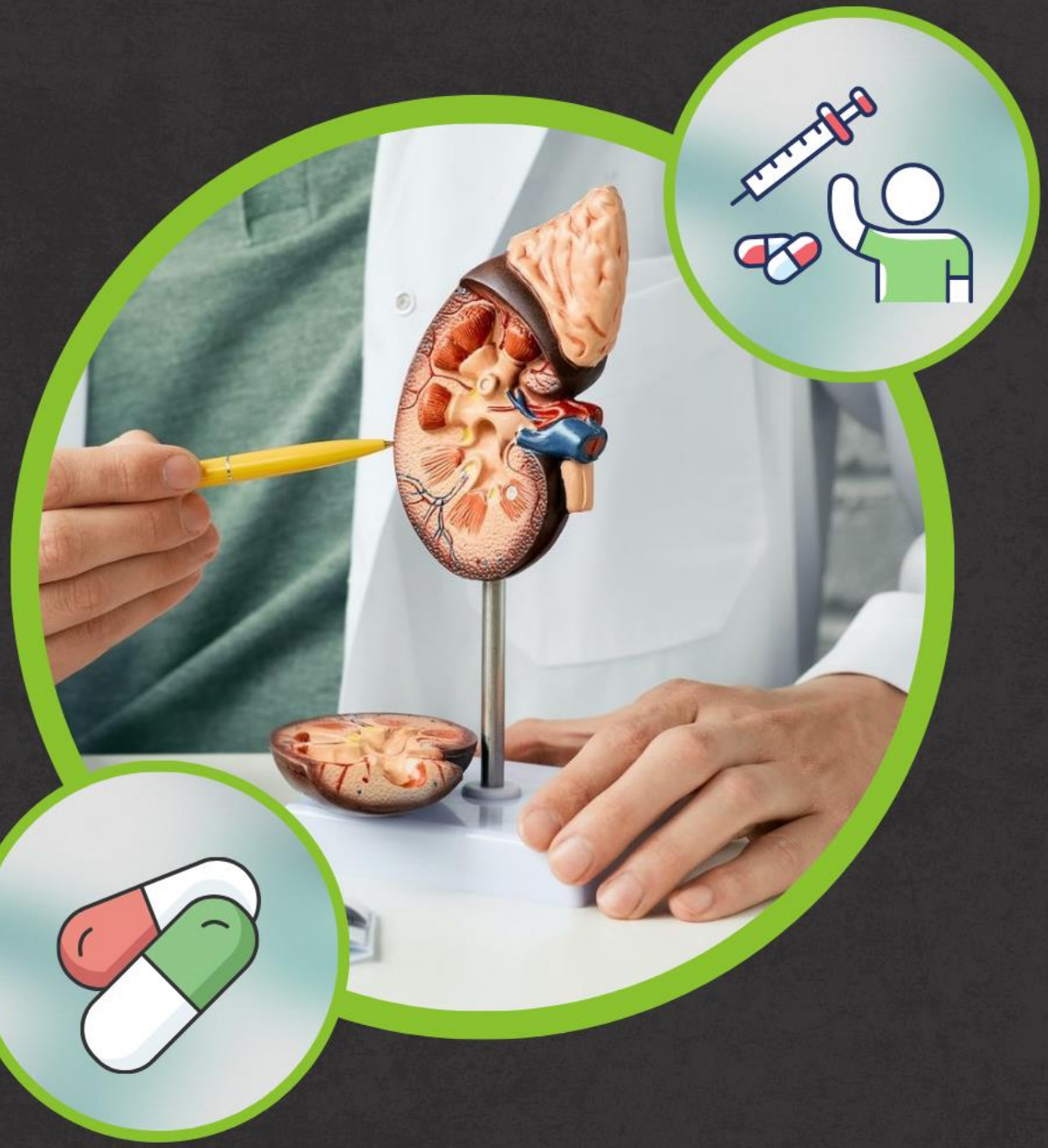

PHARMA

MODIFIED NO. 1

الكُتّاب: إسماعيل العارضة وصهيب زعيتر

المدققين: خديجة ناصر

الدكتور/ة: يعقوب ارشيد

Diuretics

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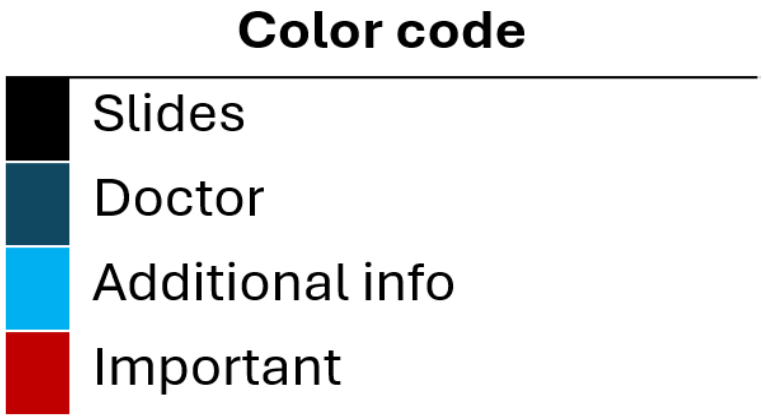

- Before talking about the individual classes of diuretics, as we know from the physiology ,we have the nephrons and we will identify the sites of action of different diuretic agents that we will talk about.

- We have the glomerulus ,then proximal convoluted tubules, then loop of henle (thin descending ,thin ascending and thick ascending) ,distal convoluted tubules ,collecting tubules (gather with collecting tubules of other nephrons) and finally the collecting duct.

- We have 7 or 8 classes of diuretics and we will only talk about five of them.

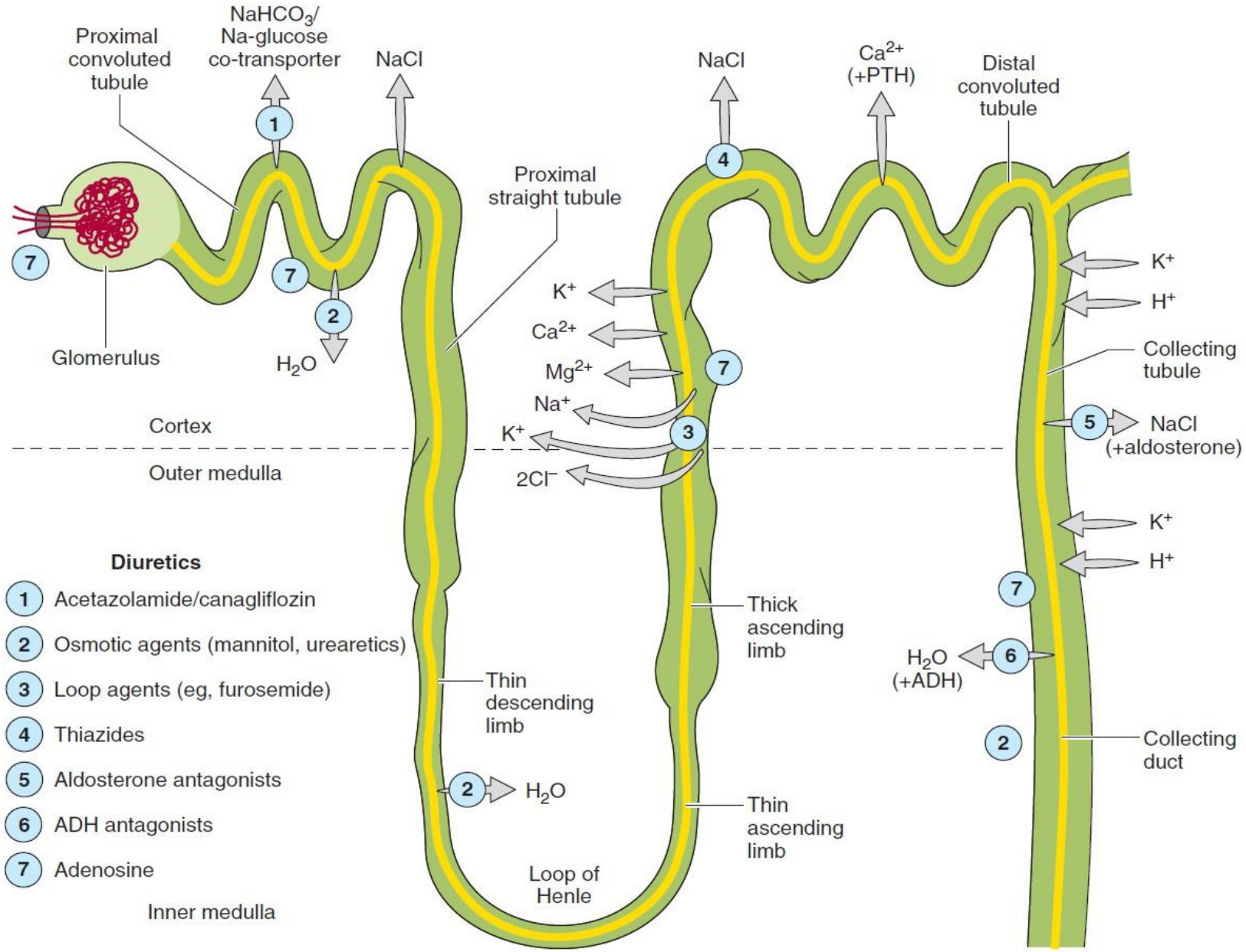

FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

Keep tracing the photo while reading

In the beginning in number (1), **NaHCO3/Na-glucose co-transporter** are actually two things not one:

1- we have **NaHCO3** reabsorption in the proximal convoluted tubule facilitated by an enzyme called carbonic anhydrase (if we inhibit this enzyme ,it will cause diuresis)

2- **Na-glucose co-transporter** will reabsorb less than 50% of filtered glucose

Effects of the drugs that inhibit the Na-glucose co-transporter:

- **Treatment of DM:** these drugs were originally developed to treat diabetes mellitus by enhancing glucose excretion from the body
- **Diuresis:** glucose does not get excreted alone, water will follow and is also excreted, causing diuresis.
- **Treatment of heart failure:** (in addition to the conventional diuretics), because they have an effect on the hospitalization and mortality in heart failure patients, (they were not developed originally as diuretics, but they have a diuretic action, which helps in cases of heart faliure to prevent fluid overload).

Now let's talk about **adenosine** (number 7): it is found in the proximal convoluted tubule (PCT), the thick ascending limb of Henle, and the collecting duct. It is more relevant physiologically than pharmacologically, since drugs that inhibit adenosine (like caffeine) are not commonly used as diuretics, so we will not discuss it further.

Carbonic Anhydrase Inhibitors

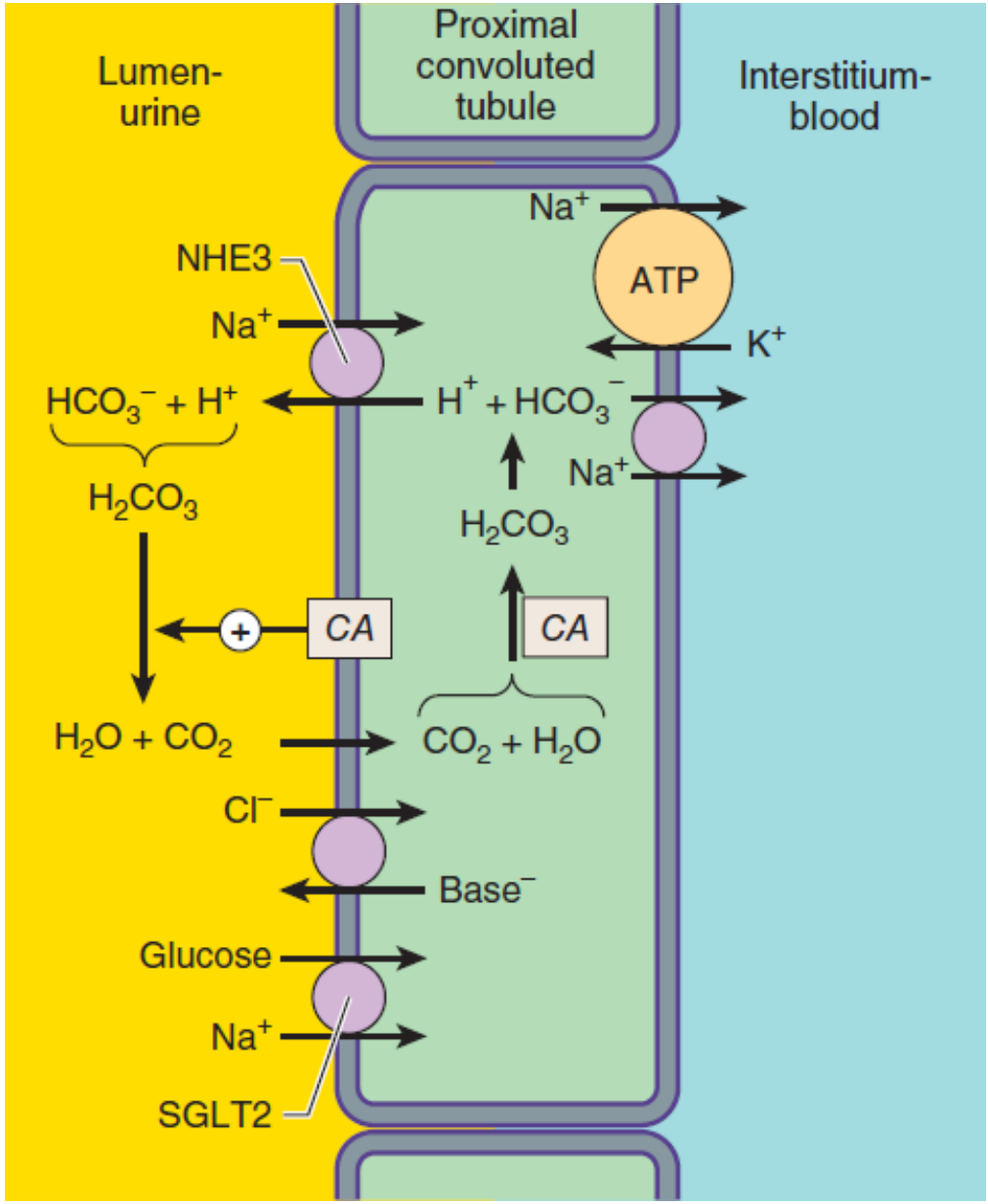

FIGURE 15–2:

- **Apical membrane Na^+/H^+ exchange (via NHE3) and bicarbonate reabsorption in the proximal convoluted tubule cell.**
- **Na^+/K^+-ATPase is present in the basolateral membrane to maintain intracellular sodium and potassium levels within the normal range.**
- **Because of rapid equilibration, concentrations of the solutes are approximately equal in the interstitial fluid and the blood.**
- **Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane.**
- **SGLT2, Na^+/glucose co-transporter.**

General notes before we start:

- No ion will be transported without water, water molecules will always follow transported ions in the same direction.
- No ion (positive or negative) is being absorbed or transported alone; there should be a counter-ion moving along.

- We will start with **carbonic anhydrase inhibitors**, so we will talk about sodium bicarbonate reabsorption, and we will take a cell from the PCT.

- The cell has an interstitium (blood side) and a luminal side. We have bicarbonate reabsorption by co-transport with sodium.

- Bicarbonate comes from an interaction of bicarbonate in urine with hydrogen ions, forming carbonic acid. Then, carbonic anhydrase will convert it to water and CO_2, and both are permeable through the membrane, so they will enter the cell. Again, they form carbonic acid, then undergo hydrolysis into a hydrogen ion and bicarbonate. Then it is reabsorbed with sodium by a co-transport mechanism.

- We have Na-K ATPase in the basolateral membrane to keep the composition of ions (Na+ and K+) normal inside the cell (note: K+ concentration is higher inside than outside the cell).

- We have Cl transport in exchange with a base- . when there is a high concentration of carbonate in the lumen ,something should be pushed and it should be negatively charged like the bicarbonate out to achieve an electrical balance inside the lumen, so the chloride will enter in exchange with a base like bicarbonate (HCO3-) ,citrate, asitate etc.

When we **inhibit carbonic anhydrase** (by drugs):

- no bicarbonate will be formed in the cell
- no carbonic acid or CO2 and water in the lumen

So: bicarbonate will be excreted in the urine and will pull sodium with it ,so we **lose sodium bicarbonate (NaHCO3)**(most important), potassium and hydrogen ions, increasing **urine alkalinization** (in overdose, **metabolic acidosis** in the blood could happen).

Carbonic Anhydrase Inhibitors

Acetazolamide
Dichlorphenamide
Methazolamide

- The **prototype drug:** the first drug discovered or developed in a certain drug family and we compare the newer agents with it (the prototype drugs is the reference for the advantages and disadvantages).
- **The prototype carbonic anhydrase inhibitor:** Acetazolamide

Pharmacological Actions:

1. Reduce sodium bicarbonate reabsorption in the proximal convoluted tubule. (85% of the HCO_3 reabsorption capacity of PCT is inhibited).

- Very effective in prevention of bicarbonate reabsorption (85%).

Carbonic Anhydrase Inhibitors

2. **Alkaline diuresis: HCO_3^- depletion → enhanced NaCl reabsorption by the remainder of the nephron → tolerance to the diuretic action (reduced efficacy) over several days.**

- Increasing urine pH

- Check the next slide

3. **Reduce formation of aqueous humor by the ciliary body of the eye (HCO_3^- - dependent) and thus intraocular pressure.**

- **The aqueous humor in the eyes is formed by a carbonic anhydrase and HCO3- dependent mechanism.**
- If we inhibit the carbonic anhydrase, we reduce the formation of the aqueous humor and reduce the pressure on the optic nerve and its effect on the vision, so we can **treat glaucoma.**

Note:
Aqueous humor can be reduced by either reducing its production (CA inhibitors) or by increasing its drainage (other drugs).

Regarding the second point:

- Our bodies can tolerate diuretics by recognizing them as foreign substances and responding through changing excretion, metabolism, or physiological counter-regulatory mechanisms.

- So, we will have Na+ and Cl- reabsorption instead of the excreted HCO3-, because we need a negative charge (which is Cl-) to be exchanged for the negative charge being excreted (HCO3-), and Cl- needs a positive ion to enter with it like Na+ mostly, so we have Na+ and Cl- retention.

- This leads to the development of **tolerance** to the action of diuretics.

- In diuresis, the goal is to reduce plasma volume by promoting the loss of fluids, sodium (Na^+), and other specific ions and water from the body, because we have a congestion and excess water. Here, the NaCl will enter instead of bicarbonate and inhibit diuresis, so these agents will not be used as diuretics and they have other uses that will be discussed later on. (**they induce diuresis initially, but this effect diminishes over time as counter-regulatory mechanisms are activated)**.

Carbonic Anhydrase Inhibitors

4. **Reduce formation of cerebrospinal fluid by the choroid plexus by a similar mechanism.**

- The **CSF is formed under the influence of bicarbonate and a carbonic anhydrase-dependent mechanism.**
- Carbonic anhydrase inhibitors will reduce the formation of CSF and reducing the high intracranial pressure

5. **Metabolic acidosis(mild): this increases the threshold for epileptic seizures.**

- Due to loss of alkaline urine, we will have metabolic acidosis in the body.
- If it's sever, it's considered pathological and needs an administration to the hospital.
- But here it's mild, and will help prevent epileptic seizures by increasing the threshold for them (for treatment of patients resistant to anti-siezure drugs)

General note:

- Advere effects are of two types:

1- Type A: side effects related to the pharmacological actions of the drug

2- Others: not related to the pharmacological actions

Carbonic Anhydrase Inhibitors

Adverse Effects:

1. Hyperchloremic metabolic acidosis due to reduction of body HCO_3 stores.
2. Calcium phosphate renal stones.

- Calcium phosphate is insoluble in alkaline urine.
- Reduction of renal excretion of calcium solubilizing factors ($citrate^-$) with chronic use.

Treatment of these stones:
1. Acidifying the urine
2. Increasing excretion of solubilizing factors (citrate: -vely charged, so it combines with calcium, making the calcium soluble)

- Same concept applies to treatment of gout, when we need to prevent uric acid stones, we induce alkalinisation of urine to make it soluble.
- We need a pure vitamin C (not orange juice) to make acidification of the urine.

Carbonic Anhydrase Inhibitors

3. **Renal potassium loss** (can lead to hypokalemia)**: Bicarbonate loss in urine increases negative charge in the collecting tubule which enhances potassium secretion** (in addition to other +ve ions)**.**

General rule
All diuretics cause K+ loss except:
1- caffaine
2- K+-sparing diuretics

4. **Hypersensitivity reactions (fever, rash, <u>bone marrow suppression</u>, <u>interstitial nephritis</u>).**

Any drug can induce hypersensitivity reactions even drugs used to treat hypersensitivity !

But here, BM suppression and interstitial nephritis are special symptoms

- All diuretics cause K+ loss except caffeine and K+ sparing diuretics.
- All drugs cause hypersensitivity reactions even drugs used to treat hypersensitivity, but there are some special symptoms here, like **bone marrow suppression** as a hypersensitivity reaction (rash ,IgE formation ,mast cell degradation, hypotension etc, these all can be caused by any drug ,but not all drugs make bone marrow suppression as an allergic reaction). (The cause of bone marrow suppression in this case is allergy)
- If the term **interstitial nephritis** is due to drugs, this is an allergy inside the kidney (dangerous 🚨).
- On the other hands, Allergy in the liver will cause **cholestatic hepatitis.**

Carbonic Anhydrase Inhibitors

5. **Reduction of urinary excretion of NH_4^+ (by converting it to rapidly reabsorbed NH_3) → <u>hyperammonemia</u> (as a result of urinary alkalinization and metabolic acidosis). This contributes to <u>hepatic encephalopathy</u> <u>in patients with hepatic cirrhosis.</u>**

- The –vely charged bicarbonate in urine will react with the +vely charged ammonium producing ammonia which is then reabsorbed
- Accumulation of ammonia (which can pass through BBB) in the brain in patients with liver failure will cause hepatic encephalopathy

Carbonic Anhydrase Inhibitors

Therapeutic Uses:

1. **Rarely used as diuretics.**
2. **Glaucoma, most common use, topical.**
3. **Used for urinary alkalinization to enhance elimination of acidic drugs and toxins.**
4. **Metabolic alkalosis.**

- Through the induction of metablic acidosis

- The loss of bicarbonate will make the urine alkaline and acidic drugs or toxins will be eliminated because they will be ionized and not reabsorb-able increasing elimination.

Carbonic Anhydrase Inhibitors

5. **Acute mountain sickness (high altitude 3000 m): By decreasing CSF formation and by decreasing the pH of the CSF and brain, they can increase ventilation and diminish symptoms of mountain sickness. This is also useful in the treatment of sleep apnea.**
6. **Adjuncts in treatment of epilepsy.**

- Sleep apnea (stopped or reduced ventilation during sleep): these drugs can be useful by the induction of hyperventilation

Now we will start talking about Loop Diuretics 

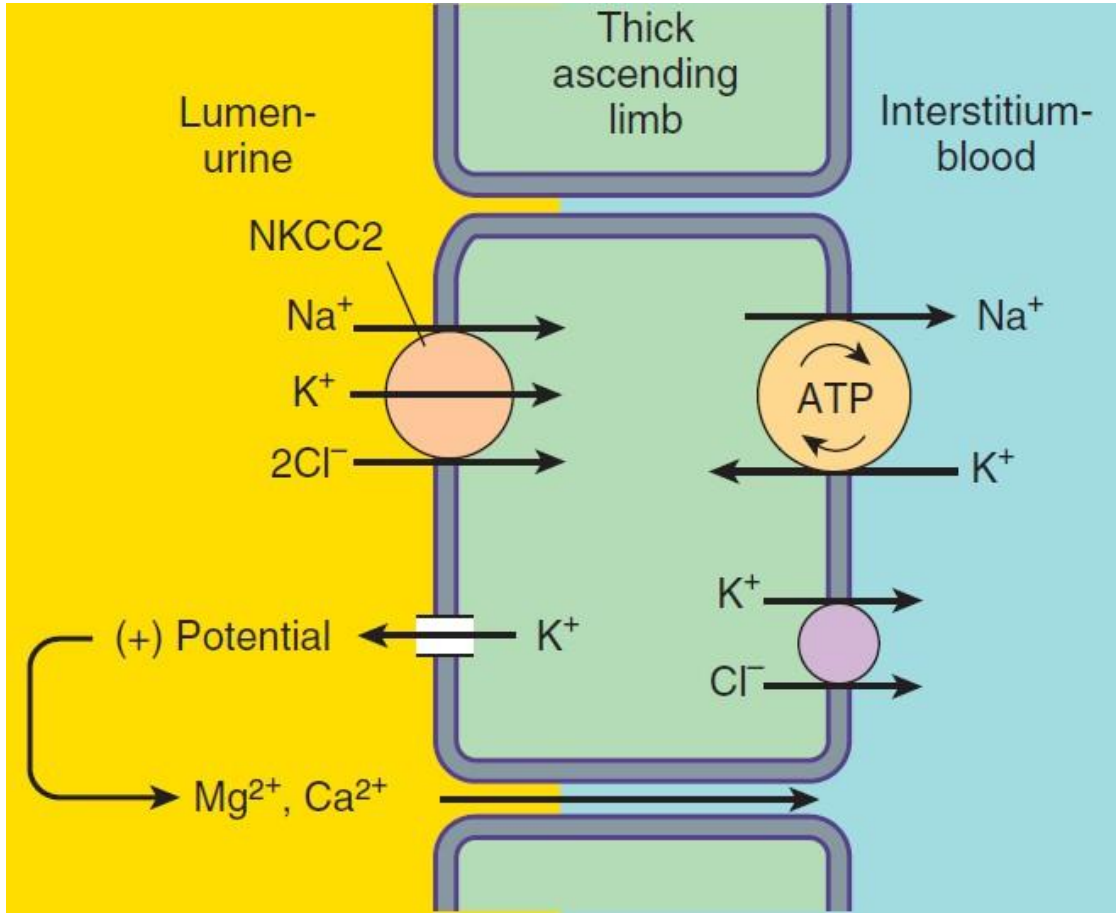

FIGURE 15–3:

- **Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell.**
- **The lumen positive electrical potential created by K^+**
- **back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway.**
- **NKCC2 is the primary transporter in the luminal membrane.**

- They are called **loop diuretics** because they act on the **loop of Henle**. In the **thick ascending limb** of the loop of Henle, there is a **sodium-potassium-2 chloride co-transporter (NKCC2)**. This transporter is responsible for the reabsorption of sodium, potassium, and chloride ions.

- On the **basolateral (interstitial) side** of the tubular cells, there is a **sodium-potassium ATPase pump** that helps maintain the proper intracellular concentration of sodium and potassium.

- Since both the NKCC2 and the sodium-potassium ATPase pump bring potassium into the cell, potassium may accumulate inside. This **excess potassium** is either secreted into the **lumen** through potassium channels, generating a **positive electrical potential** in the tubular lumen, or it is reabsorbed into the interstitium via **basolateral co-transport with chloride**.

- This **positive potential in the lumen** facilitates the **paracellular reabsorption** of positively charged ions like **magnesium (Mg^{2+})** and **calcium (Ca^{2+})** into the interstitium.

- When NKCC2 is **inhibited**, all of these processes are disrupted. This results in the loss of **Na^{+}, K^{+}, Cl^{-}, Mg^{2+}, and Ca^{2+}**, along with a significant amount of water. That's why loop diuretics are considered the **most effective diuretics**.

- Drugs that inhibit NKCC2 are called **high-ceiling diuretics**, meaning their effect increases with dose without developing tolerance—unlike carbonic anhydrase inhibitors.

- Loop diuretics are used in conditions involving **fluid overload**, especially in **heart failure**. In such cases, loop diuretics are often administered by **injection**, leading to a **rapid onset of action**—within seconds to minutes.

- However, in some patients with excess tissue fluid (edema), loop diuretics can be problematic. These drugs cause **rapid loss of fluid from the blood**, while the movement of fluid from tissues back into the bloodstream is slower. This mismatch can lead to **dehydration**, **renal failure**, and **low plasma volume**, even though the patient still has excess fluid in the tissues.

Loop Diuretics

- **Also called high ceiling diuretics.**
- **The most efficacious diuretic agents available.**
- **Tolerance do not develop to their diuretic actions.**

Loop Diuretics

New in pharmacology means in the last 10-15 years

1. **Sulfonamide derivatives:**

Newer ones

the most used one

- **Furosemide, Bumetanide, Torsemide.**

2. **Phenoxyacetic acid derivatives:**

the oldest one, rarely used

- **Ethacrynic acid.**

Loop Diuretics

Pharmacological Actions:

1. **Inhibit the luminal $Na^+/K^+/2Cl^-$ co-transporter in the thick ascending limb of Henle's loop.**
2. **Diminish the lumen-positive potential that comes from K^+ recycling.**
3. **Increase urinary loss of Na^+, K^+, Cl^-, Mg^{2+} and Ca^{2+}.**

- However, there is an **active transport mechanism for calcium** in the **distal tubules**, which helps prevent **severe hypocalcemia** (low calcium levels). On the other hand, **dangerous hypomagnesemia** can occur, **hypokalemia**, **hyponatremia** can occur too, and so on.

Loop Diuretics

4. **However, calcium is actively reabsorbed under the effect of PTH in the distal convoluted tubule and its intestinal absorption can be increased, thus, hypocalcemia is rare).**

There is another pharmacological action contributes to the diuresis and protects the kidney from damage which is:

5. **Induce renal prostaglandin (Especially PGE_2) synthesis (antagonized by NSAIDs) → increase renal blood flow, which contributes to the diuretic action.**

Vasodilator, Prevents ischemia of the kidney which is good and induces diuresis.

Prostaglandins are antagonized by NSAIDs, that's why NSAIDs damage the kidney more than you expect them to do so, they cause vasoconstriction in the medulla of the kidney because they inhibit the synthesis of PGE_2

Loop Diuretics

5. **Furosemide and ethacrynic acid reduce pulmonary congestion and reduce left ventricular filling pressure in heart failure before increasing urine output (this is also due to prostaglandins).**
6. **Furosemide and bumetanide inhibit carbonic anhydrase also. But this is not their major action.**

- When a patient with **pulmonary edema** is injected with **Furosemide** or **Ethacrynic acid**, their **breathing often improves before any urine appears in the collection bag**.
- This early improvement happens because these drugs cause **vasodilation**, especially of the **pulmonary veins relieving the congestion on the lungs.**

Veins are known as **capacitance vessels**, meaning they have the ability to **expand and hold more blood**.

- When the veins dilate, they **store more fluid** and **lowers the pressure in the lung.**
- **So: NSAIDs exert an opposite effect harming the lungs**

Loop Diuretics

See next slide

Pharmacokinetics:

- Rapidly absorbed, and extensively bound to plasma proteins.
- Eliminated by tubular secretion as well as glomerular filtration.
- Furosemide and ethacrynic acid are partially metabolized.
- Torsemide has an active metabolite with a t½ longer than that of parent compound.

- **Rapidly absorbed** → This means they can be given **orally**.

- **Extensively bound to plasma proteins** → This is important in the context of **drug–drug interactions**. When a drug is highly protein-bound, it can compete with other protein-bound drugs for binding sites. **Displacement** from the binding site increases the **free (active) fraction** of the drug in plasma, which can temporarily **enhance its action or toxicity**, but also **increase its elimination**. Overall, this can disrupt the intended therapeutic effect and is an important consideration in pharmacology.

- **Eliminated by tubular secretion as well as glomerular filtration** → When discussing diuretics (such as **carbonic anhydrase inhibitors** and **loop diuretics**), it's important to note that they act on the **lumen** side of the nephron—specifically on the **apical (brush border) membrane**. Therefore, they must be **excreted into the urine** to be active. Most diuretics are **actively secreted** into the urine via the **organic acid transport system**.

- If the drug is not secreted into the urine, it **will not work**. For example, **carbonic anhydrase inhibitors** or **thiazide diuretics** are ineffective in **renal failure**, even if the dose is increased. However, **loop diuretics (high-ceiling diuretics)** can still be effective in such cases if the **dose is sufficiently increased**. This concept is essential for understanding the mechanism and clinical use of diuretics.

- **Furosemide and ethacrynic acid are partially metabolized** → This means they are eliminated through both **renal secretion** and **hepatic metabolism**.

- **Torsemide has an active metabolite with a half-life longer than that of the parent compound** → This means that the **metabolite** contributes more significantly to the drug's **therapeutic effect** than the parent compound itself.

Loop Diuretics

All of the adverse effects are explained three slides ahead.

Adverse Effects:

1. Hypokalemic metabolic alkalosis due to increased renal secretion of K^+ and H^+.
2. Ototoxicity & deafness – reversible, dose-related hearing loss.
3. Hypomagnesemia: most often in patients with dietary magnesium deficiency

Loop Diuretics

4. **Hyperuricemia: due to hypovolemia-associated enhancement of uric acid reabsorption in the proximal tubule, and competition for the organic acid transporter. May precipitate attacks of gout.**
5. **Allergic reactions (rash, eosinophilia & interstitial nephritis).**

Loop Diuretics

6. **Severe dehydration.**
7. **Hyponatremia.**
8. **Hypocalcemia (?)**
9. **Hyperglycemia: due to hypokalemia-induced inhibition of insulin release.**

Some of the adverse effects are related to the pharmacological action of loop diuretics, while others are not:

🧪 **Hypokalemic metabolic alkalosis due to increased renal secretion of K+ and H+.**

🔊 **Ototoxicity & Deafness**

- This effect is **not related to the pharmacological action** of the drug. It occurs due to the **accumulation of the drug in the perilymph of the inner ear**, affecting balance and hearing. This side effect is more common with **ethacrynic acid**, which is why its use is limited.

🧂 **Hypomagnesemia**

- This can lead to **cardiac arrhythmias**, similar to hypokalemia. Since most diets are **not rich in magnesium**, this side effect is **clinically significant**. Patients may need **magnesium supplements** or be advised to consume **magnesium-rich foods**.

🦶 **Hyperuricemia (Can Trigger Gout)**

- Loop diuretics can increase **uric acid** levels through two mechanisms:

1- Competition for active transport: Uric acid is actively secreted into urine by the **organic acid transporter**. Loop diuretics (like furosemide) are also secreted via the same pathway. This competition **reduces uric acid excretion**, increasing its concentration in the blood and potentially triggering a **gout attack**, especially in predisposed patients.

2- Enhanced reabsorption in the proximal tubule: When loop diuretics act on the **thick ascending limb**, the body tries to compensate by increasing **reabsorption in the proximal convoluted tubule**. This includes not only ions but also **glucose and uric acid**. This adaptive mechanism may contribute to **hyperuricemia** and **hyperglycemia**.

🧬 **Allergic Reactions**

- These may include **rash**, **eosinophilia**, and **interstitial nephritis**—an immune-related inflammation of the kidney.

💧 **Severe Dehydration**

- Due to their strong diuretic effect, loop diuretics can cause **severe dehydration**, leading to: **Hypotension, Acute renal failure, Dizziness**, **encephalopathy**, or even **coma, Inadequate blood supply** to organs.

⚠️ **Hyponatremia & Hypokalemia**

- These have already been discussed earlier. Both are **common and clinically significant** electrolyte disturbances.

🦴 **Hypocalcemia (?)**

- This is **less concerning** because there is **active calcium reabsorption** under the influence of **parathyroid hormone (PTH)** in the **distal segments of the nephron**. This mechanism helps maintain calcium balance.

🍼 **Hyperglycemia**

- As discussed, **compensatory reabsorption mechanisms** in the proximal tubule help.

Loop Diuretics

Therapeutic Uses:

1. **Acute pulmonary edema, Congestive heart failure – increase systemic venous capacitance.**
2. **Acute hypercalcemia.**
3. **Hyperkalemia: Effect is enhanced by simultaneous NaCl and water administration.**

1- This is the **most common therapeutic use** of loop diuretics. **All heart failure patients** generally need to take loop diuretics to manage **fluid overload** (by getting rid of the excess fluid + through venodilation (increasing venous capacitance) by prostaglandins synthesis).

2- Loop diuretics are also used in cases of **acute hypercalcemia**, but **not in chronic hypercalcemia**, as the underlying **pathophysiology in chronic cases does not respond to diuretics**.

3- Insulin can also be used to treat **hyperkalemia**, but it must be administered **alongside glucose** to prevent **hypoglycemia**, which could result in **brain damage**.

Loop Diuretics

4. **Acute renal failure: increase the rate of urine flow and enhance potassium excretion and ameliorate intratubular obstruction.**
5. **Part of forced diuresis to enhance excretion of reabsorbable toxins and certain anions (Br^-, F^-, I^-). Saline solution must be administered to replace urinary losses of Na^+ and to provide Cl^-, so as to avoid extracellular volume depletion.**

"You can lead a horse to water, but you can't force it to drink.": these drugs are not helpful in cases of chronic renal failure (الكِلية خلص ودّعت), they only help in acute cases (لسا في أمل)

4- **Acute Renal Failure (ARF)**:

- In **acute renal failure**, loop diuretics can be given to help **clear the renal tubules** of debris caused by:

- **Precipitation** of substances inside the tubules
- **Cut-off of blood supply** (ischemia), and other factors.

- This can help restore some level of tubular flow and kidney function.

5- **Forced Diuresis**:

- This is a method used to **enhance the excretion of toxins**. If the toxin is normally excreted in urine, loop diuretics can induce **forced diuresis**.

- The patient is given **large amounts of fluid** along with a **loop diuretic**, which increases urine production. As the excess fluid is excreted, it **carries toxins and certain ions** with it.

لا الليلُ يحضنُ مافي القلبِ من ألمٍ
ولا الصباح إذا ما جاء يؤويهِ

حملتُ قلبي على كفي وسرتُ بهِ
لما تيقنتُ أنّ الله يكفيهِ!

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	35	**Hypoglycemia**	**Hyperglycemia**
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!