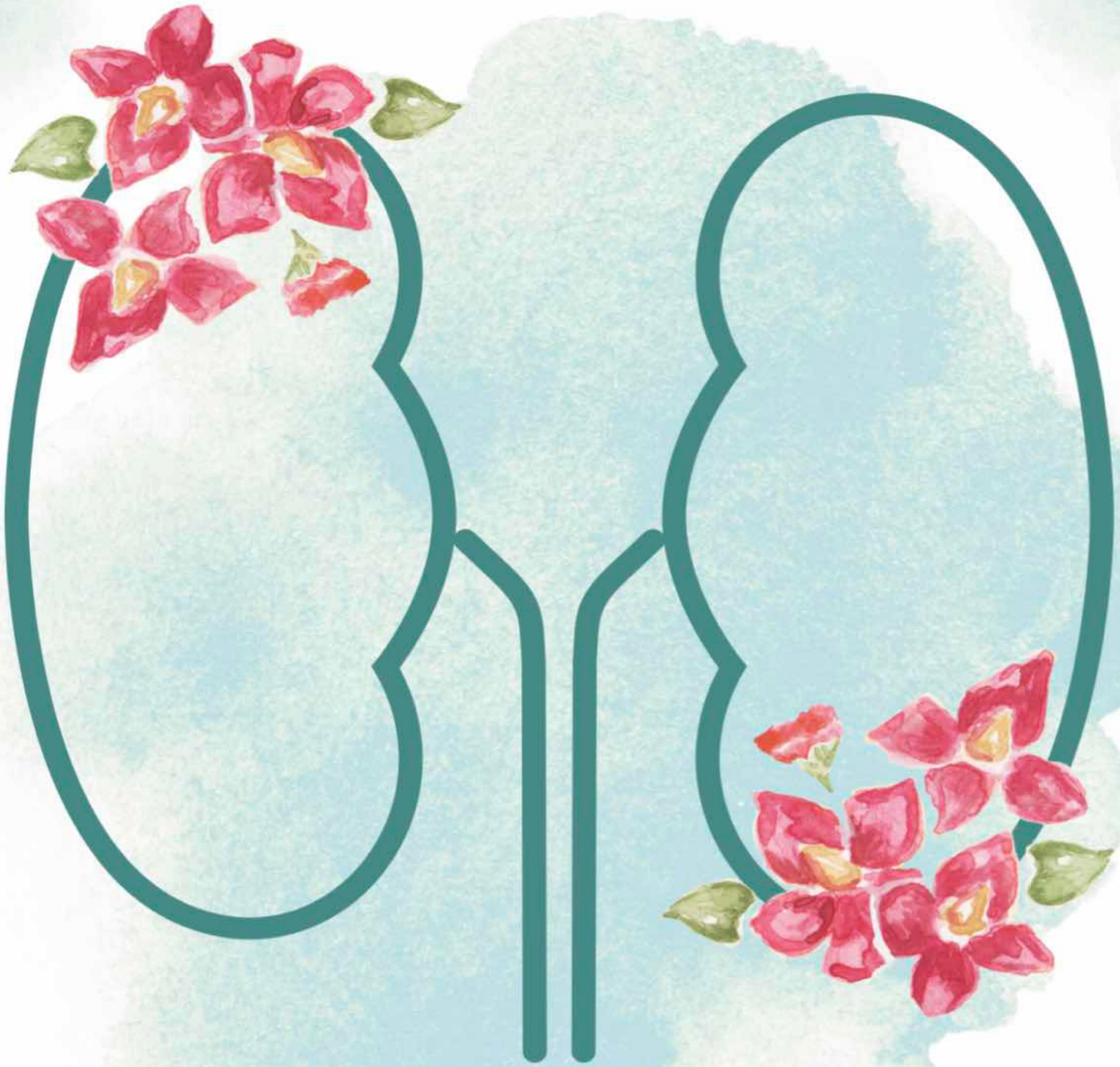

PHYSIOLOGY

- SHEET NO. 5
- WRITER : Dentistry 019
- CORRECTOR : Sawsan alqeam
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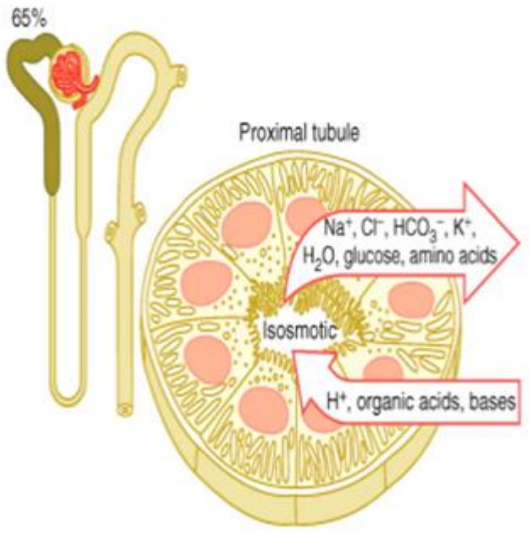
Proximal Tubules

- The proximal tubules reabsorbs about 67% of filtered water, Na^+, Cl^-, K^+, HCO_3^-.
- The proximal tubules reabsorbs almost all glucose and amino acids filtered by the glomeruli.
- The key transporter element is the Na, K- ATP ase in the basolateral membrane.



: Guyton & Hall: Textbook of Medical Physiology 11e - www.student

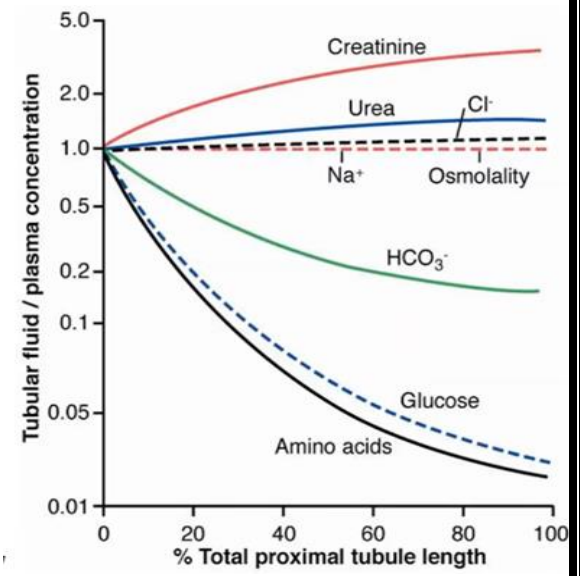
Note about the slide: Take a look to the scheme, the upper arrow represents the substances that get reabsorbed by the PCT, the lower arrow represents the substances that are secreted (H+, organic acids, bases) actively.

Remember: H+ is secreted actively by counter transporter along with Na+

Changes in concentration of different substances in PCT

On x-axis we have **% total proximal tubule length** which demonstrates the length crossed from of the PCT (on 0% it is the beginning, 20% means we cross about 20% of the whole length of the PCT, 100% is the end).

On the y-axis we **have tubular fluid divided by plasma conc of each substance**. For each substance, we calculate the *ratio* of its concentration in the tubular fluid out of the plasma conc of this substance.



In the beginning of PCT length we notice that there is a relatively high conc of *creatinine* and *urea* and the conc stays high and even *increases* along the PCT

length. So conc of creatinine and urea in the tubular fluid is higher than the conc in plasma which we can tell because the ratio is **> 1** and this give us indication that they have *poor reabsorption* because their conc remains high in the tubular fluid in the PCT.

But regarding *Na+* and *Cl-* their conc is **≈1** which means their conc in tubular fluid & plasma is close.

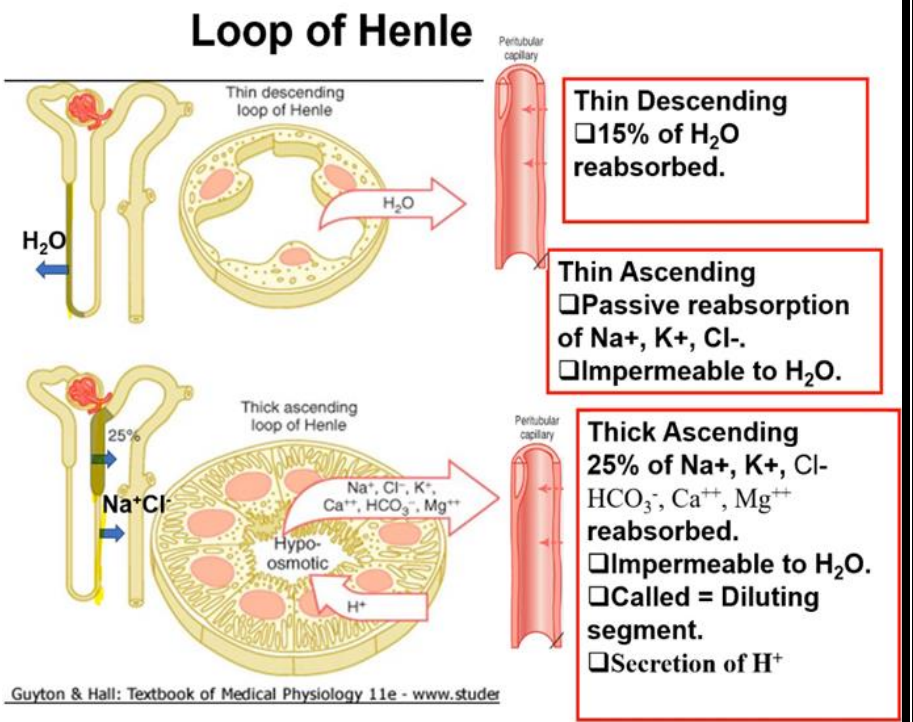
Bicarbonate & glucose & amino acids we notice that the percentage **< 1** and even *decreases* along the PCT. So for HCO_3^- , and more so for glu & amino acid, the plasma conc is higher than their tubular fluid conc. This means they undergo *extensive reabsorption*- especially amino acids and glucose. Reabsorption is high as by the end of this segment they become completely reabsorbed (ratio approaches 0). At the end of PCT also bicarbonate (electrolyte) is reabsorbed & has ratio 0.2 which means its conc in plasma > tubular fluid.

الصورة بالصفحة الماضية بتوضح كيف اعادة الامتصاص للمواد هاي ماشية، كيف بختلف ال reabsorptionبالاقسام المختلفة من ال PCT للمواد المختلفة، ركزوا عليهم.

Now we will talk about the reabsorption mechanisms in the loop of Henle (LOH).

LOH is composed of a thin descending tubule & then thin ascending tubule & then thick ascending tubule or limb. Each of those segments has different characteristics in terms of permeability & transport that takes place across these cells.

In the **thin descending**, osmosis of water =15%;



because 1- in the matrix or interstitium the osmolarity of substances is higher than in the tubular fluid 2- cells in interstitial space more permeable for water due to aquaporin channels and paracellular route, and because of all of that the water flow from tubular fluid to interstitial spaces so passive reabsorption of water occurs by osmosis.

In **thin ascending** limb of Henle, already we had reabsorption of water الدكتورة: بالتالي بصير عنا تركيز للالكترولايتس، But these cells are characterized by being impermeable to water, so we have passive transport for NaCl from the tubular fluid to interstitial space and capillaries until equilibrium. Note: *no active transport* occurs only passive because there is no conc for active transport in this segment.

In **thick ascending** limb of Henle its cells are large cuboidal so it has extensive production of energy & extensive distribution of Na+/K+-ATPase channels and Na+ channels and Cl- channels. With spending energy, 25% of Na+, K+, Cl-, HCO_3^-, Ca++, Mg++ are reabsorbed. So we have extensive transport for electrolytes in this segment enough, to cause a very hypoosmotic conc at the end of the thick ascending loop.

'Why does thick ascending loop of Henle have a hypoosmotic concentration?'
Because of electrolytes extensive reabsorption (secondary active). At the same time there's secretion of hydrogen by counter transport, everything depends on Na+/K+-ATPase pump. Also, this segment is impermeable for water so water can't flow by osmosis from inside (hypoosmotic region) to outside and can't follow the solutes so dilution occurs in this segment so it is called diluting segment.

General notes:

- Thin descending permeable for water thin ascending and thick ascending is not.
- Thin ascending = passive reabsorption for Na/K/Cl.
- Thick ascending =active reabsorption for

Loop of Henle

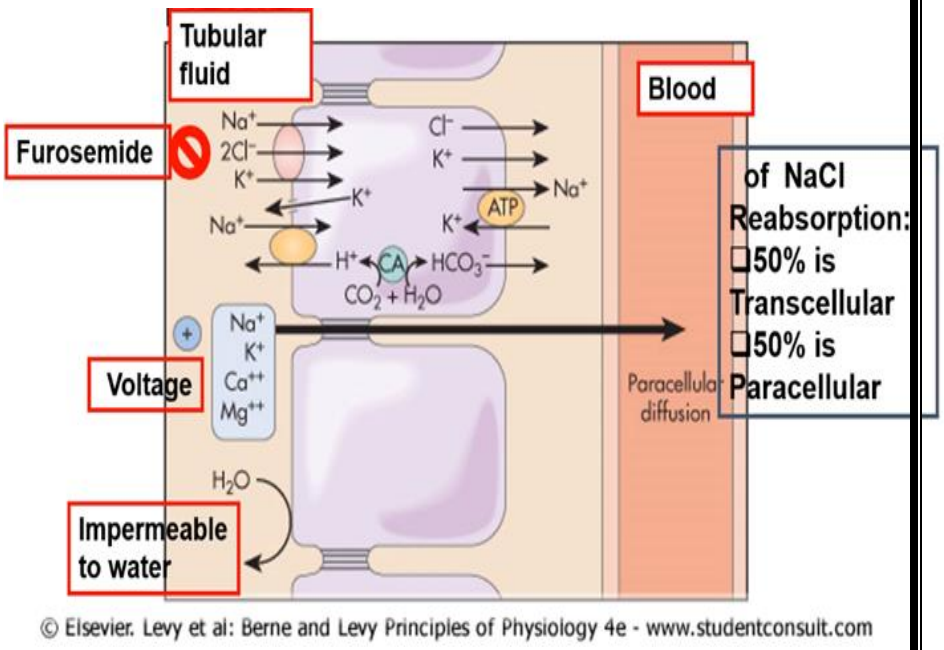
- Water reabsorption occurs exclusively in the **thin descending** limb of Henle via AQP1 water channels.(**Aquaporins**)
- Reabsorption of **NaCl** occurs in both thin and thick **ascending** limb of Henle.
- In thin ascending limb NaCl is reabsorbed passively. However, in thick ascending limb NaCl is reabsorbed through Na^+-K^+ ATPase in basolateral membrane ans .
- Ascending limb is impermeable to water.
- Reabsorption of Ca^{++} and $HCO3^-$ occurs also in Loop of Henle.

Notes about the above slide:

- Remember thin descending is permeable for water.
- In the end of thick ascending limb there is dilution for tubular fluid.

Thick ascending limb of Henle

It is an important part of the nephron & it has a lot of pharmaceutical applications on the transport mechanism that take place in it. Look at the scheme here (left) is the tubular fluid or luminal side of tubules & here (right) is the basal side of tubules that faces the peritubular capillaries. On luminal side we have different types of transporters that are densely present in the thick ascending limb. The first one called **sodium chloride potassium channel.** This channel transports Na+ & 2Cl- & K+ from the luminal or tubular fluid into the tubular cells. The second is **Na+/H+ exchange channel** which reabsorbs Na+ by using the gradient that is produced by the Na+/K+-ATPase, so it can secrete the H+. Another process that takes place is **voltage drag**, it is the transportation of positive ions, because of density of positive charge on the luminal side, due to the transport channels present. The high density of positive



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The positive charge is due to the leak of potassium into the lumen mainly because of high intracellular potassium and leak channels.

charge causes high *repulsion* between the positive ions that causes it to escape this density through the paracellular route, without any fluid flow
Only positive ions flow by the paracellular route by paracellular diffusion (only +ions especially bivalent ions, the more the +charge the more repulsion so it gets reabsorbed by paracellular route).
Transcellular route by Sodium chloride potassium channel that uses the Na+ gradient which is produced by the Na+/K+-ATPase so Na+ reabsorbed and H+ is secreted.

ايونات ثنائية الكفؤ مثل: Mg++, Ca++

How does the hydrogen that is secreted regenerate?

By this reaction:

Occurs inside the tubular cells. H+ is eliminated by Na+/H+ exchanger, and is secreted into the tubular fluid in the urine. HCO_3^- is reabsorbed by blood.

Remember this segment -thick ascending- is impermeable to water (no aquaporin, no H2O reabsorption, yes dilution).

NaCl reabsorption: 50% transcellular, 50% paracellular (by voltage drag).

The same mechanisms previously discussed, but in this scheme we are going to talk about some drugs that are synthesized to block the sodium chloride potassium (Na-K-Cl) channel in the thick ascending limb of Henle these drugs called **Loop diuretics** ex. *Furosemide (Lasix)*. When we inhibit the reabsorption of Na, K, Cl, but

Sodium chloride and potassium transport in thick ascending loop of Henle

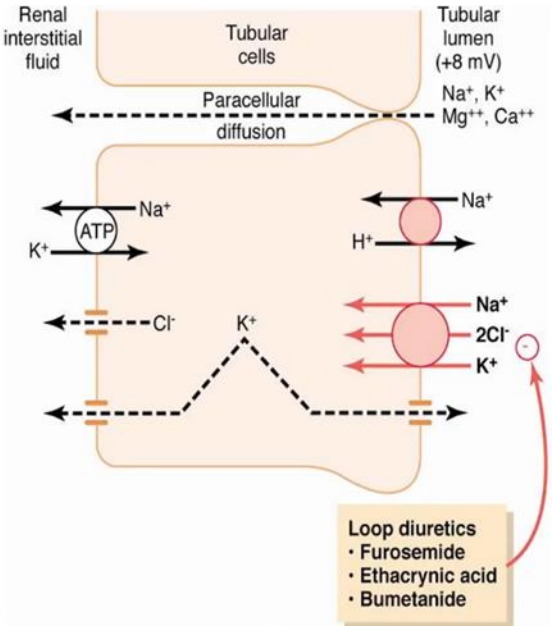
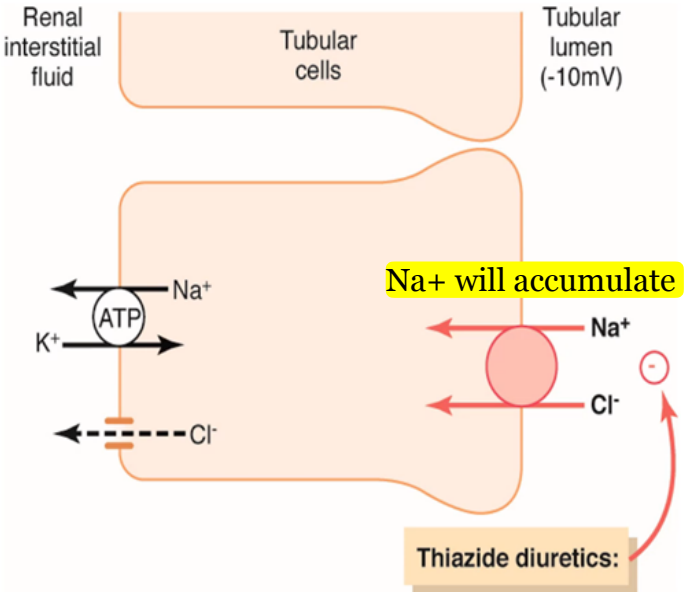


Figure 27-9

mainly Na+, its conc in urine will increase, therefore more excretion of water will occur in other segments, because there's a law that says: water follows solutes. So if we decrease reabsorption of solutes, we also decrease reabsorption of water, this cause diuresis (diuresis: increasing in urine fluid volume). Diuretics aim to decrease blood volume/the extracellular compartment volume, so blood pressure decreases. This is the pharmaceutical application of transporter in this segment.

Early distal tubule



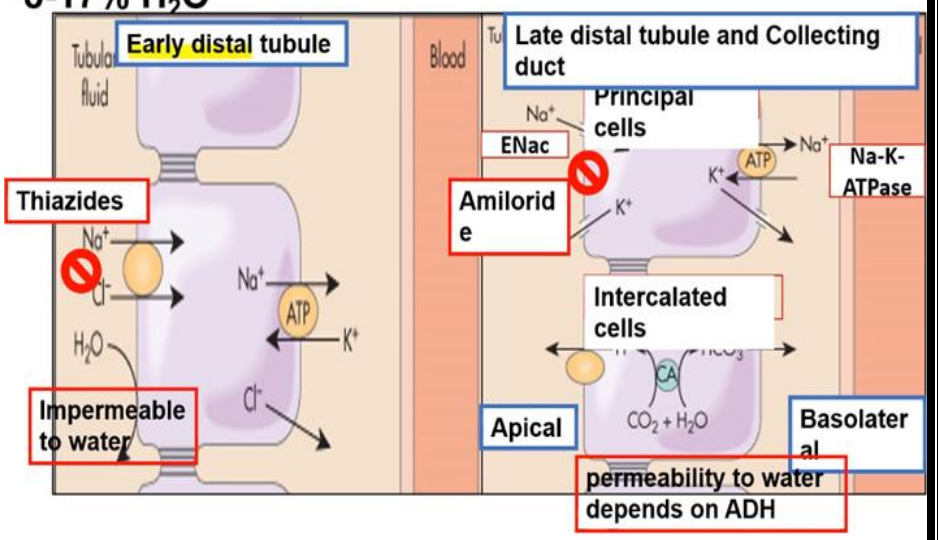
The distal convoluted tubule is divided into early distal and late distal due to characteristic differences between the two. Early distal have a Na+/Cl- channel on the luminal side it transports Na+/Cl- by using the Na+ gradient that... (you should guess the rest of this sentence by now) so the Na and Cl are reabsorbed. There is a drug specialized to block this channel called **Thiazide diuretic** it selectively Blocks this channel, therefore it functions as a diuretic, because when it blocks the Na+ and Cl- reabsorption, a large amount of it will be stuck in tubular fluid, and water follows solute, so diuresis happens. Early distal tubule is impermeable to water.

Early distal tubule

- Functionally similar to thick ascending loop — Both do active transport for NaCl.
- Not permeable to water (called diluting segment)
- Active reabsorption of Na^+, Cl^-, K^+, Mg^{++}
- Contains macula densa — Macula densa: part of juxtaglomerular apparatus

The ENac reabsorbs Na+, but because Na+ should be pumped out by Na+/K+ atpase this will increase K+ secretion indirectly not through ENac as K+ leaks to the lumen (due to increased Na+ reabsorption)

Late Distal Tubule and Collecting Duct



This scheme is clearer for early distal tubule (left). Notice the sodium chloride channel which is blocked by thiazides diuretic, and it's impermeable to water.

Late distal tubule and collecting duct are paired together because they have very similar characteristics, cells are divided into two: principal cells & intercalated cells.

Principal cells: One of the important channels in the principal cells in late distal tubule and collecting duct is epithelial sodium potassium channel (ENac) it reabsorbs sodium ofc but the different thing is that it secretes potassium. This channel is blocked by *Amiloride*, it's a diuretic because it blocks the reabsorption of Na+ & it is also called **potassium-sparing diuretic** because it blocks the secretion of k+ into the tubular fluid. This means it causes diuresis but it doesn't decrease k+ conc in blood.

Principal cells are the site of action of **aldosterone** hormone, it increases the insertion and production of ENac (increase activity) therefore aldosterone increases the Na+ reabsorption by ENac channels & increases k+ secretion. Therefore, one function of aldosterone is that when we have hyperkalemia (increased blood conc of K+), the aldosterone increases the activity of ENac, and so secretion of K+ is increased and excess K+ is eliminated from the body. Amiloride inhibits ENac. Aldosterone stimulates ENac. (There is a summary of diuretics at the end of the sheet.)

Intercalated cells: function is acid-base balance by CO2+H2O equation (in the previous pages), H+ is a secreted product frequently, these cells often secrete the H+ because our body tends to produce acids more than bases so we have a lot of acids already. Classically intercalated cells secrete hydrogen to tubular fluid &

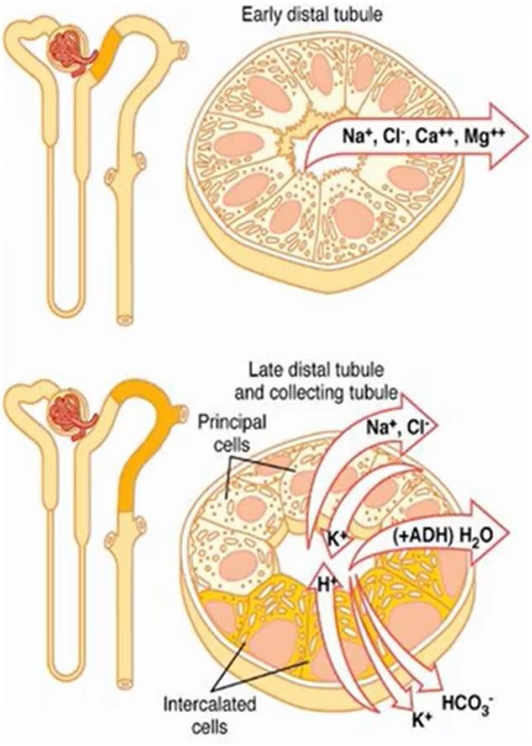
reabsorb the bicarbonate back to blood to neutralize the acids that the body produced to *prevent acidosis*.

BUT intercalated also have the ability to oppose the direction of those transporters if alkalosis occurs in the body! These cells are very important in acid base balance whether acidosis or alkalosis take place.

Permeability to water in late distal and collecting ducts is variable and depends on antidiuretic hormone **(ADH)**. If this hormone is present, *insertion of aquaporin* channels on luminal and basal sides of these cells takes place, so these segments become permeable to water. So if water permeability is switched on due to ADH & we know that due to extensive reabsorption of electrolytes mainly Na+ in the earlier segments (thick ascending, early distal) and that water was not allowed to be reabsorbed, *osmolarity in tubular fluid becomes very low*, so if water became able to pass by osmosis in late distal and collecting, because of aquaporin and ADH presence, there will be very *high reabsorption* of water from tubular fluid to blood capillaries. So ADH مانع لادرار البول prevents the high volume of urine & increases the extracellular fluids and blood pressure. This is the mechanism of action for ADH in late distal and collecting duct.

Here H+ atpase is way more effective in secreting H+ than Na+/H+ exchanger in TAL as it can secrete H+ against gradient 1000 times more.

To summarize:



~5% of filtered load NaCl reabsorbed

- not permeable to H_2O
- not very permeable to urea

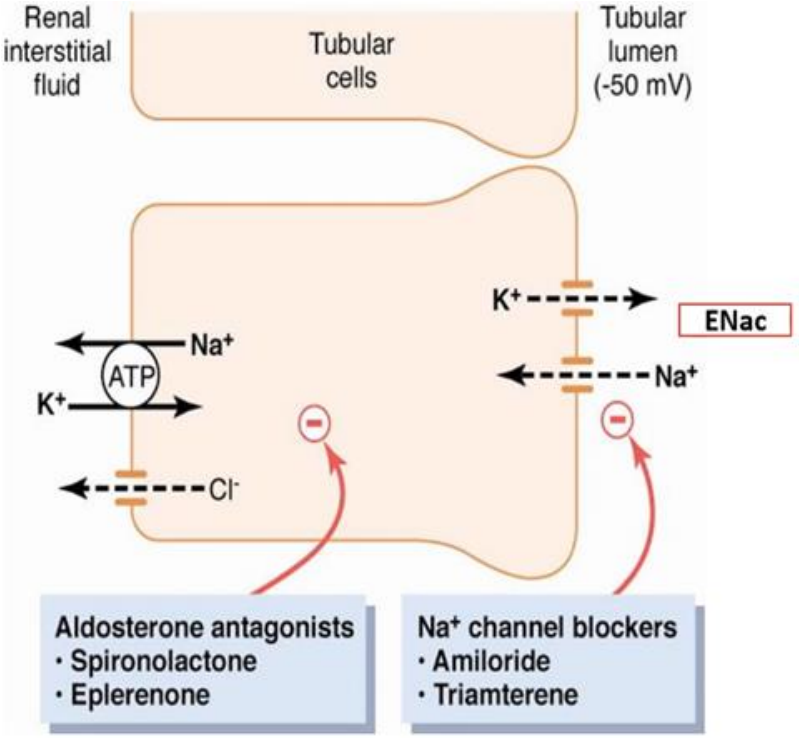
- permeablility to H_2O depends on ADH
- not very permeable to urea

← **Cortical**

Demonstrating principal cells

The main characteristic in these cells is their ENac channels which reabsorb Na+ and secrete K+ into tubular fluid.

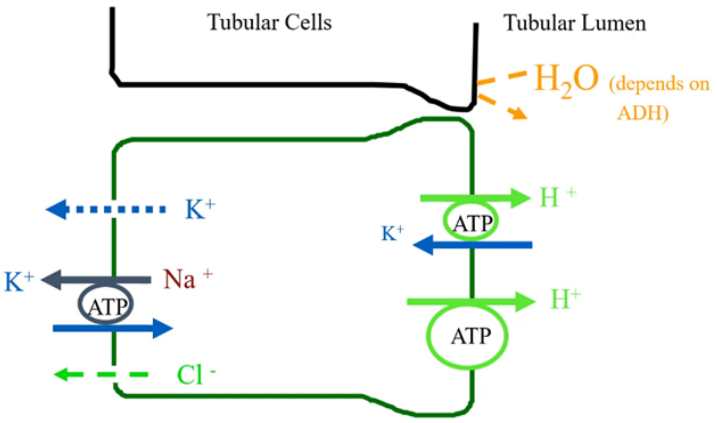
Notice that when amiloride blocks ENac, it blocks the Na+ reabsorption (diuresis function) & blocks K+ secretion (preserves K+ inside the body). This is the opposite of what happens in the other diuretic types we discussed which do not preserve K+.



Aldosterone also affects this channel, increasing its activity so that there is reabsorption of Na+ & secretion of K+. But there are drugs that work as **aldosterone antagonists** (also diuretics), their function is as same as amiloride ex**. spironolactone**, it blockades aldosterone function which is Na+ reabsorption, K+ secretion.

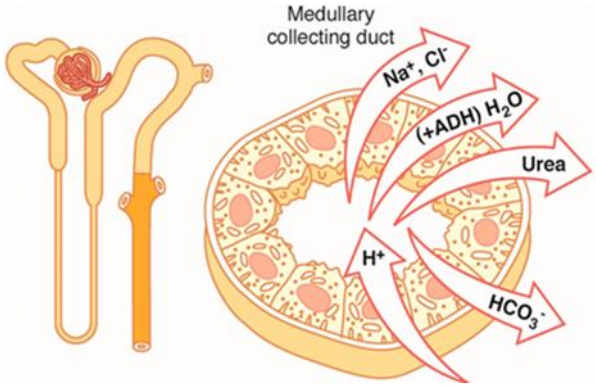
Demonstrating intercalated cells

This image represents the secretion of hydrogen, which mainly occurs in the late distal tubule and collecting duct in intercalated cells, but sometimes it may have the opposite direction in case of alkalosis.

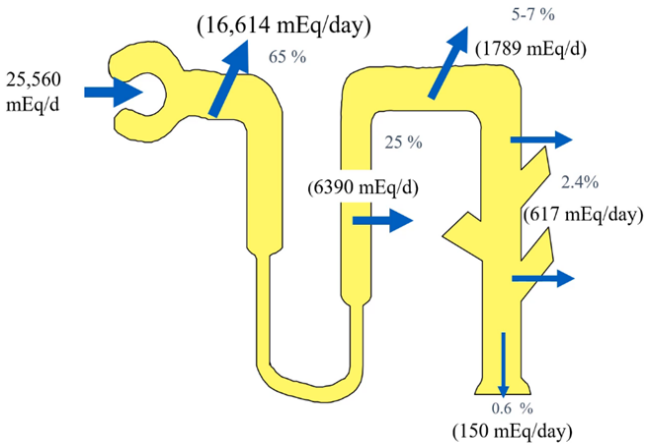


Transport characteristics of medullary collecting ducts

In medullary 'specifically' there is urea reabsorption, its conc increase in the matrix. If ADH is present, urine becomes more concentrated, water is highly reabsorbed to get the water back from the tubular fluid.



Normal renal tubular Na+ reabsorption



Firstly, in the proximal tubule (65% of the tubular Na+ reabsorbed), after that in the thick ascending limb (25% reabsorbed), after that in early distal (5%), and in late distal and collecting ducts (2%). Finally excreted Na+ (0.6%). Less than 1% from filtered Na+ is excreted.

Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

- If water is reabsorbed to a greater extent than the solute, the solute will become more concentrated in the tubule (e.g. creatinine, inulin)
- If water is reabsorbed to a lesser extent than the solute, the solute will become less concentrated in the tubule (e.g. glucose, amino acids)

Diuretic type	Channel involved	Present in	Mechanism summary
Loop-acting Ex. Furosemide (Lasix)	Blocks sodium chloride potassium (Na-K-Cl) channel	Thick ascending limb of Henle (PCT)	Inhibits Na+ reabsorption → water follows solute so H2O reabs. ↓ = diuresis
Thiazide	Blocks Na+/Cl- channel	Early distal tubule	Inhibits Na+ and Cl- reabs. → solute remains in tubular fluid → water follows solute = diuresis
Potassium-sparing Ex. Amiloride Triamterene	Blocks epithelial sodium potassium channel (ENac)	Principal cells in late distal tubules and collecting ducts	Inhibits Na+ reabs…. = diuresis Blocks K+ secretion into tubular fluid so K+ is spared from excretion
Aldosterone antagonists Ex. Spironolactone Eplerenone	ENac Note: aldosterone stimulates ENac, aldosterone antagonists inhibit aldosterone	Principal cells in late distal tubules and collecting ducts	Aldosterone stimulates ENac→ inc. Na+ reabs., inc. K+ secretion into tubular fluid = prevent diuresis. Antagonist inhibits this (does the opposite).
Antidiuretic Hormone (ADH)	Inserts aquaporins into	membranes of late distal tubules and collecting ducts	Inc. H2O permeability → inc. H2O reabs. = *prevents* diuresis

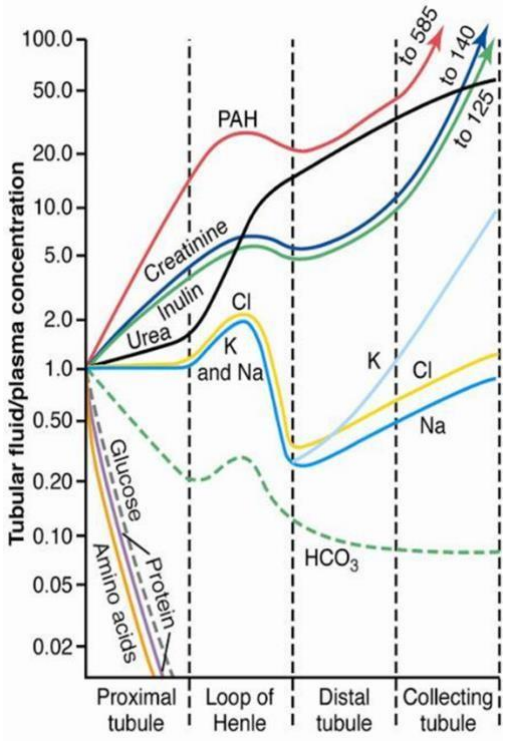
This lecture is a continuation for the **RENAL/ TUBULAR REABSORPTION**

- The concentration of solutes in different parts of the tubule depend on the relative reabsorption of the solutes compared to the reabsorption of water.
  - For example, if water was reabsorbed to a **greater extent** than the solute reabsorption, the solute will become **more concentrated** in the tubule **(e.g., creatinine, inulin)**
    - Creatinine is a waste product which has a poor reabsorption.
    - Inulin is an exogenous substance that we infuse the patient with, for different reasons (will be discussed later on...)
  - If water was reabsorbed to a **lesser extent** than the solute, the solute will become **less concentrated** in the tubule **(e.g., glucose and amino acids specially in the proximal convoluted tubule)**

Changes in concentrations of substances in the renal tubules

- The graph on the right depicts the changes in concentrations of different substances in different segments of the renal tubule.
- Remember: the different concentrations are measured as **Tubular Fluid Concentration** of the substance divided by **Plasma Concentration**
- In different segments we can notice different concentration percentages.
- Notice that in the **Loop of Henle** the Urea, Inulin, Creatinine and PAH have a **poor reabsorption** → we can notice an increase in their concentrations because of the poor reabsorption of water specially in the thin ascending and thick ascending parts of the loop.
- **After the thin ascending part** of the

TDL



From the Book: The substances represented toward the bottom of the figure, such as glucose and amino acids, are all strongly reabsorbed; these are all substances that the body needs to conserve, and almost none of them are lost in the urine.

Changes in this ratio are due to tubular fluid concentration changes not plasma concentration, either due to reabsorption of solute vs water.

loop, we can notice an Decrease **in the concentrations** of [redacted], [redacted], [redacted], [redacted] **Chloride**, **sodium, and potassium** due to the **passive** reabsorption processes.

- At the **end of the Loop of Henle (thick ascending loop of Henle),** we can notice a **decrease in the concentrations** of the **Chloride**, **sodium, and potassium** because there will be an **extensive active reabsorption** of the solutes in comparison to water.

- In the distal tubule, we have an early and a late segment.
  - The early segment of the distal tubule is **impermeable** to water; therefore,we can notice a slight **decrease** in the sodium, potassium, and chloride concentrations.

Due to the effect of ADH hormone on the late segment, water reabsorption increases and therefore the concentration of solutes increases.

- In the collecting tubule & late distal, an increase in the solutes concentrations occurs, especially if the antidiuretic hormone was present
  → NOTE: An antidiuretichormone works on reabsorbing the water.

- **The higher the reabsorption of water in the collecting tubule, the higher is the concentration of the tubular Fluid.**

Note from the Book for better understanding:

Whether a solute will become concentrated in the tubular fluid is determined by the **relative degree of reabsorption of that solute versus the reabsorption of water**. *If a greater percentage of water is reabsorbed, the substance becomes more concentrated. If a greater percentage of the solute is reabsorbed, the substance becomes more diluted.*