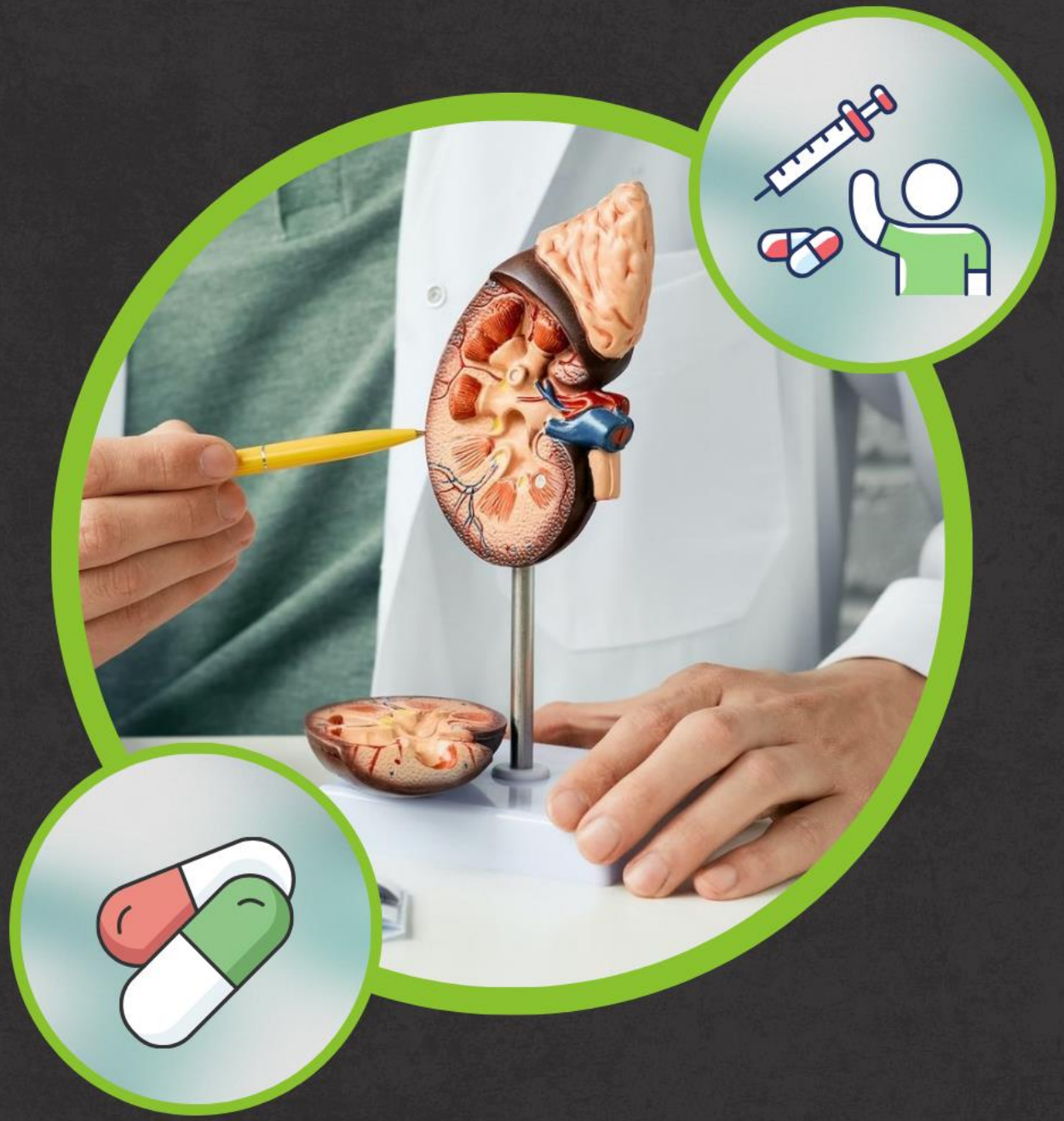

PHARMA

MODIFIED NO. 2

الكُتّاب: صهيب زعيتر ومتطوع آخر

المدققين: خديجة ناصر

الدكتور/ة: يعقوب ارشيد

- **Note:** the doctor reads every single word in the slides, so make sure not to skip any

Diuretics

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Color code
Slides
Doctor
Additional info
Important

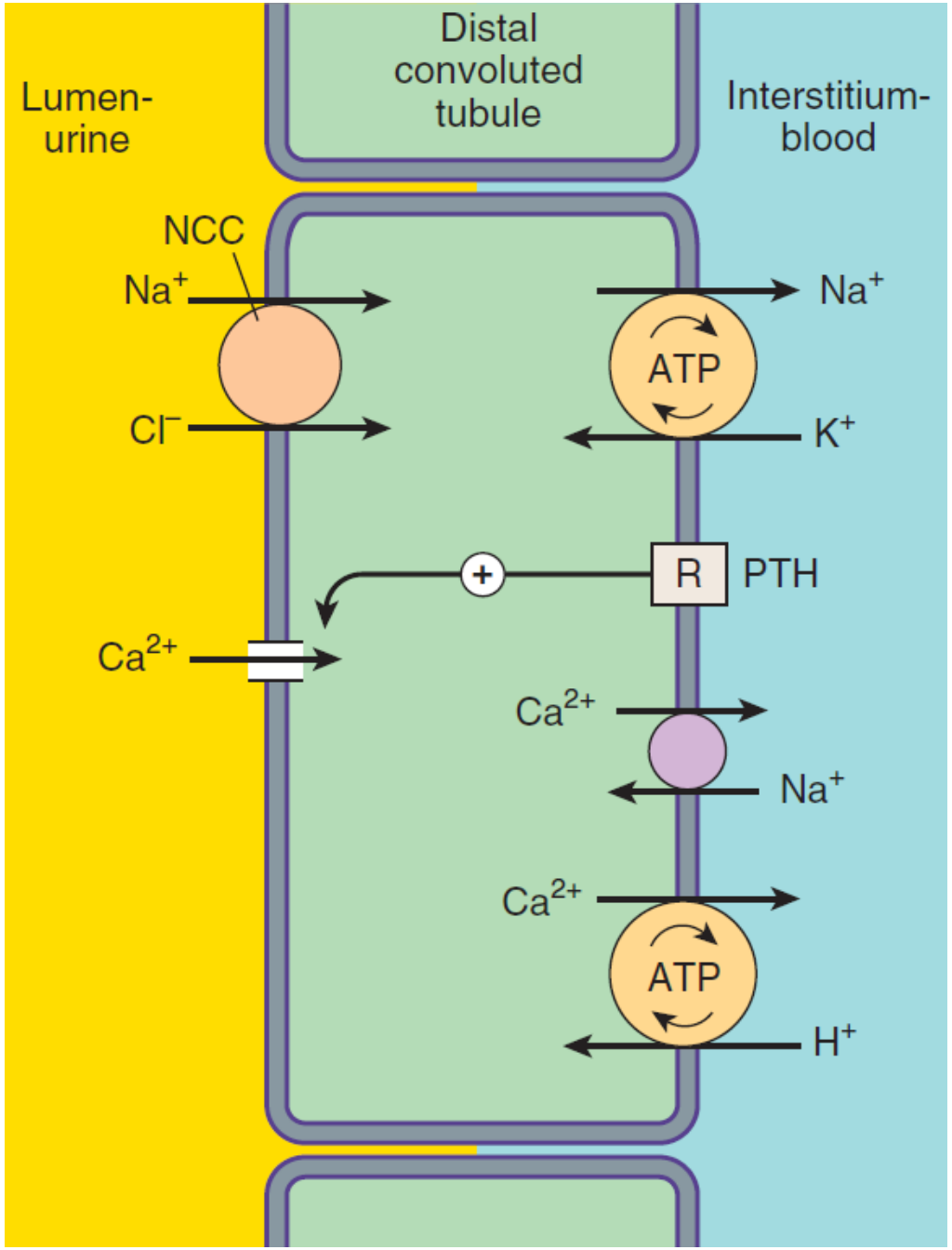


FIGURE 15–4

- **Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell.**
- **As in all tubular cells, Na^+/K^+-ATPase is present in the basolateral membrane.**
- **NCC is the primary sodium and chloride transporter in the luminal membrane.**
- **R, parathyroid hormone (PTH) receptor.**

Thiazide diuretics act on the distal convoluted tubules.

وانت بتقرأ تتبّع مع الصورة الي فوق 😁

- Their primary site of action is the **sodium-chloride cotransporter (NCC)**, which normally facilitates the reabsorption of sodium and chloride.

- In this segment, there are also **sodium-potassium ATPase** and **calcium-hydrogen ATPase** pumps that mediate exchange between calcium and hydrogen ions. Additionally, **calcium channels** function under the influence of **parathyroid hormone (PTH)**.

- Stimulation of **PTH receptors** promotes **calcium reabsorption** from the distal convoluted tubules.

- When the **sodium-chloride cotransporter (NCC)** is inhibited by thiazides, sodium and chloride reabsorption is reduced. As a result, more sodium enters the cell from the interstitium, promoting **calcium reabsorption** via **calcium-sodium exchange** (on the basolateral side of DCT) retaining calcium. There is also an associated effect on **hydrogen ion** exchange.

Thiazide Diuretics

Hydrochlorothiazide, Chlorthiazide
Chlorthalidone. Old ones

Indapamide, Metolazone. Thiazide-like diuretics

- **All have unsubstituted sulfonamide group.**

- There are **older** and **newer classes** of thiazide diuretics.
- The **other group** is called **thiazide-like diuretics**. This means they act in the same way as thiazide diuretics but are **not structurally classified as thiazides**.
- What they have in common with true thiazides is the presence of a **sulfonamide group.**

Thiazide Diuretics

What happens when the sodium-chloride cotransporter (NCC) is inhibited?

Pharmacological Actions:

1. Inhibit NaCl reabsorption from the distal convoluted tubule by blocking the electrically neutral, thiazide-sensitive Na^+/Cl^- co-transporter.
2. Enhance Ca^{2+} reabsorption in the distal convoluted tubule. May be due to lowering of intracellular sodium which enhances Na^+/Ca^{2+} exchange in the basolateral membrane.

Thiazide Diuretics

Thiazide-induced volume depletion leads to enhanced Na^+ and passive Ca^{2+} reabsorption in the proximal tubule.

3. **Significant carbonic anhydrase inhibitory activity.**
4. **Actions depend, in part, on renal prostaglandin synthesis.**

- When you inhibit the reabsorption of sodium via the **sodium-chloride cotransporter** in the **distal convoluted tubule**, this leads to a **decrease in intracellular sodium levels**. To compensate, sodium enters the cells through **sodium-calcium exchange**, which results in **calcium retention** (enhanced reabsorption of calcium).

- As mentioned in the previous lecture, any change that occurs in one segment of the nephron typically triggers **compensatory changes in other segments**. For example, if sodium reabsorption is inhibited in the **thick ascending limb of the loop of Henle**, the nephron compensates by **increasing sodium reabsorption in segments proximal and distal to it**.

- Similarly, when sodium-chloride reabsorption is inhibited in the **distal convoluted tubule** (as with thiazide diuretics), earlier nephron segments may **enhance sodium and chloride reabsorption**, which can lead to the development of **tolerance** to the diuretic effect of thiazides. This is because **thiazides are not high-ceiling diuretics** like loop diuretics.

- In real-life clinical practice, when thiazide diuretics are initiated, their **diuretic effect typically diminishes within 3–5 days** due to these compensatory mechanisms.

You might ask: Why do we still use thiazides, then? 🤔

- Despite their limited diuretic effect over time, **thiazide diuretics are first-line drugs in the treatment of hypertension**. When treating hypertension, we typically choose from **three main groups of medications**:

- **Thiazide diuretics**
- **Calcium channel blockers**
- **ACE inhibitors (ACEIs)** or **angiotensin receptor blockers (ARBs)**

(Note: ACEIs and ARBs are considered one class with two subclasses.)

- **Beta-blockers** are **no longer considered first-line** therapy for management of hypertension.

- Even when thiazide diuretics **lose their diuretic effect**, they **continue to lower blood pressure**. This is thought to be due to their **electrolyte-modulating effects**, by reducing the **vascular response to vasoconstrictors**. They may **act like vasodilators**, although they are not true vasodilators, they only prevent or reduce vasoconstriction.

- They have significant **carbonic anhydrase inhibitory activity**, similar to loop diuretics, which can be responsible for some confusing or contradictory effects of thiazides on the tubules

- When we discussed **loop diuretics**, we noted that they **stimulate prostaglandin E2 (PGE2)** synthesis in the **renal medulla**, contributing to their vasodilatory and diuretic effects. In contrast, **thiazides may have a similar but much weaker and less well-understood effect**.

Thiazide Diuretics

Pharmacokinetics:

- **Can be used orally.**
- **Have differences in metabolism.**
- **Chlorthiazide is the only thiazide used parenterally. Not very lipid soluble.**
- **Chlorthalidone is slowly absorbed and has a long duration of action.**

- Thiazide diuretics are **generally used orally**. However, **chlorothiazide** can be given **intravenously**, as it is **more water-soluble** (or **less lipid-soluble**) than other thiazides.
- Despite this, in the treatment of **hypertension**, we typically prefer **oral administration**, not IV.
- **Chlorothiazide and hydrochlorothiazide** differ from **Chlorthalidone** in that they have a **shorter half-life** and a **shorter duration of action** compared to chlorthalidone.

Thiazide Diuretics

- **Indapamide is primarily excreted by the biliary system.**
- **All are actively secreted by the organic acid secretory system in the proximal tubule, and compete with uric acid for that system.**

- When discussing **drug elimination**, we usually refer to **drug metabolism** or **renal excretion**. However, there are exceptions—**indapamide**, for example, is eliminated primarily via **biliary excretion**.
- Like loop diuretics, thiazide diuretics can cause **hyperuricemia**. This is because **active secretion** into the **luminal side** of the nephron is essential for their effect.
- This also explains why, in cases of **renal failure**, **thiazides** and **carbonic anhydrase inhibitors** become **ineffective**—they rely on renal tubular secretion to reach their site of action. In contrast, **loop diuretics** are still effective because they are more potent and can overcome the reduced renal function.

Thiazide Diuretics

Adverse Effects:

1. **Hypokalemic metabolic alkalosis.**
2. **Hyperuricemia.**
3. **Hyperglycemia – due to hypokalemia- induced inhibition of insulin release.**
4. **Hyperlipidemia (increase cholesterol and LDL).**

Hypokalemic Metabolic Alkalosis:

- **All diuretics—except potassium-sparing diuretics**—can cause **hypokalemia**, which is the **most dangerous side effect** (not the most common). Hypokalemia can be **fatal**, as it may lead to **cardiac arrhythmias** and potentially **heart failure**.

Hyperuricemia:

- **This occurs due to competition with uric acid** (both are actively secreted) at the **organic acid transporter** located in the **proximal tubules**.

Hyperglycemia and Hyperlipidemia.

Clinical Use and Considerations

We said the **main use of thiazide diuretics is for hypertension**. But **why do we treat hypertension?**

To: Prevent **coronary artery disease,** Prevent or delay **atherosclerosis,** Protect the **heart** and **blood vessels,** Prevent **cardiovascular** and **cerebrovascular diseases.**

- However, increasing cholesterol levels by thiazides can **increase the risk of atherosclerosis**, potentially **counteracting the goal of hypertension treatment**. When this happens, we manage it by **adding lipid-lowering medications**—despite this side effect, **thiazides remain first-line therapy** for hypertension.

- Similarly, in the case of **hyperglycemia**, do we stop giving thiazides or loop diuretics? **No.** We **treat the diabetes** or impaired glucose tolerance **while continuing the diuretic**.

- The real concern arises when the patient has **undiagnosed diabetes or prediabetes**, as these drugs could potentially **unmask or worsen glucose intolerance**, leading to **new-onset diabetes**. This is why monitoring is important during long-term use.

Thiazide Diuretics

5. Weakness, fatigue and parasthesia (CAI).
6. Impotence (probably related to volume depletion)
7. Hyponatremia: is significant, due to:

- hypovolemia-induced elevation of ADH
- reduction in the capacity of the kidney to produce dilute urine
- increased thirst
- extension of pharmacological action

Weakness, Fatigue, and Paresthesia

- **These symptoms can result from electrolyte imbalances** caused by the diuretic effect.

- **Paresthesia**, in particular, is associated with the **carbonic anhydrase inhibition (CAI)** properties of thiazide diuretics.

Hyponatremia

- **Thiazides inhibit sodium reabsorption**, which can lead to **hyponatremia**. Several factors contribute to this **effect:**

- **Hypovolemia-induced elevation of ADH: Initially, diuresis causes a drop in blood volume. In response, ADH (antidiuretic hormone)** is released, promoting **water retention** without sodium, leading to **dilutional hyponatremia**.

- **Prolonged pharmacologic action**

- **Increased thirst: causing blood dilution**

- **Reduced renal capacity to dilute urine: The diluting segment of the nephron**—mainly the **thick ascending limb of the loop of Henle**—is responsible for reabsorbing electrolytes **without water**. When thiazides act on the **distal convoluted tubule**, the kidney's ability to produce dilute urine is impaired. This, combined with **increased water retention**, contributes to hyponatremia.

Thiazide Diuretics

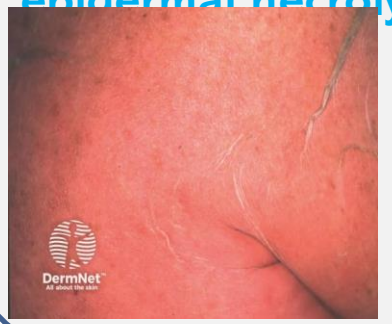
8. **Allergic reactions (hemolytic anemia, thrombocytopenia & acute necrotizing pancreatitis, necrotizing alveolitis, bone marrow suppression, dermatitis, cholestatic hepatitis).**
9. **Photosensitivity.**

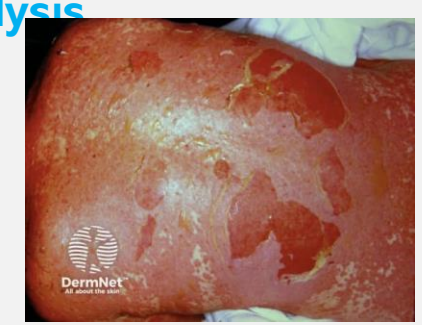
Allergy:

- Some adverse reactions to thiazide diuretics are related to their **sulfonamide component** (like the ones mentioned in brackets). So these allergic reactions can also occur with other **sulfonamide-containing drugs**, such as:

- **Sulfonylureas** (used in diabetes)
- **Thiazide diuretics**
- **Sulfonamide antibiotics** (antiparasitic or antimicrobial agents)

Dermatitis: also called necrotizing epidermal necrolysis





Photosensitivity:

- **Photosensitivity** is a reaction **similar to an allergy**, but it is **triggered by UV light exposure**, not by a traditional allergen.

- When a patient develops **photosensitivity from a thiazide diuretic**, even minimal sun exposure can cause **skin irritation, redness, or rash**. This can make it difficult for the person to **walk in the sun** or spend time outdoors.

Management:

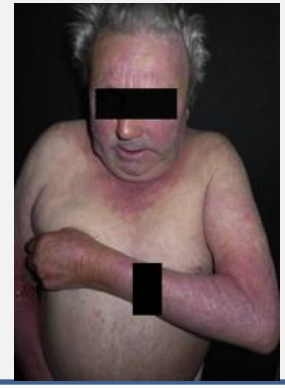
- The patient should apply **sunscreen lotion** to **all exposed skin areas**—including the **face, hands, and legs**.

- Sunscreens are often sold in pharmacies as **cosmetic products**, but their primary role is to **block UV light**.

- However, sunscreens are **not universally effective against all UV wavelengths**. Each type of sunscreens offers protection over a **specific range of UV light**.

- Drugs that cause photosensitivity (like thiazides) typically cause reactions at **specific UV wavelengths**, not across the entire UV spectrum.

Therefore, when a patient has thiazide-induced photosensitivity, it's important to:
1- **Identify the UV range** responsible for the reaction.
2- **Choose a sunscreen that effectively blocks that specific range**.



Photosensitivity Due to Thiazides

Thiazide Diuretics

Therapeutic Uses:

1. **Hypertension (the main use)**
2. **Edema of:**
   a. **mild-moderate congestive heart failure (very rarely, these patients are often given low dose loop diuretics instead)**
   b. **hepatic and renal insufficiency (explained in the next slide)**
3. **Nephrolithiasis due to hypercalciuria. Thiazides reduce urinary calcium**

- **Calcium phosphate** in urine is **insoluble**, so it deposits (precipitates), which can lead to formation of renal stones
- Thiazides **lower urine calcium levels** by increasing its reabsorption, which helps in the **treatment of nephrolithiasis** (kidney stones)

💡 How is ***Thiazide*** helpful in hepatic and renal insufficiency?
In **liver cirrhosis**, fluid accumulates in:

- The **abdomen** → forms **ascitic fluid**
- Other **body tissues**

❌ You can't give loop diuretics in cases of liver cirrhosis! Because they remove accumelated fluids mainly from the **bloodstream** but **do not** effectively remove fluid from tissues or ascitic spaces

⚠️ **Abdomen is made of chambers**, not loose tissues! Accumulated fluid in the abdomen returns to circulation **very slowly**. So, loop diuretics won't effectively remove abdominal fluid.
And giving them would primarily reduce blood volume which can lead to ➡️ **dehydration**

✅ **What's Used Instead?**
✅ **Weak diuretics** are preferred, like **thiazides**
💉 In some cases, doctors may need to **drain the abdominal fluid manually**

🌿 **Actually Thiazide diuretics can be helpful in hepatic and renal insufficiency because:**
▶️ **They act on the distal convoluted tubule, causing mild diuresis, which avoids rapid volume depletion**
▶️ **They help remove excess sodium and water gradually, reducing ascites without causing hypovolemia**
▶️ **They are less aggressive than loop diuretics and better tolerated in patients with impaired liver or kidney function**

Thiazide Diuretics

4. Nephrogenic diabetes insipidus: NaCl & water loss in the distal nephron enhances NaCl & water absorption by the proximal nephron, and decreasing delivery of fluid to the diluting segment. Dietary sodium restriction can potentiate this effect.

In cases of low sodium intake, the body tends to retain sodium instead of excreting it. Therefore, sodium restriction (**when you don't get enough salts in the diet)** leads to increased sodium retention (**you retain sodium in the body)** . This mechanism, when combined with thiazide diuretics, can be helpful in the treatment of nephrogenic diabetes insipidus.

More explanation➡️🤯

- **Diabetes Insipidus (DI) :**

occurs when there is a **low level of antidiuretic hormone (ADH)**, leading to excessive urine production and thirst.

- **Nephrogenic Diabetes Insipidus (NDI):**

Is a specific type of DI where the **kidneys are unresponsive to ADH**.
In this case, **ADH is present**, but the kidneys **do not respond** to it properly.

How NDI Affects Kidney Function:
Normally, ADH helps the kidneys reabsorb water and concentrate urine.
In NDI, the kidneys fail to respond to ADH, resulting in **inability to reabsorb water**, and thus, **excessive dilute urine**.

How thiazides treat NDI?
When the **reabsorption of sodium (Na) and chloride (Cl)** is prevented by thiazides in the **distal convoluted tubule**, there is a **compensatory reabsorption** of sodium and water in the **proximal segment** of the nephron.
This reabsorption helps **reduce urine output** by reclaiming more sodium and water

- **And this effect is potentiated by restricted sodium diet**

Keep going for more understanding

How sodium restriction and thiazide diuretics work to treat NDI:

1.Sodium Restriction:

1. When you **restrict sodium (salt)** in the diet, the body **tries to retain sodium** because it's losing too much.
2. **Less sodium is excreted**, and the kidneys hold onto more sodium and water to maintain balance.

2.Thiazide Diuretics:

1. Thiazide diuretics usually cause the kidneys to **excrete more sodium** and **increase urine output**.
2. But in **NDI**, thiazides actually have a **paradoxical effect**:
    1. They **cause mild dehydration** (a little volume loss).
    2. This triggers the kidneys to **reabsorb more sodium and water** in the **proximal tubules** (an early part of the nephron).
    3. As a result, less fluid reaches the parts of the kidney responsible for diluting urine, and the **total urine volume decreases**.

Why does this help with NDI?

Sodium restriction and **thiazide diuretics** together help **reduce the amount of urine** your body produces by:

- Promoting **sodium and water retention**.
- Decreasing the fluid that reaches the parts of the kidney that would normally cause the body to lose more water

Potassium Sparing Diuretics

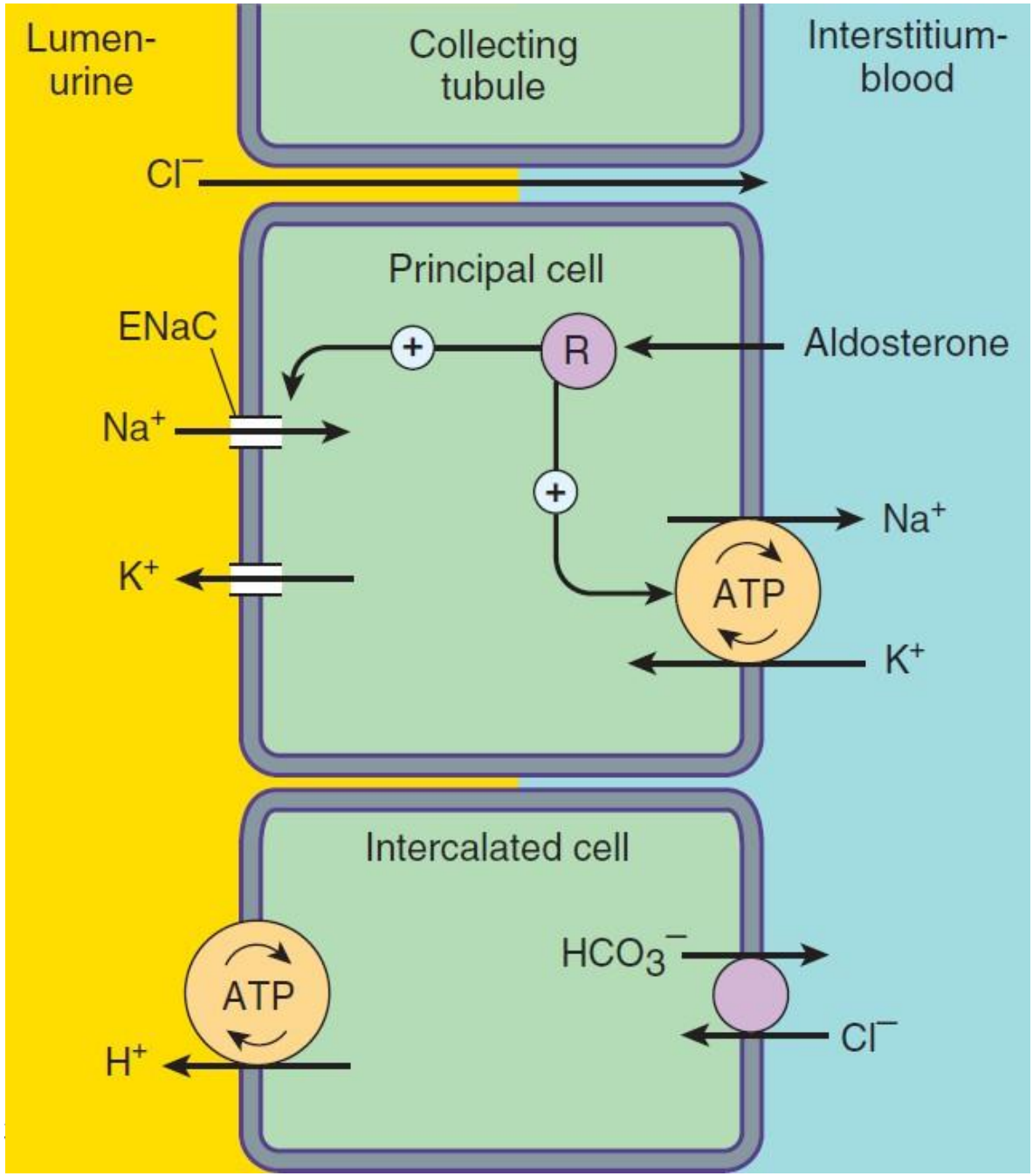


FIGURE 15–5

- **Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells.**
- **Inward diffusion of Na+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl– and efflux of K+.**
- **R, aldosterone receptor.**

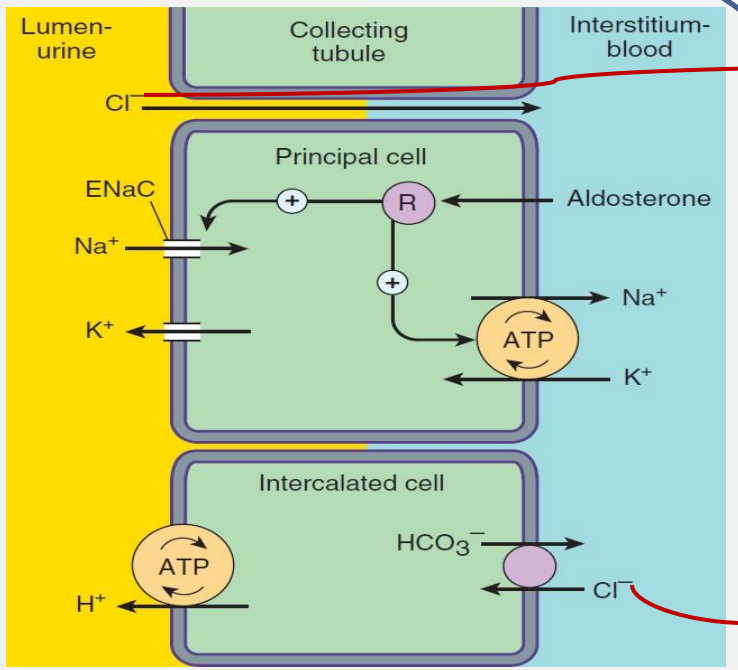
Collecting Tubule Components:

- Aldosterone receptor
- Na^+/K^+ ATPase
- Na^+ channel
- K^+ channel
- H^+ ATPase *(in intercalated cells)*
- Bicarbonate/Chloride exchanger *(in intercalated cells)*

Main Effect of Aldosterone:

- ✔ Sodium (Na^+) retention and Water retention (follows Na^+)
- ✔ Potassium (K^+) excretion and Hydrogen ion (H^+) excretion
- 📌 **Summary:**

Aldosterone = Na^+ and H_2O retention // K^+ and H^+ excretion



What happens if you inhibit the Na^+ channel and block aldosterone receptors (aldosterone antagonists):

1) Prevent Na^+ and H_2O entry
2) K^+ and H^+ are **retained**

➤ So **aldosterone antagonists** are called **potassium-sparing agents**

Key Points on Potassium-Sparing Agents:

- ▶ Not effective diuretics
- ▶ Not a good choice if the goal is to remove excess fluids
- ▶ Used mainly to prevent **hypokalemia, although when they do so, they may cause hyperkalemia!**

(و هيك منبلش موضوع: كيف نعالج hyperkalemia 😬😆)

Note: During sodium chloride retention, chloride does **not** pass through the principal cells. Instead, it can move via **Paracellular pathway** – between the cells, then into the interstitium, and finally into the blood. Also it can pass through **intercalated cells**

Potassium Sparing Diuretics

A. Aldosterone Antagonists

Spironolactone

Eplerenone (newer or second-generation agent)

Pharmacological Actions:

- **Block aldosterone receptors competitively and thus:**

1. **Interfere with sodium & water reabsorption and potassium excretion in the collecting tubules.**

Potassium Sparing Diuretics

2. **Also interfere with H^+ handling in the intercalated cells.**

   Such actions may depend on prostaglandin production.

لو علمَ العَبد استماع الله لهُ حال دُعائه، لاستحىٰ أن يَظنّ أنها لن تُقبل!
فاستغيثوه يغثكم، واطلبوا منه يُجبكم، وألحّوا عليه، فإنه يُحب المُلحين. 🌱🌱

Potassium Sparing Diuretics

Spironolactone: Pharmacokinetics:

- **Absorbed after oral administration.**
- **Extensive enterohepatic cycling,** when a drug is absorbed from the intestines, it first goes to the liver. Then the liver sends it back to the intestines through the bile. This means the drug keeps cycling between the liver and intestines instead of reaching the bloodstream — which **lowers its bioavailability**.
- **Extensive binding to plasma proteins. (**Highly protein-bound drugs can **compete** with each other for binding sites. This competition can lead to **displacement**, causing one drug to be freed from the protein. As a result, this can lead to **drug-drug interactions)**
- **Canrenone is an active metabolite. (**When **spironolactone** is metabolized, it produces an **active metabolite** called **Canrenone**. Part of spironolactone's **pharmacological effect** is due to this active metabolite.)

Potassium Sparing Diuretics

Adverse Effects:

1. **Hyperkalemia: can be dangerous especially when combined with other drugs that increase potassium, such as, potassium supplements, NSAIDs, ACEIs, AT-blockers, β-blockers, etc.**

   (this may lead to cardiac arrest)

   OR in renal failure.

2. **Metabolic acidosis.**

Potassium Sparing Diuretics

3. **Gynecomastia (breast enlargement) , Impotence and benign prostatic hyperplasia – not seen with eplerenone (more with spironolactone,** which is not typically problematic in females, but it can be a significant issue in males. Where they develop a new organ, and its tissues may produce fluids (galactorrhea) and, in rare cases, could increase the risk of breast cancer)

4. **GIT upset. CAUTION:**

1. **Reduce dose in hepatic disease (**as these drugs are metabolized by the liver. If the original dose is administered without correction, it may lead to hyperkalemia)

2. **Ketoconazole and itraconazole can increase blood levels of eplerenone due to inhibition of CYP3A4. (which is a Cytochrome P450**, that is an enzyme that metabolizes about **50%** of therapeutically available drugs that are eliminated by metabolism. If we consider 1000 drugs, 500 are metabolized, and 250 of those are metabolized by this specific isoenzyme. This makes **Cytochrome P450** a key site for **drug-drug interactions**, as drugs may compete for metabolism. This competition can lead to an **increased concentration** of one or more drugs, which may cause **adverse reactions)**

يا للشآمِ ..علَتْ فوقَ الجميعِ بما وفّتْ، وحين تهاوت ..لم تجد كلبا!
عن الشعوبِ التي لم تقترف ذنبا إلا تبلُّدَها ..مَعْ أنَّها غضبى!
عن كلِّ رأيٍ وراءَ الشَّمسِ صاحبُهُ موتاً فموتاً، ورُعباً باعثاً رُعبا
وعن بلادٍ تُسمى الشَّرقَ ..ما بقيت منها سوى ذكرياتٍ، تُحرقُ الصبّا
عن إرثِ خالدَ، عن ما أهدرَت يدُنا نيابةً عن دمانا ..أُعلنُ الحربا!

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!