# Artery Academy

**Done by Mariam**

# Diuretics

Pharmacology I
Dr. Heba Khader

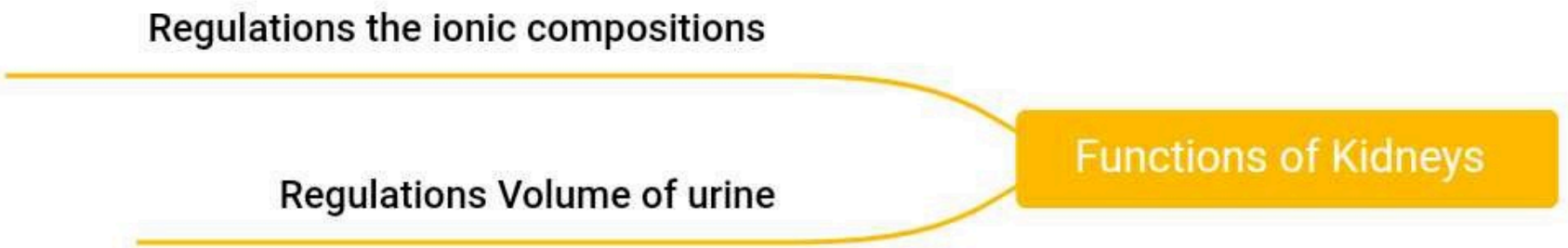
# Introduction

- Approximately 16 to 20 percent of the blood plasma entering the kidneys is filtered from the glomerular capillaries into the Bowman capsule.
- The filtrate, although normally free of proteins and blood cells, does contain most low-molecular-weight plasma components in approximately the same concentrations as are found in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes as well as electrolytes, such as Na+, K+, and Cl–.

تقريبًا ١٦-٢٠٪ من ال **blood plasma** رح يدخل عال **kidney** ويصيرله **glomerular filtration**
وبعدين إما بصيرلهم **reabsorption or excretion** ف بنتج عنا **urine**
هلأ هاد ال **filtrate** إلّي نتج رح يكون خالي من البروتينات وال **blood cells** والجلوكوز وال **nutrients**، لكن ممكن نلاقي منهم بكميات قليلة
مع العلم بإنه وجودهم لازم يكون بنسب معينة لحتى نستدل على وجود **deficit**
كمان من هاي الأشياء **sodium bicarbonate, Amino acid, electrolytes (Na,K,Cl)**

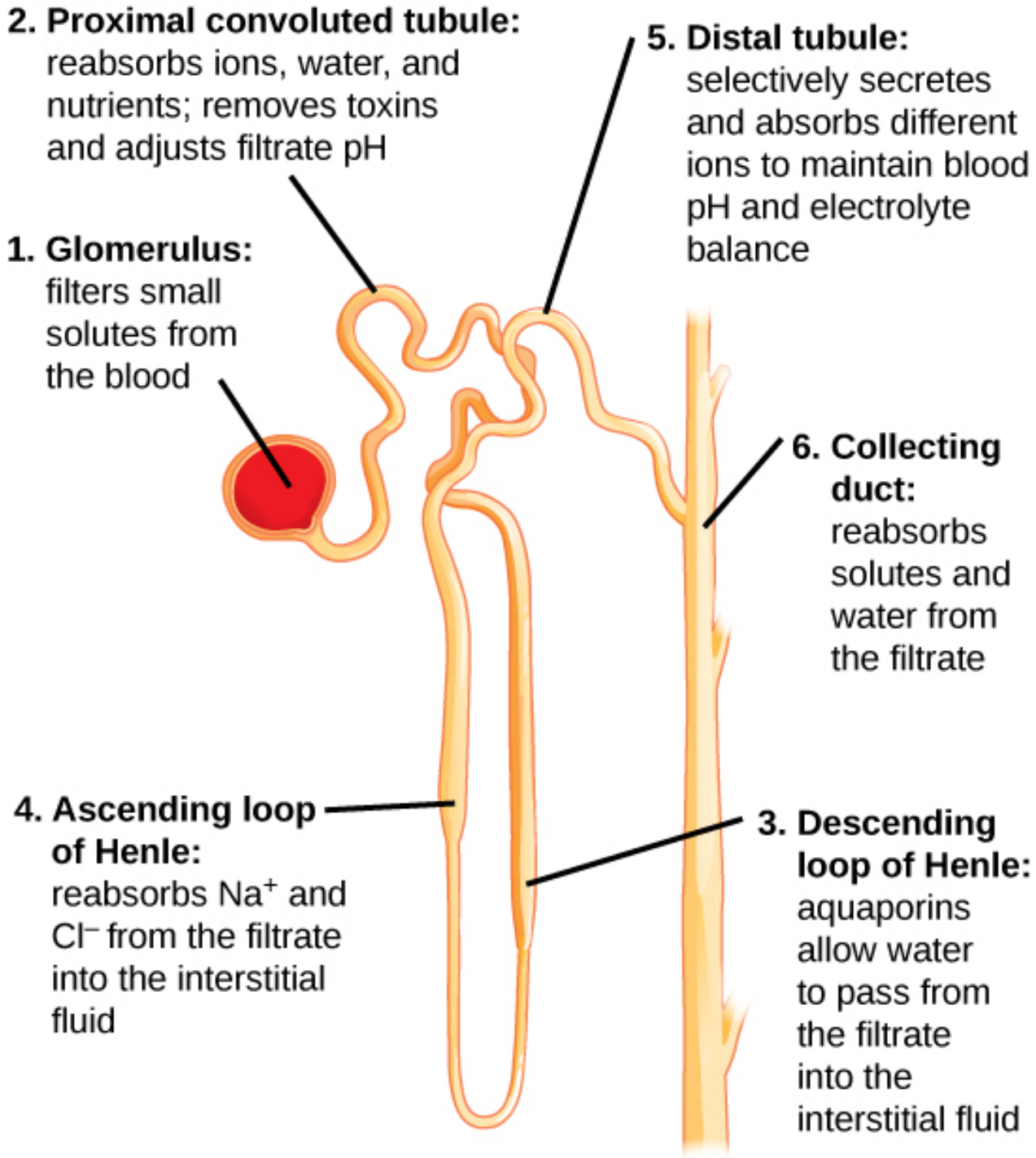
- The kidney regulates the ionic composition and volume of urine by the active reabsorption or secretion of ions and/or the passive reabsorption of water at five functional zones along the nephron:

1) the proximal convoluted tubule
2) the descending loop of Henle
3) the ascending loop of Henle
4) the distal convoluted tubule
5) the collecting tubule and duct



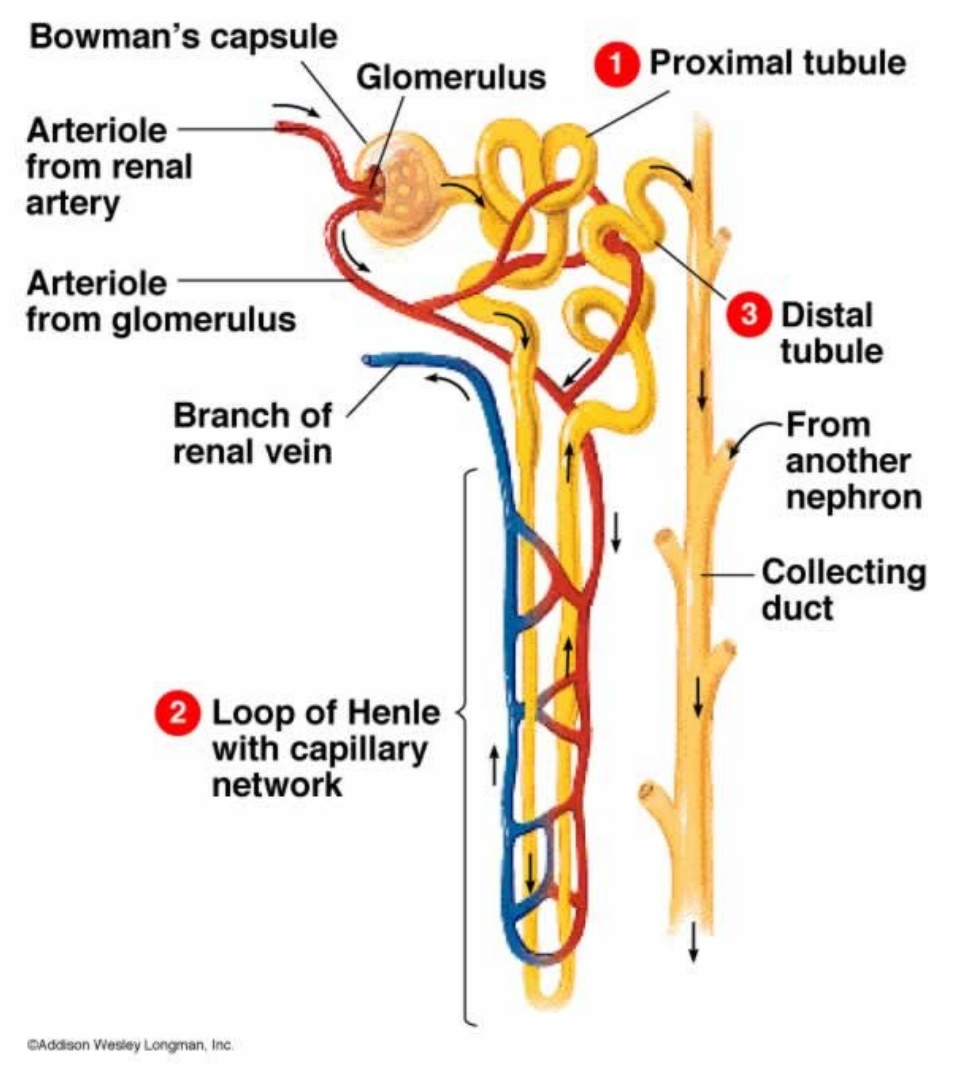

هاد ال **regulations** بصير عن طريق :

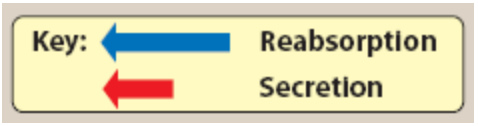

وهاد الإشي بصير بخمس مناطق عليهم هايلايت بالسلايد

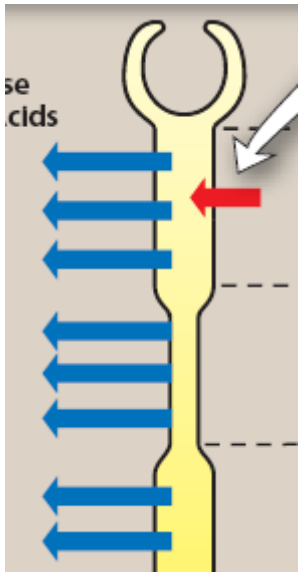



هي صورة بتوضّح ال 5 functional zone of nephron:

بهمني أعرف كل بارت عشان أعرف ال **diuretic** وين ح يشتغل لييه ؟ لأنه كل بارت ح يصير فيه **reabsorption and secretion** ل **certain ions** فقط



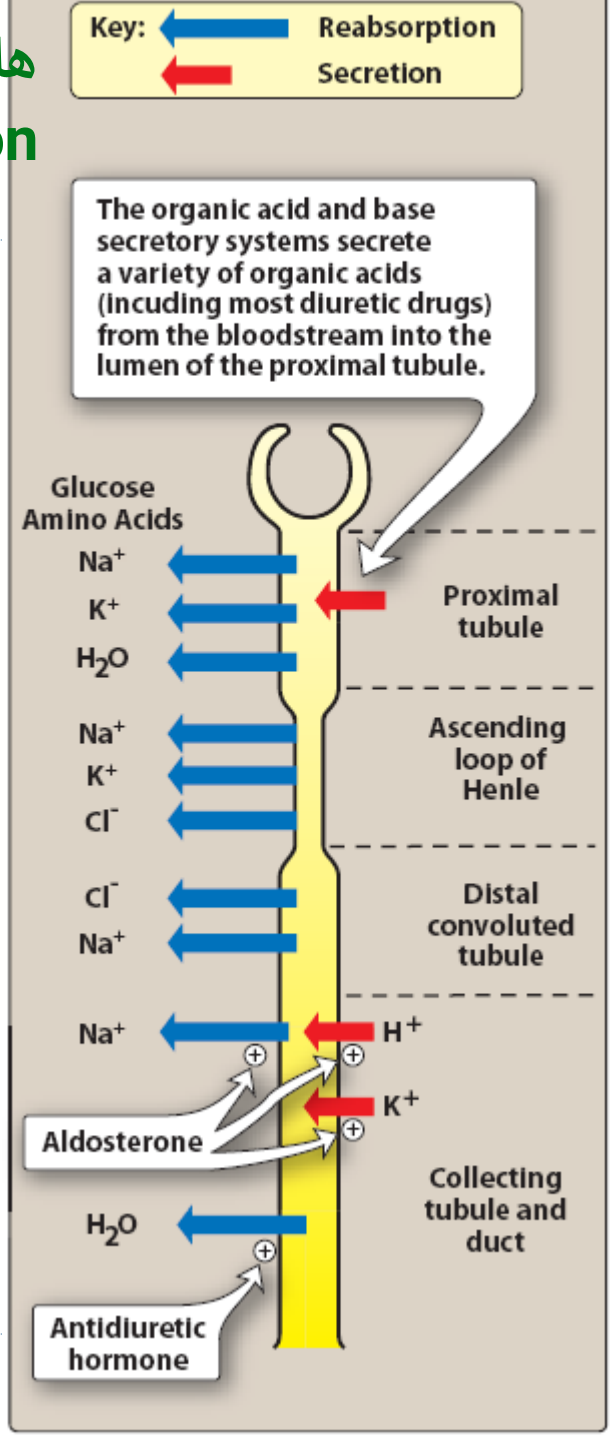



هاد السلايد بفرجينا حركة الأيونات بأجزاء ال **functional zone of nephron**

# Acid and base secretory systems

- Organic acid secretory systems are located in the middle third of the straight part of the proximal tubule.
- These systems secrete a variety of organic acids (uric acid, nonsteroidal anti-inflammatory drugs [NSAIDs], diuretics, antibiotics, etc) from the blood into the luminal fluid.
- These systems thus help deliver diuretics to the luminal side of the tubule, where most of them act.



# Diuretics

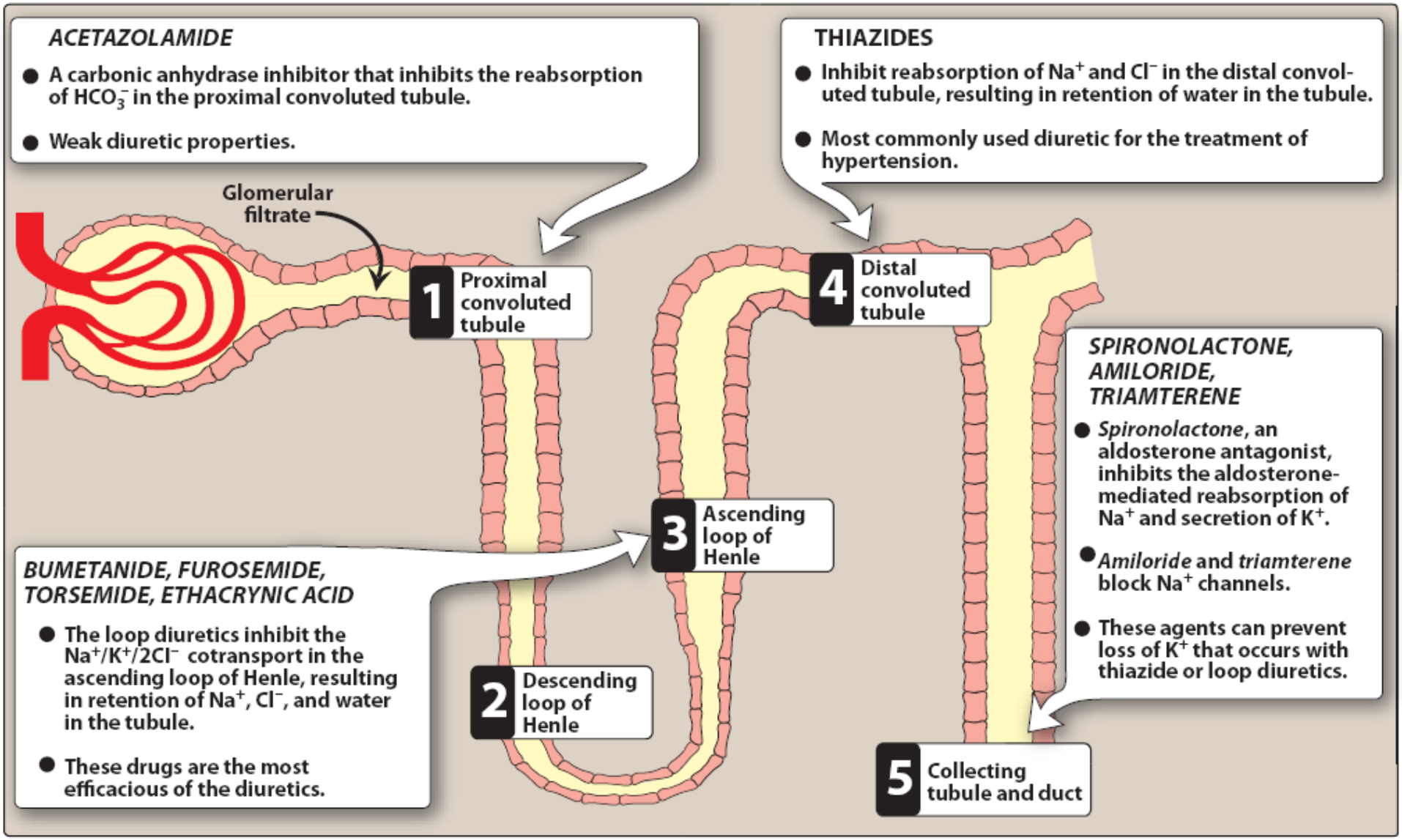
تعريفها: هي الأدوية إلّي بتزيد معدل خروج الurine

- Diuretics are drugs that increase the rate of urine flow. There are several classes of diuretic drugs:

1. Thiazide and thiazide-like diuretics: **hydrochlorothiazide, chlorthalodone**
2. Loop diuretics or the high ceiling diuretics: **furosemide, torsemide**
3. $K^+$ sparing diuretics
   1. Na channel inhibitors: **amiloride, triamterene**
   2. Aldosterone receptor antagonists**:** **spironolactone, eplerenone**
4. Carbonic anhydrase inhibitors: **acetazolamide**
5. Osmotic diuretics: **mannitol**

تصنيف ال diuretic مع أمثلة ع كل تصنيف :

# Sites of action of diuretic drugs



أولاً: Acetazolamide بعملوا inhibition re absorption of HCO3 لداخل ال proximal convoluted tubule ويُعتبر ال diuretic effect إله ضعيف

عنا ال Thiazides بعمل inhibition re absorption لكل من الNa, CL لداخل ال distal convoluted tubule ف هيك رح يزيد ال retention of water وهاد أكتر شي مستخدم بعلاج ال Hypertension

عنا كمان نوع هو ال spironolactone, amiloride : شو بعملوا ؟ عنا ال spironolactone يُعتبر aldosterone antagonist يعني رح يثبط ال aldosterone -mediated reabsorption of sodium and secretion of potassium
بالمقابل عنا ال amiloride و trimamterene رح يعمل إغلاق لقنوات الصوديوم المهم نتيجتهم الكلية هي منع فقدان وخسارة البوتاسيوم ف لهيك ممكن يعملوا hyperkalemia

آخر شي bumetanide, furosemide, torsemide, ethacrynic acid هدول ال agents كلهم رح يعملوا inhibition Na K Cl transport in the loop of Henle ف نتيجة لهيك رح يصير retention of Na Cl water بداخل هاي ال tubule
وهاي أكتر ادوية فعالية ك diuretic

# Thiazide diuretics

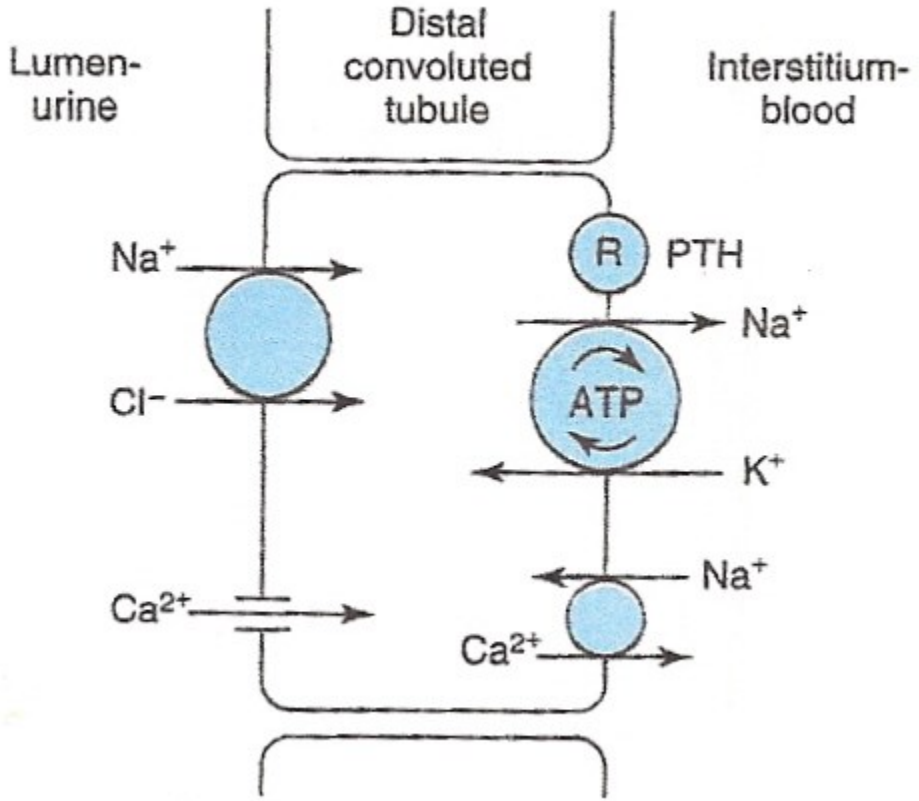
- **Mechanism of action:**
- The thiazide diuretics act mainly in the cortical region of the ascending loop of Henle and the distal tubule to decrease the reabsorption of Na+ by inhibition of a Na+/Cl– co-transporter on the luminal membrane of the tubules.
- These drugs increase the concentration of Na+ and Cl– in the tubular fluid (urine).
- Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.

هي الأدوية الوحيدة إلّي بنعطيها في حال كان الشخص عنده **hypertension**
وما عنده **athor contraindications** طبعًا هم بشتغلوا بشكل أساسي على
**ascending loop of Henle and distal tubule** ف بالتالي رح يقلل ال
**reabsorption of sodium** عن طريق إنه يعمل **inhibition of Na/Cl**
**transport**
هاي الأدوية بتزيد من تركيز الصوديوم والكلورايد بداخل ال **tubular fluid**

ما بنستخدم هاي الأدوية بحالات ال **renal failure** شو السبب ؟ لأنه
هاد النوع من الأدوية بشتغل على ال **luminal membrane** وبصيرلها
**excreted into the tubular lumen** لحتى تعطينا نتيجة فعالة
ف وقت يكون في انخفاض بال **renal function** ما رح يكون استخدام
ال **Thiazides** هون فعّال

موضّح ال **action of Thiazides** بالسلايد الجاي

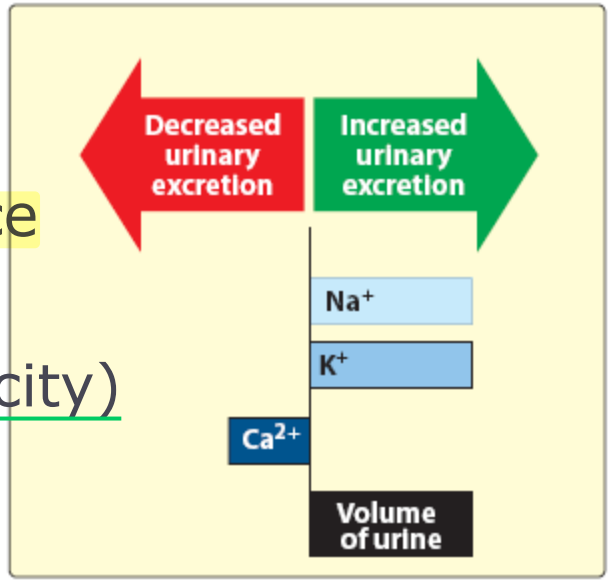
# Thiazide Diuretics




These agents act in the distal convoluted tubule and block a $Na^+$, $Cl^-$ symporter that is associated with the luminal membrane. This transport system moves both $Na^+$ and $Cl^-$ into the cell using the free energy produced by the $Na^+$, $K^+$, ATPase. The $Na^+$ is pumped out of the epithelial cell via this transport system in the basolateral membrane. The $Cl^-$ exits the cell via a $Cl^-$ channel.

# Thiazide diuretics

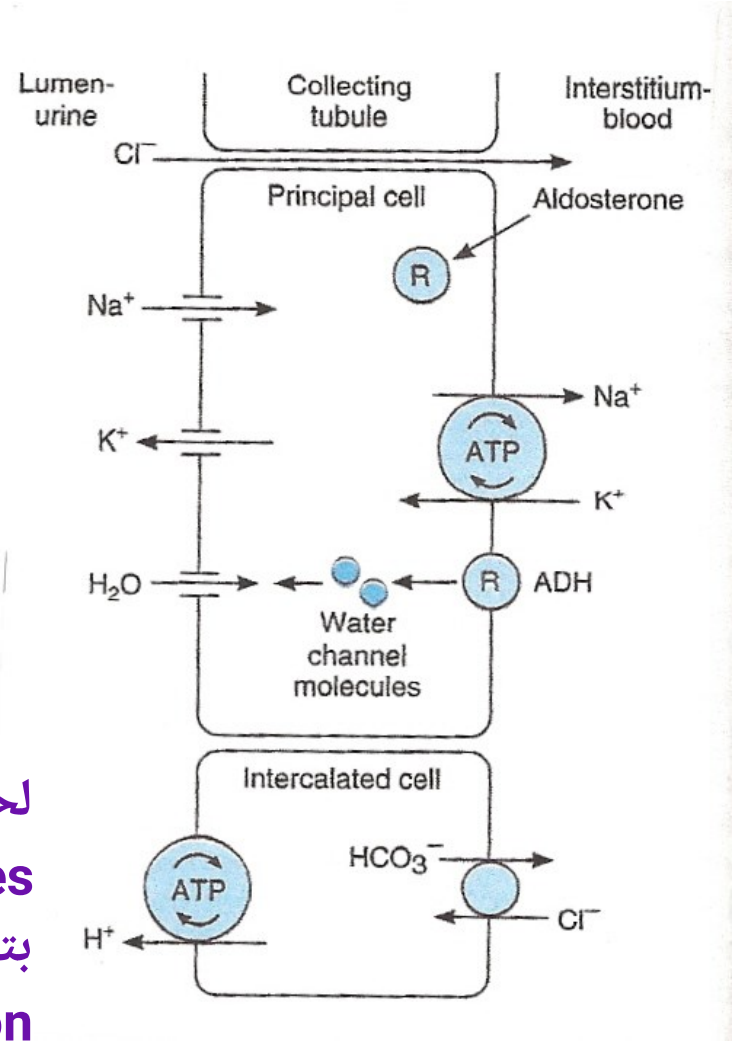
- Actions:
  - Increase Na+, Cl- and K+ excretion
  - Decrease Ca++ excretion
  - Reduce peripheral vascular resistance
- Side effects:
  - Hypokalemia (increases digoxin toxicity)




يعني في حال كان الشخص بياخد
**Thiazides** مع **digoxin** ، ومن ال **side**
**effects** لل **Thiazides** هو ال
**Hypokalemia** ف رح يصير زيادة بسمّية ال
**digoxin** عند هاد المريض

# Why do thiazide and loop diuretics induce hypokalemia?

- The heavy load of sodium presented to the collecting tubule results in increased exchange of tubular Na+ for K+ with the possibility of inducing hypokalemia.
- Potassium-sparing diuretics block Na+ channels or decrease their expression preventing hypokalemia.



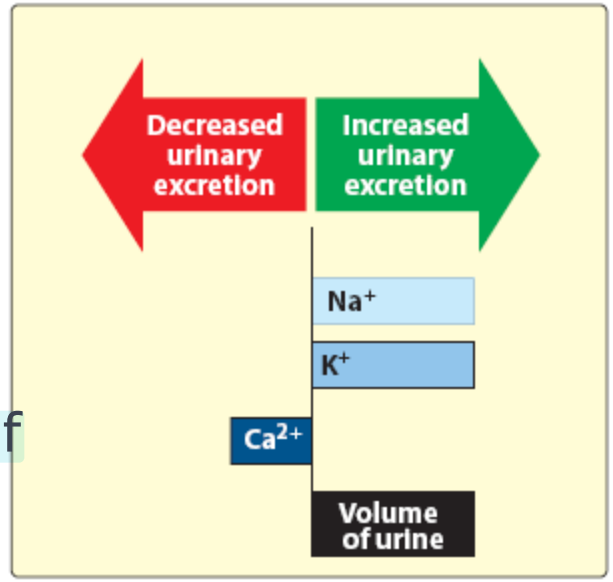

لحتى نمنع يصير **Hypokalemia** ممكن نعطي مع ال **Thiazides** شو ؟ **potassium sparing diuretics** إلّي بتعمل **blocking** لقنوات الصوديوم أو **decrease their expression** وهيك بنمنع يصير **Hypokalemia**

# Thiazide diuretics ال **side effects** لل **Thiazides** واضحين

- Side effects:
  - Hypokalemia (increases digoxin toxicity)
  - Hypercalcemia
  - Hyperuricemia (is caused by hypovolemia-associated enhancement of uric acid reabsorption in the proximal tubule and the competition with uric acid secretion at the DCT)

نسبة ال **uric acid** بالجسم بتزيد

  - Hyperglycemia
  - Hyponatremia (It can be prevented by reducing the dose of the drug or limiting water intake).
  - Hypersensitivity (The thiazides are sulfonamides)




**sulfa allergy** ما بنعطيهم للناس إلّي عندها

# Thiazide diuretics

متى بستخدمهم ؟ يُعتبر ال **first line** بعلاج ال **Hypertension** ، **treatment**
وبقدر أستخدمه بحالة **heart failure** لكن
يُفضّل هون استخدام **loop diuretics**

- Therapeutic used:
  - HTN (first line treatment)
  - HF (loop diuretics are preferred)
  - Hypercalciurea (for pts with calcium oxalate stones in the urinary tract)
  - Diabetes insipidus (is due to deficient production of ADH or inadequate response to ADH). Thiazide diuretic increases interstitium osmolarity.

بنمنع تجمّع ال **calcium oxalate stone** بال **urinal** **tubule**

هون لا يعني إنه معهم سكري وإنما بكون عندهم نقص او
كمية غير كافية من ال **ADH** ف بهاي الحالة بتيجي ال
**Thiazides** بتزيد من **interstitium osmolarity**

**Thiazides** أمثلة على أدوية

- Specific agents:
  - Hydrochlorothiazide
  - Chlorthalidone
  - Metolazone (can be used in advanced renal failure)
  - Indapamide

**ADH: antidiuretic hormone**

# Thiazide diuretics

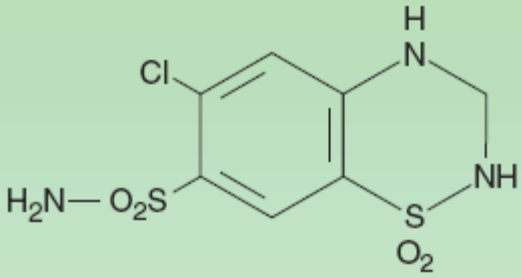
**TABLE 15–5 Thiazides and related diuretics.**

| Drug | Total Daily Oral Dose | Frequency of Daily Administration |
|---|---|---|
| Bendroflumethiazide | 2.5–10 mg | Single dose |
| Chlorothiazide | 0.5–2 g | Two divided doses |
| Chlorthalidone[1] | 25–50 mg | Single dose |
| Hydrochlorothiazide | 25–100 mg | Single dose |
| Hydroflumethiazide | 12.5–50 mg | Two divided doses |
| Indapamide[1] | 2.5–10 mg | Single dose |
| Methyclothiazide | 2.5–10 mg | Single dose |
| Metolazone[1] | 2.5–10 mg | Single dose |
| Polythiazide | 1–4 mg | Single dose |
| Quinethazone[1] | 25–100 mg | Single dose |
| Trichlormethiazide | 1–4 mg | Single dose |

[1]Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

All thiazides can be administered orally, but there are differences in their metabolism.

Example: Chlorothiazide, the parent of the group, is not very lipid-soluble and must be given in relatively large doses. It is the only thiazide available for parenteral administration.




Hydrochlorothiazide