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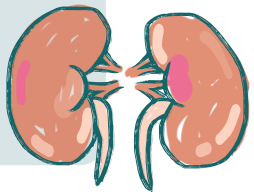
بسم الله الرحمن الرحيم

Diuretics (pt.1)

FINAL | Lecture 1

﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

Done by: Hala Alnajjar



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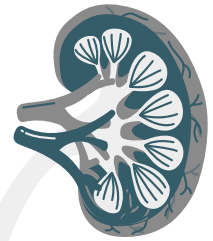


Diuretics differ mainly in their site of action

For example the PCT is the site of action for the **carbonic anhydrase inhibitors** and the **SLGT2 inhibitors**. **SLGT2 inhibitors** are **diuretic-like agents**, used in **diabetes mellitus** and **congestive heart failure**. Their applicability in heart failure is due to their **diuretic action**, that **reduces the preload**.

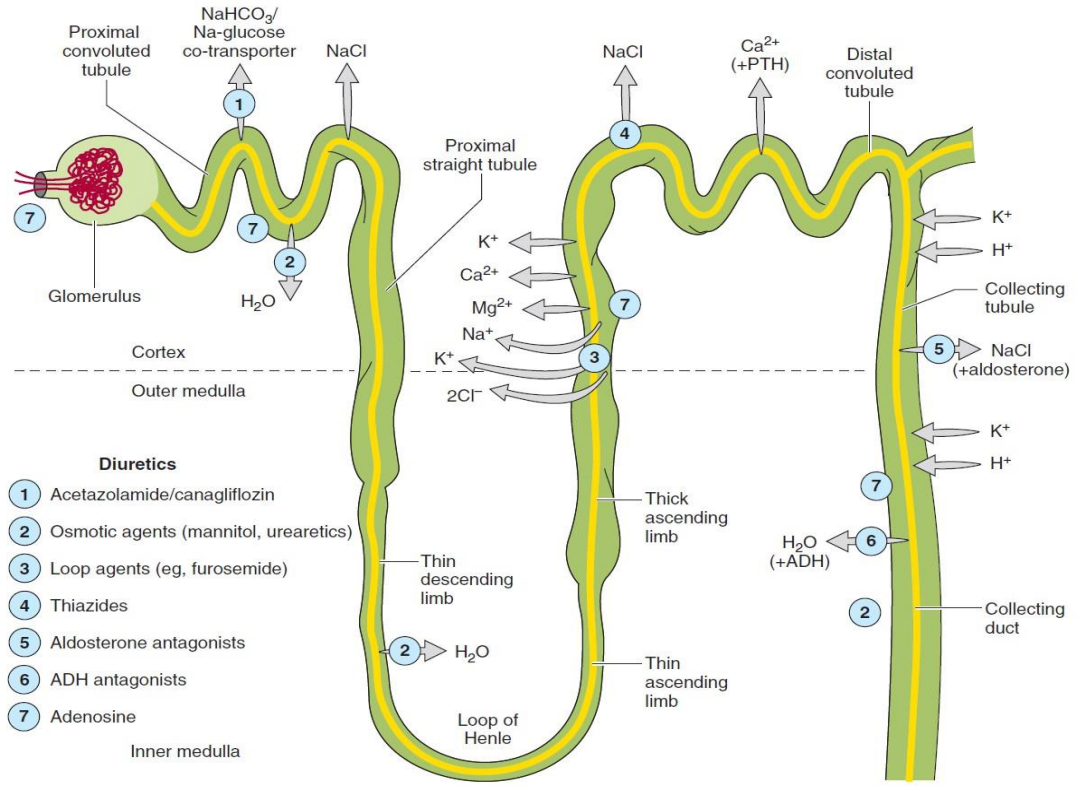
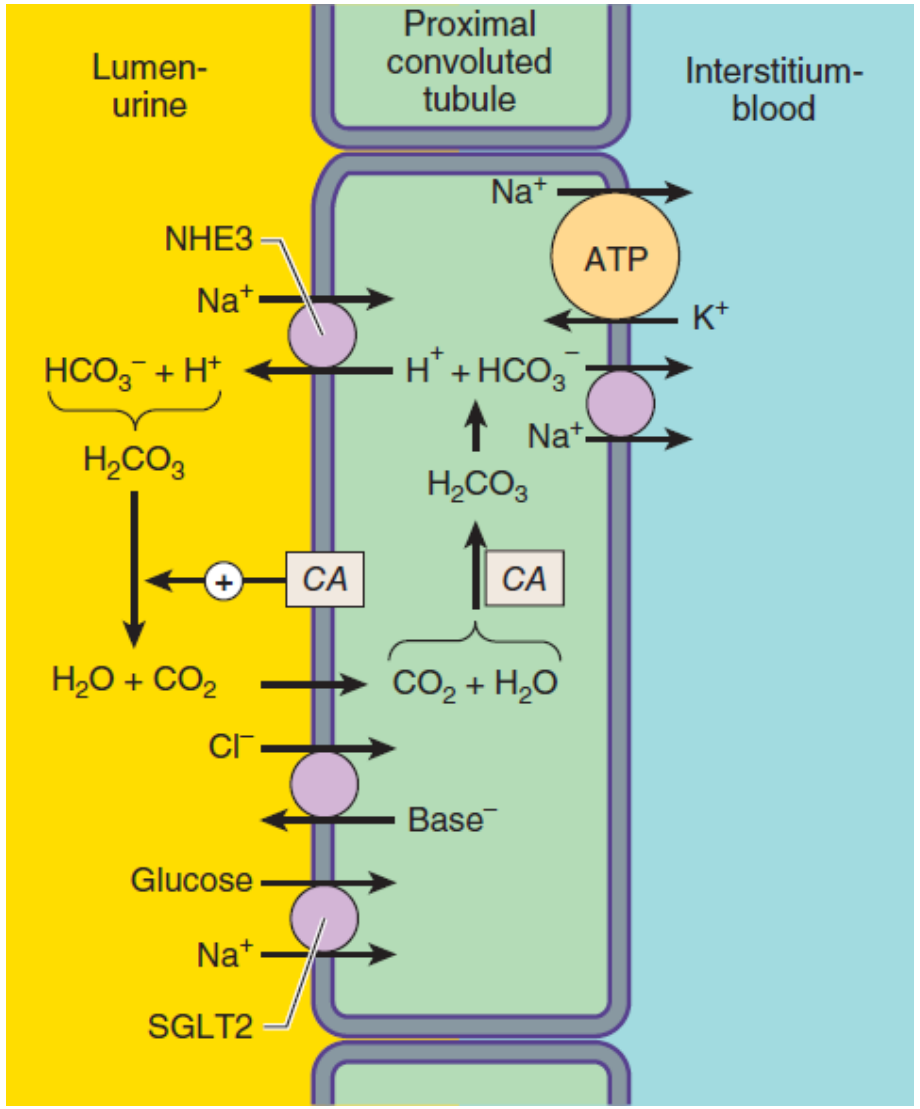


FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

No. 7 adenosine- the doctor wont be covering adenosine

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.**

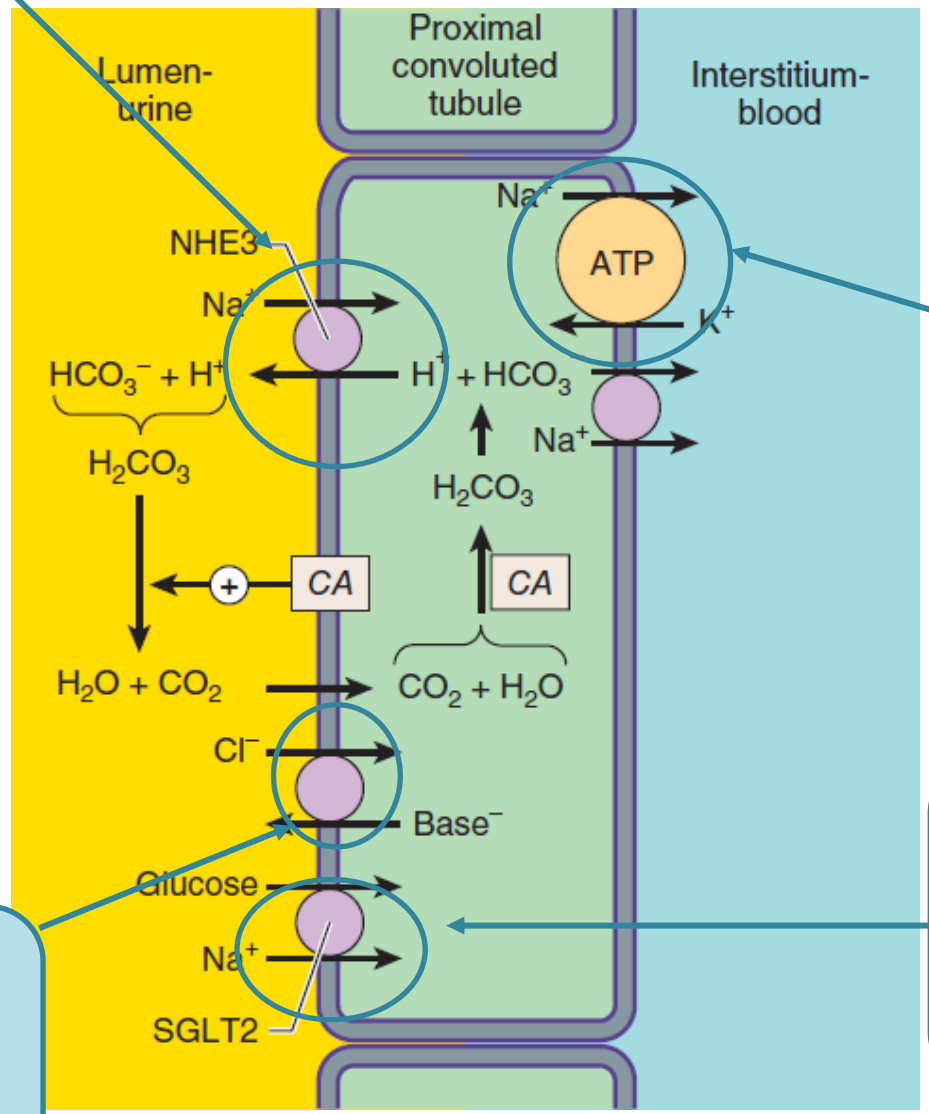
Go to the next slide

Carbonic Anhydrase Inhibitors

FIGURE 15–2:

This represents the PCT

A Na+/ H+ exchanger facilitates the entry of Na+ and exit of H+, the HCO3- excreted via glomerular filtration in the lumen reacts with the H+ forming H2CO3, that carbonic anhydrase breaks down into CO2 and H2O. CO2 is freely permeable re-entering the cells and getting converted to carbonic acid, that makes HCO3- and H+, thus bicarbonate gets reabsorbed.



The most important structure is the Na+/K+ ATPase, it regulates the intracellular ion concentration, maintaining a low concentration of Na+ inside the cell and a high concentration of K+, the opposite is seen in the extracellular fluid

There's also a CL- and base exchanger, a base exits whilst Cl- gets reabsorbed it could be any base, (negatively charged)

Theres also a glucose, Na+ co-transporter- SGLT- we have SGLT2 inhibitors that we will discuss later on

Carbonic Anhydrase Inhibitors

Key to help memorization- ends in “amide”

Both carbonic anhydrase present in the membrane and the cytosol are inhibited by those drugs

Acetazolamide The prototype

Dichlorphenamide

Methazolamide

Pharmacological Actions:

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

Reabsorption of bicarbonate is **reduced**, since we are inhibiting the break down of carbonic acid in the lumen and thus the diffusion of CO2 in the cell. Bicarbonate is excreted in urine, pulling with it Na+ (a positive charge.) Loss of bicarbonate from the serum leads to metabolic acidosis. This is an **expected pharmacological effect** that should be **accounted** for and **prevented** by the practitioner.

Carbonic Anhydrase Inhibitors

2. **Alkaline diuresis: HCO3–depletion → enhanced NaCl reabsorption by the remainder of the nephron → tolerance to their diuretic action (reduced efficacy) over several days.**
   Alkaline diuresis takes place before metabolic acidosis. Following the bicarbonate loss, **Cl- reabsorption increases** to maintain electroneutrality. (Remember the Cl-/ base exchanger? Bicarbonate acts as the base in this scenario). **Na+ also gets reabsorbed more distally in the nephron as compensation.** This causes **tolerance** to the diuretic action, but the **metabolic acidosis and alkaline diuresis** stays. Due to the reduced efficacy over a few days **we do not use carbonic annhydrase as diuretics**, we will talk about their uses shortly

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 eye is **secreted** via the **carbonic anhydrase mechanism**, Thus those drugs will lead to a **decrease in the intraocular fluid**, acting as treatment to **glaucoma**.(A pathology characterized by increased intraocular pressure that could lead to damage to the optic nerve.) There are different methods for treating glaucoma, **reducing the formation** is an example, we could also increase its **drainage**.

Carbonic Anhydrase Inhibitors

4. **Reduce formation of cerebrospinal fluid by the choroid plexus by a similar mechanism.** **CSF secretion is also dependent on carbonic anhydrase.**

5. **Metabolic acidosis which increases the seizures threshold.** Metabolic acidosis is an adverse reaction, but a **slight increase**, leads to **increasing the seizures threshold**. Meaning individuals with **epilepsy** require a **higher threshold to undergo a seizure**, thus could be used as **adjuncts** In the treatment of **drug resistant/ unresponsive epilepsy… 25/30% of individuals do not response to anti-sezuires medication in the first year.** Note the epilepsy is treated with a **single drug** maximum **2 drugs.** This is due to the drug-drug interactions between the anti-seizure drugs themselves, which leads to enhanced elimination. Carbonic Anhydrase is **not routine treatment** for epilepsy.

Carbonic Anhydrase Inhibitors

Adverse Effects:

1. **Hyperchloremic metabolic acidosis due to reduction of body HCO_3^- stores.** Due to the **Cl-/Base exchanger (increased reabsorption of Cl- following bicarbonate loss)**

2. **Calcium phosphate renal stones.**

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

Following prolonged metabolic acidosis, citrate reabsorption **increases** leading to **reduced urinary citrate**. Citrate is a solubilizing factor in urine, without it we have the formation of **stones**. + the **alkaline urine** plays a role

Carbonic Anhydrase Inhibitors

3. **Renal potassium loss: Bicarbonate loss in urine increases negative charge in the collecting tubule which enhances potassium secretion.** All diuretics cause **potassium loss** with the exception of **potassium sparring diuretics.** In this drug bicarbonate **attracts a positive charge** that could be Na+, K+ or Ca+2 ..

4. **Hypersensitivity reactions (fever, rash, bone marrow suppression, interstitial nephritis).**

Hypersensitivity is an **unpredictable side effect, that's occurrence is not the doctor's fault.** Hypersensitivity comes in **varying severity**, starting from the mildest form: a **skin rash** to, **non-infectious drug-induced fever**, **myelotoxicity** that prevents the proliferation of blood cells and **drug-induced interstitial nephritis**. (This manifestation is always allergic)

Note: Similar to how drug induced cholestatic hepatitis is also mainly allergic, its not an adverse effect of carbonic anhydrase though!!

Carbonic Anhydrase Inhibitors

Contraindications:

- **Alkalinization of the urine decreases urinary excretion of NH_4^+ (by converting it to rapidly reabsorbed NH3) and may contribute to the development of hyperammonemia and hepatic encephalopathy in patients with liver cirrhosis.**

The **alkalization of urine reduces excretion of ammonium**. This causes the **accumulation of ammonium** that gets **converted to ammonia**. In patients with **hepatic failure**, they're not able to **detoxify the ammonia**. Since **ammonia is lipid soluble and can cross membranes**, such as the **BBB**, this leads to **encephalopathy**.

Carbonic Anhydrase Inhibitors

Therapeutic Uses:

1. **Rarely used as diuretics.** Almost never
2. **Glaucoma, most common use, topical.** Common
3. **Used for urinary alkalinization to enhance elimination of acidic drugs and toxins**

When we want increased excretion of an acidic drug we alkalinize the urine (using $NaHCO_3$ for example), similar to how we acidify the urine to excrete alkaline drugs or toxins, (using Ascorbic acid for example).

4. **Metabolic alkalosis** Due to the increased bicarbonate excretion

Carbonic Anhydrase Inhibitors

Acute mountain sickness (high altitude 3000 m): By decreasing CSF formation and by decreasing the pH of the CSF and brain, they can improve ventilation and diminish symptoms of mountain sickness. This is also useful in the treatment of sleep apnea. Reducing the **CSF formation** + the **metabolic acidosis** leads to a more **acidic CSF**. This **increased acidity** stimulates **ventilation**, which is crucial in **high altitudes** due to the **reduced partial pressure of O2**. The **mild acidosis** is also useful in **sleep apnea** since it **prevents the brain from suppressing breathing during sleep**. Thus **reducing apnea episodes** in certain patients. This is applicable in **obstructive** and **central** sleep apnea.

5. **Adjuncts in treatment of epilepsy.**
6. **Treatment of high ICP pressure**

Thick ascending limb of loop of Henle

The site of action of loop diuretics

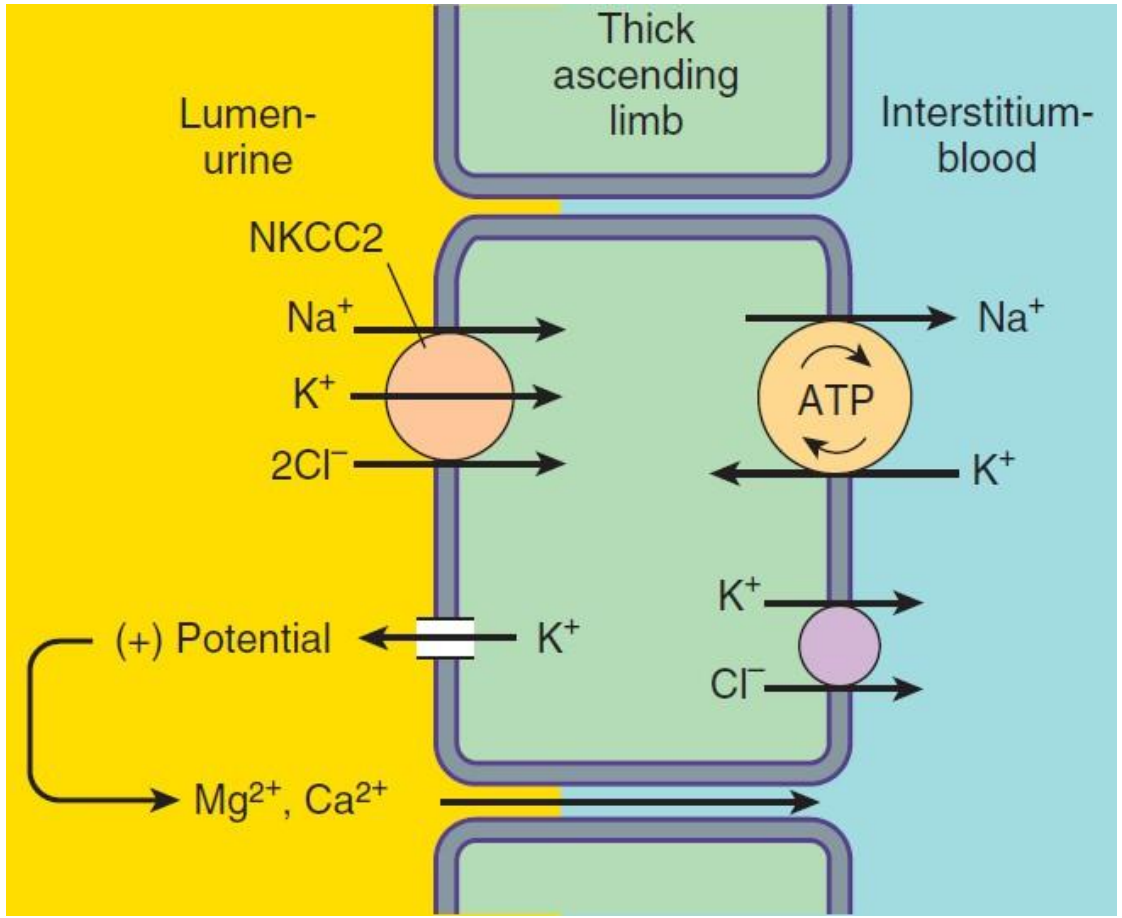


FIGURE 15–3:

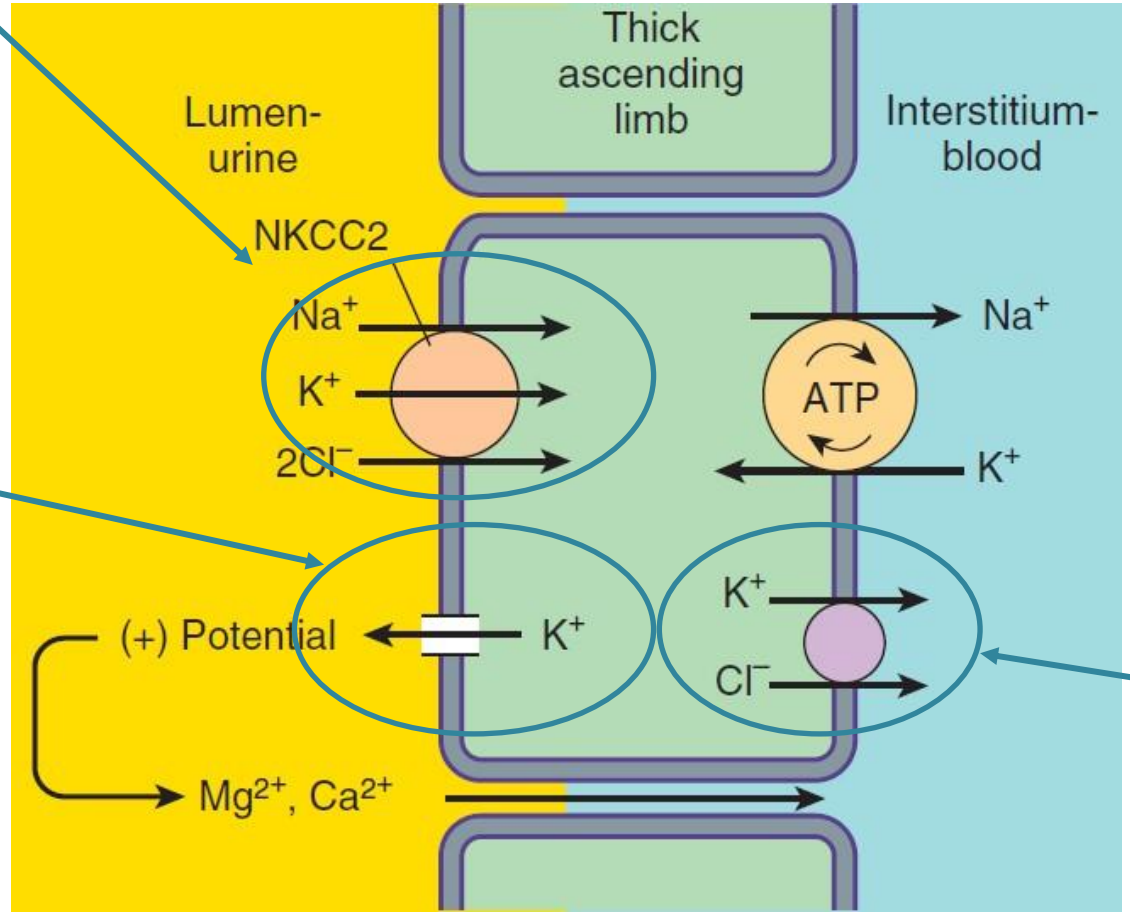
- **Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell.**
- **Na^+, K^+, and $2Cl^-$ is the primary transporter in the luminal membrane.**
- **The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway.**

Thick ascending limb of loop of Henle

The site of action of loop diuretics

We have a Na+ , K+,2 Cl-, co-transporter, the transporter gets inhibited with loop diuretics, resulting in loss of Na+, K+ and Cl-

There's also an ion channel for potassium, excess potassium exits to the lumen. The excretion of K+ forms a positive charge in the lumen, that encourages, the reabsorption of Ca+2 and Mg+2

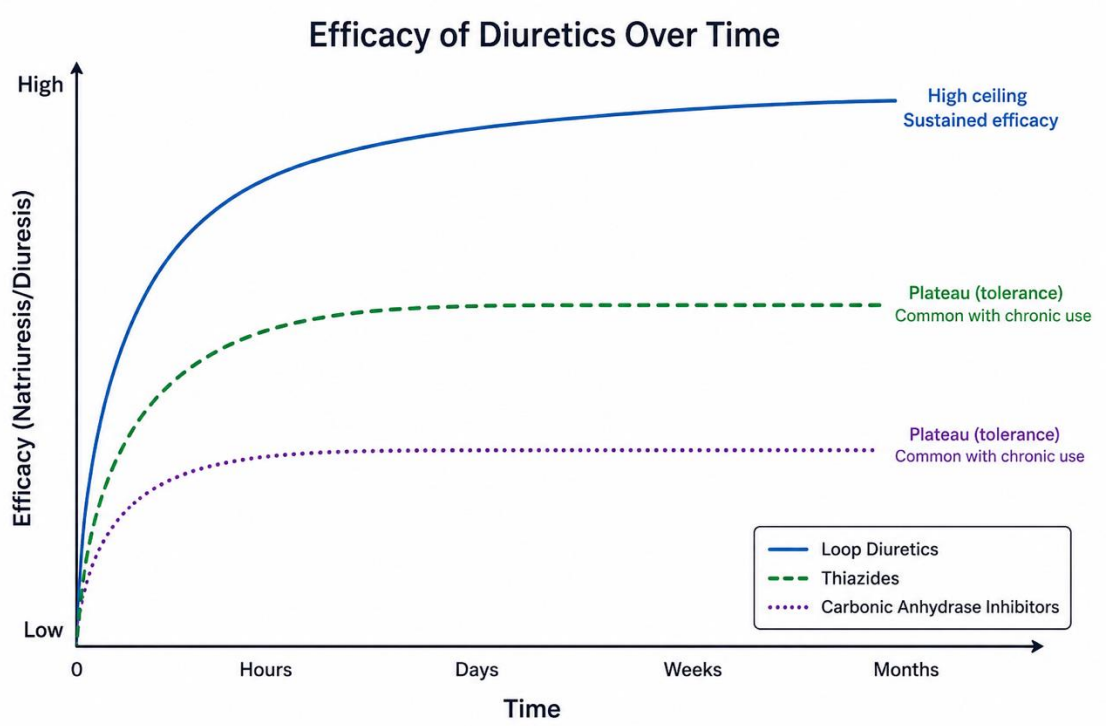


Theres also the K+, Cl- co-transporter,

Loop diuretics lead to loss of Na+, K+, Cl-, Mg+2, Ca+2, that pull along water, making them the most effective diuretics. They could potentially lead to dehydration

Loop Diuretics

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



Extra image, showcasing the high ceiling seen in loop diuretics compared to thiazaids and Carbonic Anhydrase inhibitors

Loop Diuretics

1. **Sulfonamide derivatives:**

Prototype 2nd generation drugs

- **Furosemide, Bumetanide, Torsemide.**

2. **Phenoxyacetic acid derivatives:**

- **Ethacrynic acid.** Not used in Jordan, but used outside

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+}.**

Remember that **potassium forms a positive charge** in the **lumen** to encourage the **reabsorption of Mg+2, Ca+2.** Thus loop diuretics lead to loss of **Mg+2** and **Ca+2**, but due to the effect of **PTH**, **Ca+2 gets reabsorbed distally** (in the DCT and the Collecting ducts) thus **rarely do we see hypocalcemia.**

Loop Diuretics

4. **However, calcium is actively reabsorbed in the distal convoluted tubule and its intestinal absorption can be increased, thus, hypocalcemia is rare).**
5. **Induce renal prostaglandin (PGE_2) synthesis (antagonized by NSAIDs) → increase renal blood flow, which contributes to the diuretic action.**

PGE2 are **vasodilators**, that increase the Renal blood flow, persevering the kidney from ischemia. Patients taking **NSAIDs** have **reduced renal blood flow** that causes **renal damage**, and with **chronic use**: **chronic renal failure**. **End stage renal disease** is labeled as **30% idiopathic** but research done on patients with "idiopathic" end stage renal failure proved a **high percentage of over the counter NSAIDS use**.

Clinical note for the Dr: there are 3 things patients don't tell you
1) Any over counter medication they're taking
2)Herbs, such as the Chinese tea thats extremely hepatotoxic
3)Any vitamins they're taking
You need to actively ask !

Loop Diuretics

6. **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).** **PGE2** causes **venous dilation** (**decreased preload**) that happens **before** any **meaningful diuresis**. This **reduces** the **pulmonary capillary pressure** and thus the **pulmonary congestion**.
7. **Furosemide and bumetanide inhibit carbonic anhydrase also.** Causing initial alkaline diuresis, this is also seen in thiazides (will be discussed next lecture)

Loop Diuretics

Pharmacokinetics:

- **Rapidly absorbed, and extensively bound to plasma proteins.**
  Can be given **orally**, can also be **displaced** by other **drugs bound to plasma proteins.** Giving **2 drugs** that are **highly bound causes competition towards the binding**, **increasing their free fraction**, thus their **action** and their **adverse effects**, it even increases the **elimination**, so it could be described, as "**sharp**, **acute** and **short lived effect"**
- **Eliminated by tubular secretion as well as glomerular filtration.**
  All diuretics need to be secreted or filtered since they act on the luminal side, transporters present there are the ones getting inhibited. Patients with renal failure might be given **diuretics** that are **ineffective** since they **do not reach the lumen.**
- **Furosemide and ethacrynic acid are partially metabolized.**
- **Torsemide has an active metabolite with a t½ longer than that of parent compound.** You need to take into account the active metabolites of the drug when timing doses.

Loop Diuretics

Adverse Effects:

1. **Hypokalemic metabolic alkalosis:**

- **By inhibiting salt reabsorption in the thick ascending limb, loop diuretics increase Na^+ delivery to the collecting duct. Increased Na^+ delivery leads to increased secretion of K^+ and H^+ by the duct, causing hypokalemic metabolic alkalosis.**

Due to **increased Na+ in the lumen of collecting ducts**, it increases the **secretion of K+ and H+.** This leads to **loss of acidity**. Causing **hypokalemic metabolic alkalosis**. Again this is a **pharmacologically expected response** that should be **prevented**.

Loop Diuretics

2. **Ototoxicity & deafness – reversible, dose-related hearing loss.** This isn't a pharmacological reaction
3. **Hypomagnesemia: most often in patients with dietary magnesium deficiency**
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.**

Compensatory changes occur in order to correct the **hypovolemia**, such as **Uric acid reabsorption**. **Loop diuretics compete** with **uric acid** for the **organic acid transporter**, **antagonizing the excretion of uric acid**. This promotes **hyperuricemia** and **precipitates attacks** in patients with **gout**.

Loop Diuretics

4. **Allergic reactions (rash, eosinophilia & interstitial nephritis).**
6. **Severe dehydration.** Excessive loss of fluid, leads to frequent bathroom visits; So it should not be given at night
7. **Hyponatremia. May be corrected**
8. **Hypocalcemia (?) pth, action distal to the loop of henle**
   Can also be **corrected**, since the **active transport of calcium** under the influence of **PTH** is **distal to the loop of henle**
9. **Hyperglycemia: due to hypokalemia-induced inhibition of insulin release. Mechanism of insulin release depends on K+**

Loop Diuretics

Therapeutic Uses:

1. **Acute pulmonary edema, Congestive heart failure – increase systemic venous capacitance. Before diuresis, very potent ? Due to increasing systematic renal capacitance?** Remember **lung congestion improvement** occurs **before** any meaningful **diuresis**. It's also a **very potent venous dilator** (aka **increases systematic venous capacitance**) this is applicable in **congestive heart failure.**
2. **Acute hypercalcemia. K+ loss?** **Acute, not chronic**, **(this might be confusing since we said calcium gets compensated distally to the loop of henle, but the loop of henle plays a bigger role in reabsorption of Ca+2 approxamietly 20-30% whilst the DCT~ 8-10%)**
3. **Hyperkalemia: Effect is enhanced by NaCl simultaneous and water administration. Very dangerous!!**

Loop Diuretics

4. **Acute renal failure: increase the rate of urine flow and enhance potassium excretion and ameliorate intratubular obstruction. At high doses, since enough enters the lumen of the persevered tubules, increase as you like since the kidney isn't working** this occurs at **high doses**, since the renal function is reduced and we require a **sufficient** amount of the **drug to get filtered into the lumen of the nephron**, increasing dose by **10x isn't worrisome** since the **kidney isn't working anyway**
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., forced diuresis for the elimination of toxins, alkaline and acidic, but given saline to prevent loss of na+ and cl-**
6. **Diverse group of drugs**

External Resources

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