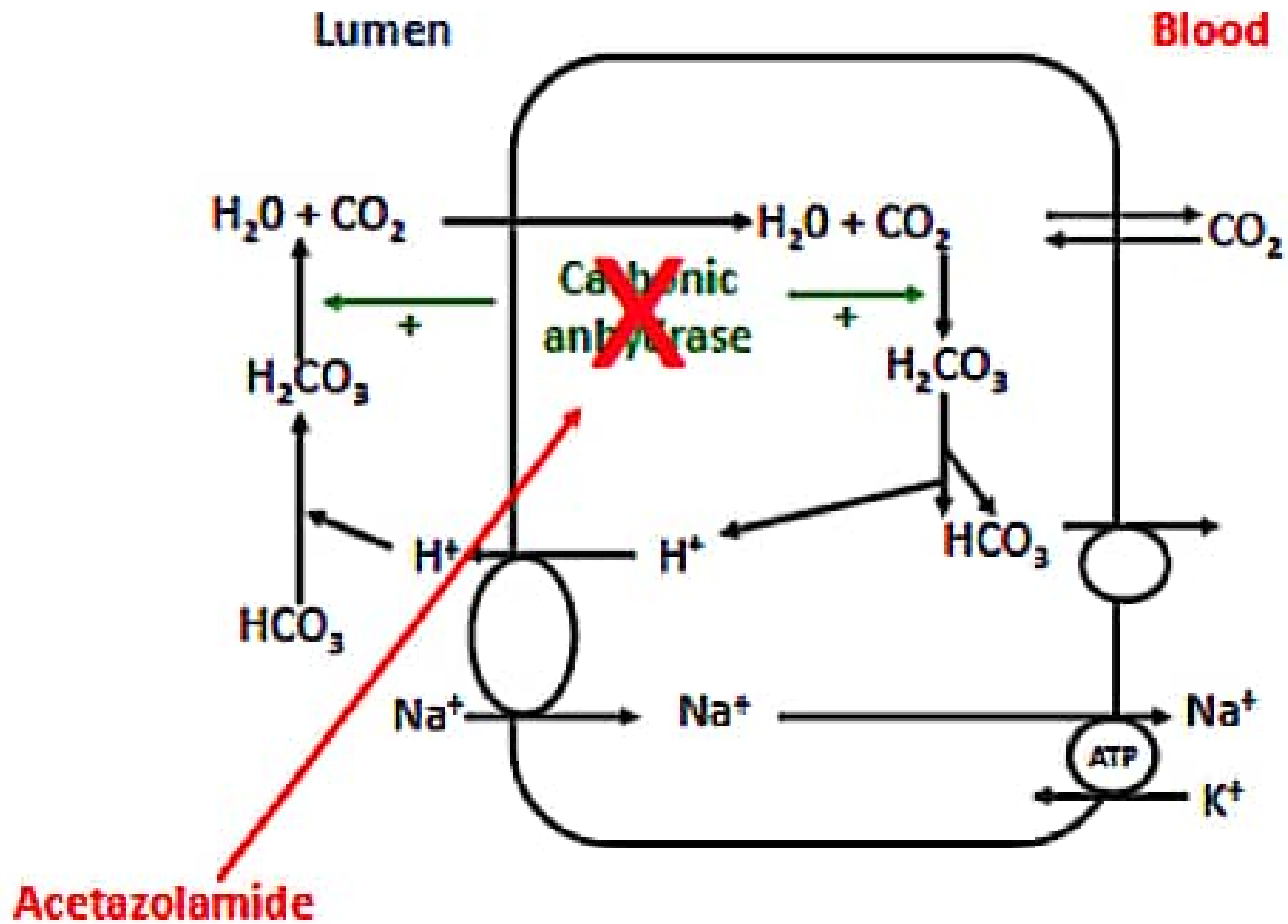
- ▶ Eplerenone not have the antiandrogen effects due to little affinity for androgen receptors.



Carbonic anhydrase inhibitors (CAI)

- ▶ **Mechanism of action:**
- ▶ They inhibit carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- ▶ Carbonic anhydrase inhibitors, by blocking the enzyme, prevent the reabsorption of NaHCO_3^- and hence diuresis occurs.
- ▶ Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH.

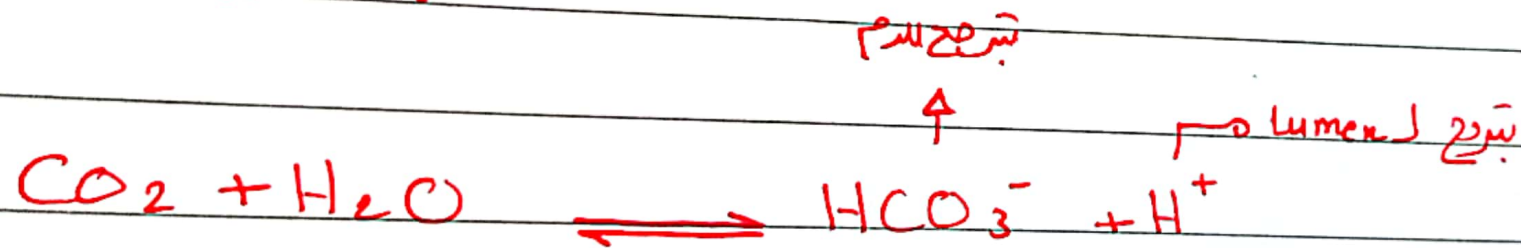




* Carbonic anhydrase enzyme :: (CA)

1. Function ::

• Catalyze the conversion of CO_2 and H_2O into HCO_3^- and H^+ .



• This reaction enhance the water and HCO_3^- reabsorption from urinary lumen to the blood.

↑ Blood
water

↑ B.P

* to inhibit its effect, we need to CA inhibitors.

• Function of carbonic anhydrase inhibitors :: (CAI)

• inhibit the conversion of H_2CO_3 in the urinary lumen to $\text{H}_2\text{O} + \text{CO}_2$ and inhibit reabsorption of water and ~~it~~ increase the excretion of HCO_3^- .

$\downarrow \text{HCO}_3^-$ in blood $\xrightarrow{\text{(metabolic acidosis)}}$ low blood pH. $\xrightarrow{\text{(urine alkalosis)}}$ high urine pH

$\downarrow \text{H}_2\text{O}$ reabsorption $\xrightarrow{\text{}} \downarrow \text{Blood Volume} \xrightarrow{\text{}} \downarrow \text{B.P.}$

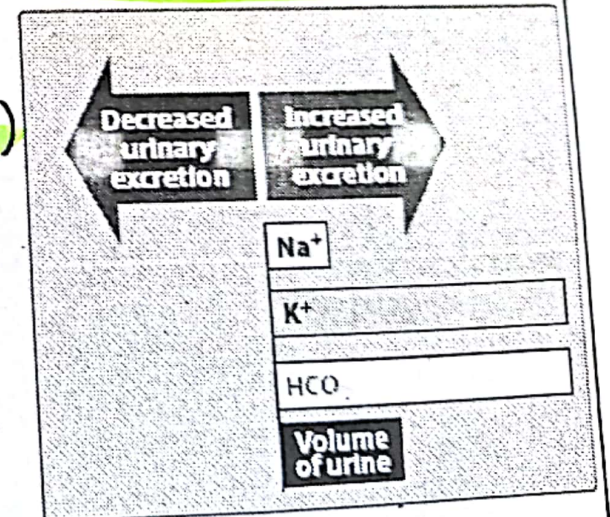
Carbonic anhydrase inhibitors

Side effects:

- ▶ Metabolic acidosis (due to loss of HCO_3^-)
- ▶ Potassium depletion
- ▶ Kidney stone formation (Calcium salts are relatively insoluble at alkaline pH, which means that the potential for renal stone formation from these salts is enhanced).

لأن pH للبول ترتفع -
فترسح كالكالسيوم ، وتتراكم
الكالسيوم لا تتكون في
الحوامد .

- ▶ Drowsiness (النعاس) خدر
- ▶ Paresthesia (numbness and tingling) وخز
تنميل وخدر



Carbonic anhydrase inhibitors

- Specific agents: الشكل الأساسي
 - Acetazolamide (prototype)
 - Dichlorophenamide
 - Methazolamide
 - Dorzolamide (topical)
 - Brinzolamide (topical)

*not used mainly as diuretic agent.

Carbonic anhydrase inhibitors

▶ Therapeutic uses:

- At present, the major clinical applications of acetazolamide involve carbonic anhydrase-dependent HCO_3^- and fluid transport at sites other than the kidney.

1. Treatment of glaucoma

Decrease the production of aqueous humor.

Topically active agents, which reduce intraocular pressure without producing renal or systemic effects, are available (dorzolamide, brinzolamide).

* بسبب خفض إخراج الماء من الجسم
وتقليل الضغط .

TABLE 15-3 Carbonic anhydrase inhibitors used orally in the treatment of glaucoma.

Drug	Usual Oral Dosage
Dichlorphenamide	50 mg 1-3 times daily
Methazolamide	50-100 mg 2-3 times daily

Carbonic anhydrase inhibitors

► Therapeutic uses:

② Urinary alkalization (لتخفيف اذابة cystine وإخراجه من الجسم)

Uric acid and cystine are relatively insoluble and may form stones in acidic urine.

Therefore, in cystinuria, a disorder of cystine reabsorption, solubility of cystine can be enhanced by increasing urinary pH from 7.0 to 7.5 with carbonic anhydrase inhibitors. In the case of uric acid, pH needs to be raised only to 6.0 or 6.5.

تحدث مع
طبيبك
الكبير

3. Mountain sickness

- Acetazolamide can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet.
- Acetazolamide given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

Carbonic anhydrase inhibitors

Therapeutic uses:

④. Metabolic alkalosis

high pH Blood.

⑤. Epilepsy (التشنجات)

Carbonic anhydrase inhibitors have been used as adjuvants in the treatment of epilepsy and in some forms of hypokalemic periodic paralysis.

نمثلة الوقت الذي يكون سببه انخفاض K^+ ~~من الدم~~

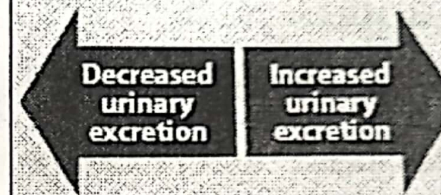
* في حالة Epilepsy يعمل (CAI) على تفضيل K^+/Ca^{+2} channel داخل smooth muscle ~~من الدم~~

* ولكن آلية عمله غير معروفة بالتفصيل.

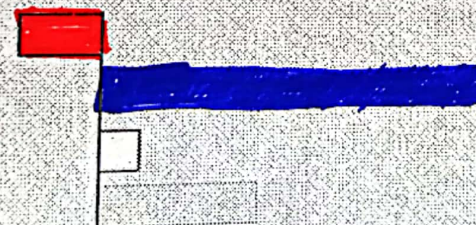
Summary

KEY

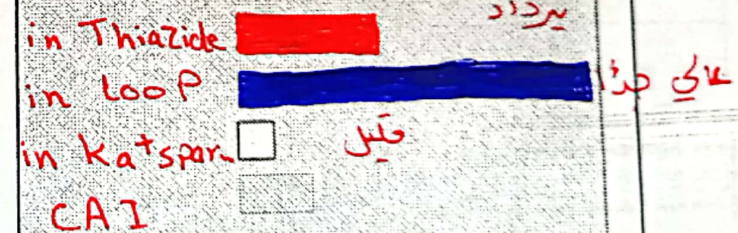
- Thiazide diuretics
- Loop diuretics
- K⁺-sparing diuretics
- Acetazolamide



Ca²⁺ excretion



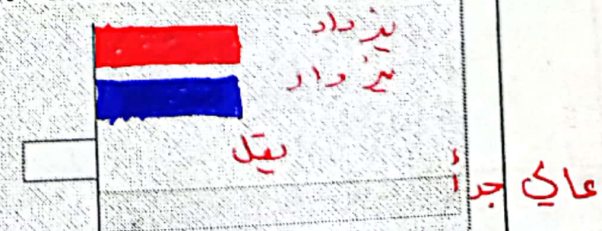
Na⁺ excretion



Volume of urine



K⁺ excretion



Summary

- ▶ **Loop diuretics:** blocks the sodium/potassium/chloride transporter in the ascending loop of Henle, *potassium-wasting*
- ▶ **Thiazide diuretics:** blocks the sodium/chloride transporter in the distal tubule, *potassium-wasting*
- ▶ **Amiloride:** directly blocks sodium channels in the collecting duct, *potassium-sparing*.
- ▶ **Spironolactone:** blocks the aldosterone receptors in the cortical collecting duct. This causes a decrease in sodium and water reabsorption and decreases potassium secreting (therefore is *potassium-sparing*)

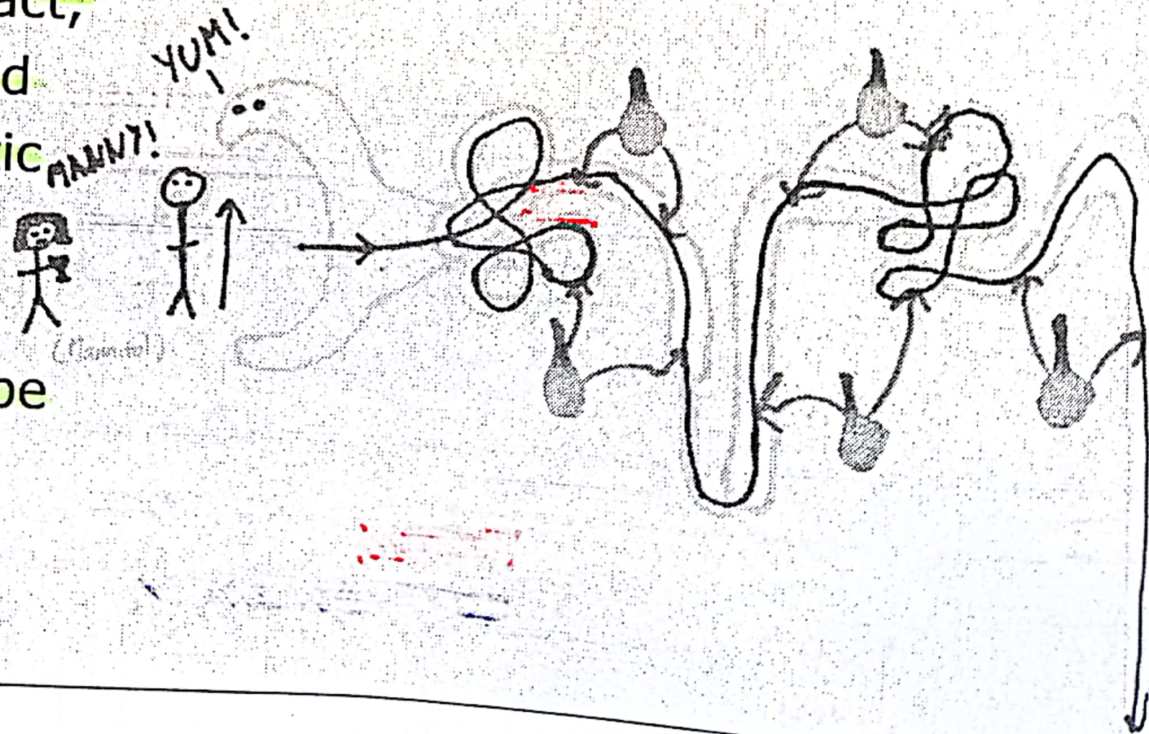
Osmotic diuretics

* ادوية بـيصير لها secretion الى قنوات البول
وما بتارجع للدم ، بتسحب معها H_2O
فيقل حجم الدم وتقل ضغط الدم .

Mechanism of Action

- ▶ Osmotic diuretics are freely filterable but not reabsorbed and prevent H_2O reabsorption in the proximal tubule.
- ▶ Specific agents:
 - ▶ Mannitol
- ▶ Mannitol is poorly absorbed by the GI tract, and when administered orally, it causes osmotic diarrhea rather than diuresis. For systemic effect, mannitol must be given intravenously.

OSMOTIC DIURETICS



Osmotic diuretics

▶ **Toxicity and Adverse Effects**

- ▶ Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells. Prior to the diuresis, this leads to expansion of the extracellular volume and hyponatremia. This increase in extracellular fluid volume could exacerbate congestive heart failure or pulmonary congestion. ^{تفاقم} ^{الاحتقائي}
- ▶ Dehydration can occur if water is not replaced adequately.

▶ **Clinical Uses**

- ▶ They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Maintaining urine flow preserves long term kidney function and may save the patient from dialysis. ^① ^②