Sheet No.6

Physiology

Genitourinary system

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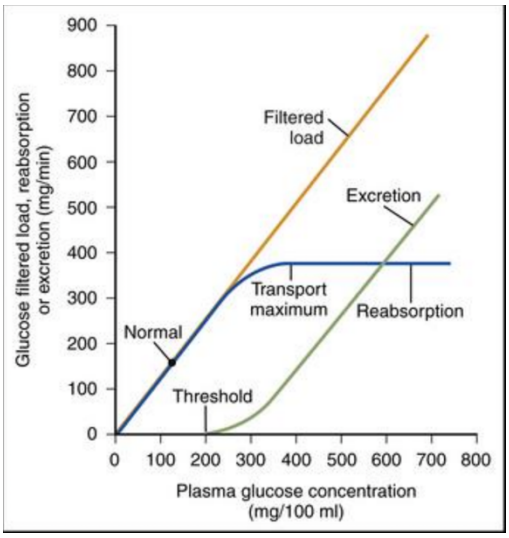
Wish you a happy ride :)

In our previous discussion, we explored how various substances, such as Sodium, Water, Glucose, and Amino Acids, are reabsorbed by the body. We discussed the significance of the Na-K ATPase in facilitating active transport for reabsorption.

We also noted that complete reabsorption of glucose and amino acids from the tubular fluid happens. We also explored the different forces and channels contributing to reabsorption. However, is it possible for the reabsorption process to continue increasing indefinitely with every increase in filtration rate? *Or is there a limit to the amount of substance that can be reabsorbed?*

First, the amount of a substance that can be reabsorbed by the kidneys can vary. Some substances can be reabsorbed without any limit, while others have a limited capacity for reabsorption. The transport of substances in the kidneys is done through transporter proteins, and the amount of substance that can be transported is limited by the number of available transporters. When the number of transporters is fully saturated with a substance, it reaches its maximum transport capacity. This is called the **transport maximum**. Once this point is reached, any excess of the substance is not reabsorbed and is instead excreted in the urine. So, obviously, there must be a limit.



To illustrate this concept better, we will take the example of glucose transportation.

On the graph, the X-axis represents plasma glucose concentration, while the Y-axis represents three variables related to the kidneys' filtering process.

The first variable, called "filtered load," represents how much of a substance is filtered by the kidneys. This value is determined by the substance's concentration in the plasma and the glomerular filtration rate (GFR), which is a constant for the kidneys.

The second variable is "excretion," which refers to how much of a substance is eliminated from the body through urine.

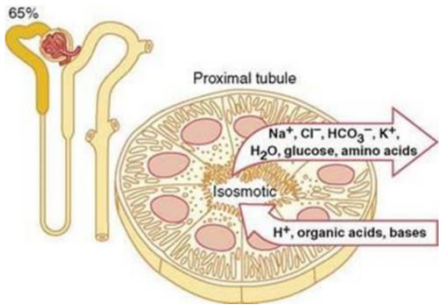
The third variable is the "reabsorption rate of glucose." Normally, the concentration of glucose in the plasma is around 100mg/dL. If the concentration increases, normally, it won't go beyond 200mg/dL due to insulin. The kidneys will increase their reabsorption rate of glucose to balance out the increase in filtered load, but there is still a limit to how much glucose can be reabsorbed based on the availability of carriers. If the carriers become saturated, any excess glucose will be excreted.

But the most interesting thing we can observes in the graph, is that the excretion of glucose by the kidneys begins when the blood sugar level reaches around 200mg/. However, it may seem puzzling since the transport maximum, which is the maximum amount of glucose that the kidneys can reabsorb, is not yet reached (it's typically over 300mg/dl).

The reason for this is that: Not all nephrons reach their transport maximum at the same rate. Some nephrons may reach their transport maximum at a lower blood glucose level, such as 200mg/dl, while others may not reach it until a higher level, say 245mg/dl. However, once the blood glucose level exceeds the transport maximum which is usually around 300mg/dl, all transporters reach transport maximum and the excess glucose will be excreted into the urine.

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

But hey, do all substances reach their transport maximum?
We will have to begin with briefly discussing the first segment of a nephron; ***Proximal convoluted tubules***.



0- Key transporter element is the Na-K ATPase in the basolateral membrane.

1- About 67% of the filtered Na+, H2O, Cl- and HCO3- , K+ are reabsorbed here.

2- 100% of glucose and amino acids are going to be reabsorbed. This happens through a process called co-transport, where glucose and amino acids move along with sodium using a gradient created by the active Na-K ATPase pump.
3- Hydrogen ions are also secreted by the proximal convoluted tubules into the tubular fluid, which ultimately becomes urine. The Na-K ATPase pump also creates a gradient that allows for this hydrogen secretion through counter transport along with Na+

Also, there's difference in the substances undergoing reabsorption according to the location in proximal convoluted tubules.
1- First half: Sodium gets reabsorbed mainly with the glucose and amino acids. [Co-transport]
2- Second half: There's a co-transport of chloride and sodium paracellularly.

Overview on the consequences of reabsorption.

We discussed before the mechanism of water reabsorption and its relation to sodium reabsorption. Sodium reabsorption would ➔

1- Increase the Lumen's negative potential
2- By osmosis, the water follows and thus the overall concentration of any solute that hadn't undergone reabsorption would increase. ➔ Luminal Chloride concentration in the second half would increase enhancing its already increased gradient, further ➔ Passive chloride reabsorption. Also, the negative ions present would rebel the negative chloride and the reabsorption of them increases [Small increase, of course].
    a. Urea, on the other hand, has poor reabsorption but a small amount of it is passively reabsorbed in the collecting duct. As water is reabsorbed, the concentration of urea in the tubular fluid increases. When the reabsorption of water increases, the urea concentration becomes very high, thus, the gradient to passive reabsorption of it is formed. On the other hand, urea is hydrophilic in nature, meaning, the osmosed water can drag it with it.

Now, back to the question of "*But hey, do all substances reach their transport maximum?*" It depends on the type of substance and the segment.

Type?
Amino acids do have a transport maximum. On the other hand, sodium does not necessarily have a transport maximum in all segments of the kidney. In the proximal convoluted tubules of the kidney, sodium appears to not have a transport maximum. *WHY?* (Not that it doesn't have a transport maximum. It just rarely reaches it.)

1. There's a massive diffusion of sodium through bulk forces. (((Paracellularly)))
2. Na-K ATPase channel expression in proximal convoluted tubules is very great that its reabsorption capacity exceeds any normal sodium demand.

So, no matter how much the sodium increases, the Na doesn't exhibit a transport maximum. In broader sense, since Na-K ATPase pumps are in great abundance them what are the limiting factors of Sodium transport?

1. Gradient: The movement of sodium across a concentration gradient is a crucial step in its transport. The more sodium that is filtered, the more it needs to be reabsorbed. In other words, the greater the concentration gradient, the more efficient the transport of sodium will be.

2. Time: The rate of flow of the tubular fluid in the proximal convoluted tubules is a key factor in the transport of sodium. When the flow rate is low, there is more time for the reabsorption of sodium to occur. Conversely, when the flow rate is high, there is less time for reabsorption, and more sodium is excreted in the urine. This is due to bulk flow and diffusion, which are more efficient at higher flow rates.

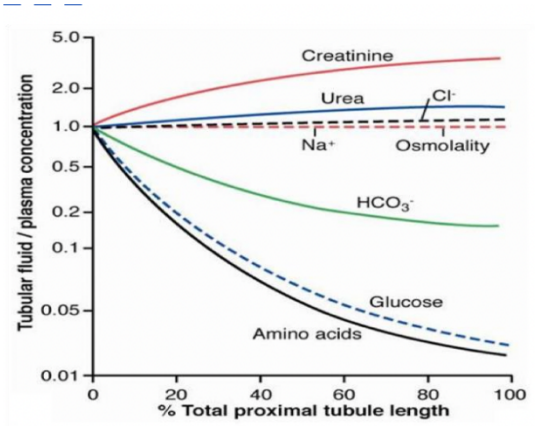
Location?
The distal part of nephrons is connected to the collecting tubules. In this region, the transport of substances like sodium (Na) is limited, and the tight junctions between

cells restrict movement. Therefore, transport of substances only occurs through specialized transporters or carriers and is also influenced by hormones like aldosterone. There is a limit to how much of a substance can be transported, known as the "transport maximum". As an ultimate answer to the question, it depends.

Changes in concentration of different substances in PCT

<1 ➔ Tubular fluid concentration of the substance < Plasma concentration of the substance
=1 ➔ Conc in plasma and tubular fluid are near equal
>1 ➔ Tubular fluid conc > Plasma conc of the substance

The graph showing the concentration of tubular fluid in relation to its concentration in plasma. Let's see what's happening to the different substance's concentration along the length proximal convoluted tubules.



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 concentration of each substance. For each substance, we calculate the ratio of its concentration in the tubular fluid out of the plasma concentration of this substance. From our previous discussion on the consequences of reabsorption, view it like a recap.

In the beginning of PCT length we notice that there is a relatively high concentration of creatinine and urea, and the concentration stays high and even increases along the PCT length. So, concentration of creatinine and urea in the tubular fluid is higher than the concentration in plasma which we can tell because the ratio is > 1 and this give us indication that they have poor reabsorption because their concentration remains high in the tubular fluid in the PCT.

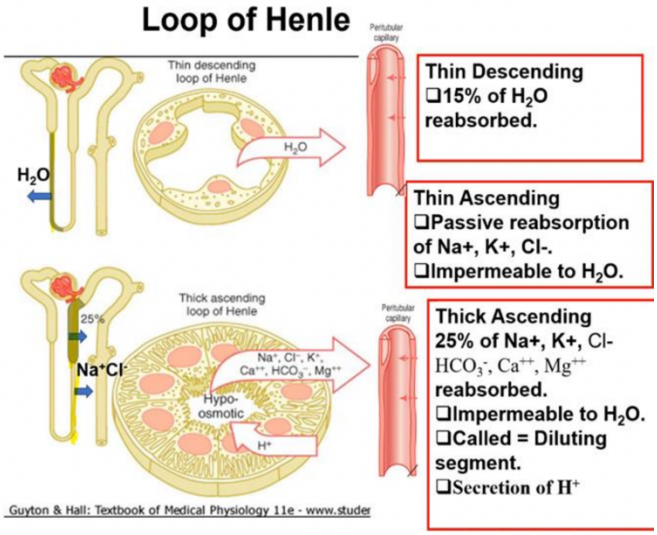
But regarding Na+ and Cl- their concentration which means their concentration in tubular fluid & plasma is close.
Why? [Na+] Because the rate of reabsorption is near equal to the rate of water reabsorption. They are reabsorbed at the same pace. So, the rate of Na+ reabsorption could reflect the reabsorption rate of water.

Creatinine and Urea have poor reabsorption, their concentration is increasing because the water is getting reabsorbed. [Urea getting a little bit reabsorbed]

Bicarbonate & glucose & amino acids we notice that the percentage < 1 and even decreases along the PCT. So, for HCO3-, and more so for glucose & amino acid, the plasma concentration 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 concentration in plasma > tubular fluid.
HCO3- undergoes in middle of sodium and amino acids reabsorption.

The Glucose and amino acids are all reabsorbed.

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.
All segments of loop of Henley are functionally distinctive.



A. Thin descending. Why is it called thin? Because the cells are mainly squamous, so you would expect them to not have a lot of tight junctions, any active transport element and so not even a mitochondrion.

They have a lot of aquaporin channels so ➔ They are permeable to water.
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 are more permeable for water due to aquaporin channels and paracellular route, and because of all that the water flows from tubular fluid to interstitial spaces so passive reabsorption of water occurs by osmosis. The solutes reabsorption is small in this segment.

B. The fluid begins to ascend the tube reaching the **thin ascending** part of the loop of Henle.

Both ascending parts are characterised by being virtually impermeable to water ➔ Because of the lack of paracellular or aquaporin channels ➔ Water is stuck -➔ Concentration of fluid and osmolarity of fluid becomes higher than the interstitium? BECAUSE reabsorbing of the water had already happened in the previous segment. So, the osmolarity increases! => Passive transport of NaCl [Small percentage] from the tubular fluid to interstitial space and capillaries till equilibrium. Active? No there's no ATPase or mitochondria or any energy supply because, again, the cells are too thin.

C. In **thick ascending** limb of Henle, the cells are large and cuboidal. So, it has extensive production of energy & extensive distribution of Na+/K+-ATPase channels and Na+ channels and Cl- channels.

Energy is spent to reabsorb **25**% of Na+, K+, Cl-, HCO3, Ca++ and Mg++ are reabsorbed. So, we have extensive transport for electrolytes in this segment enough to cause a very hypoosmotic concentration at the end of the thick ascending loop.

Why does thick ascending limb of Henle have a hypoosmotic concentration?

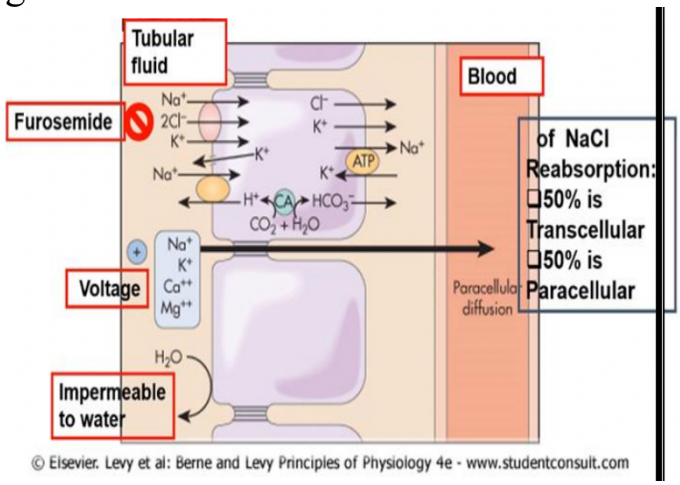
Because of extensive reabsorption of electrolytes (secondary active). At the same time, there's secretion of hydrogen by counter transport. Again and again, the gradient is made by Na+/K+-ATPase pump. Also, this segment is impermeable for water so water can't flow by osmosis from inside (hypoosmotic region) to outside and can't follow the solutes, so dilution occurs in this segment, so it is called diluting segment.

- Distal convoluting segment is also a diluting segment. So, it's not only the thick ascending limb of Henle that is a diluting segment.

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.

Let's take a closer look on the Thick ascending limb.



Thick ascending limb of Henle 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 [Apical cells] & 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.

How does the voltage drag happen in this segment?

Potassium which got reabsorbed => Some of it leak and return to tubular fluid => Through certain channels that allow leakage => Leak to tubular fluid then because there are already positive ions waiting to be re-absorbed => This creates slightly positive potential/charge causing high repulsion between the positive ions and that causes them to escape this density through the paracellular route, without any fluid flow. Only positive ions flow by the paracellular route by paracellular diffusion (only cations, especially bivalent ions, the more the +charge the more repulsion so it gets reabsorbed by paracellular route)..

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

Also, the 50% of NaCl reabsorption happens in paracellular manner due to voltage drag. [Probably the one causing increase in luminal negative potential but I'm honestly not sure. + Obviously without significant water reabsorption] and the other 50% from trans-cellular manner

Something we previously mentioned happening in this segment is Na-H counter transport but;

Where did the hydrogen come from?

From the intercellular environment => H2O + CO2 (Diffusion) => Carbonyl anhydrase => H2CO3 => H+, HCO3- (In the cell itself) => H+ secretion in the urine and HCO3- re absorption to the blood => Similar Mechanism happens in the proximal convoluted tubules (Will touch upon this in later lecture)

Pharmaceutical industries had designed a drug to block the Na-Cl-k channel, why? Because it contributes to 25% of sodium reabsorption! [In thick ascending limb again] => Blocking the sodium here would mean water will follow it in other segments [That are permeable to water] and causes diuresis [Increased urine volume] => Reduction of plasma volume => Reduction of blood pressure [Ex: Furosemide]

Problem: It causes loss of chloride and potassium => If used in long term => Hypokalaemia => Serious condition that would affect the normal function of the heart and the nervous system]

Sodium chloride and potassium transport in thick ascending loop of Henle

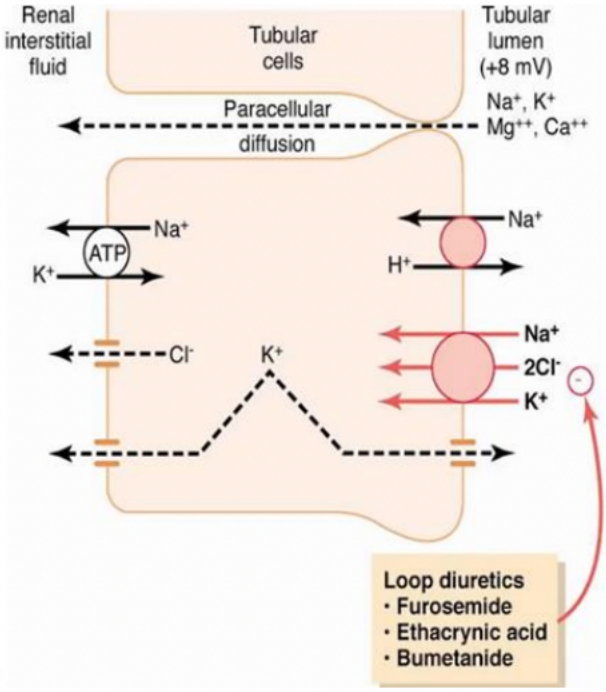


Figure 27-9

Thank you!