Human Physiology
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Lecture - 03

Welcome, everyone, to another new class of human physiology. In this class, we will discuss the proximal convoluted tubule. In the last class, you remember we discussed glomerular filtration, where we saw that it is important to filter the protein. So that the proteins do not come out of the blood because they are so important for our normal functions. Apart from the protein, the glomerular filtration could also inhibit any leakage of blood cells such as RBCs or WBCs, as well as most of the other components like small ions, sodium, potassium, calcium, glucose, and other nutrients that were able to come inside. In this class, we will see how those essential nutrients get reabsorbed back inside the nephron, mostly in the proximal convoluted area.

So, what different concepts should be covered here? We will first see the proximal convoluted structure, then we will discuss tubular secretion and the reabsorption process. We will discuss different important transport channels in the proximal convoluted tubule and how the reabsorption and secretion mechanisms occur. So, as you can see in the proximal convoluted tubule from the last class, what we discussed is like the whole nephron, as you can see here. In the last class, we discussed this part, right, the glomerulus and the Bowman's capsule.

So, initially, blood goes inside, and by the initial filtration, the remaining blood goes out, and during this filtration, all the proteins and the like blood cells get filtered; they are unable to pass inside, right? But the rest of the nutrients and ions go inside. Now, we have to see how the reabsorption of those essential nutrients occurs, right? So, this happens in the proximal convoluted tubule. This is situated mostly in the cortex area of the nephron. It is about 14 millimeters in length, and the diameter is about 55 microns. And what are the different cells that are mostly present, like they are this tight, cuboidal type of cells? So, basically, the PCT, or the proximal convoluted tubule, is made of a single layer of cuboidal epithelial cells.

And there is a very interesting kind of characteristic structure of this cell because it has these hair-like structural brushes. So, they are sometimes also called brush border cells. So, these cuboidal cells are called brush border cells because of this hairpin-like outer layer structure. So, let us try to understand two different terminologies in a basic, very basic way. What is tubular secretion versus tubular reabsorption? So, what we said initially after the glomerular filtration is that the majority of these ions, like sodium and glucose, come inside, right? Now, these are essential components of our body, like sodium, potassium, chloride, bicarbonate, glucose, and lipids.

So, our body does not want it to go out. Our body does not want this to go out via urine. So, what it does basically is that these molecules get further reabsorbed from the urinary component back to the blood. So, what happens that this all these essential component gets reabsorbed. So, this is called the tubular reabsorption process.

Then what is the tubular secretion process? Like if there is any movement of molecules from the blood directly to the proximal convoluted tubule, which basically happens via the active

transport process. And as you know, right, that active transport process requires energy or the involvement of ATP. So, this is called the tubular secretion process. So, basically, the reabsorption process is from urine to blood, and the tubular secretion process is exactly the opposite, where molecules from the blood are secreted into the PCT, which eventually starts forming urine. Then what are the different important channels or transporters present during reabsorption? There are many potentials, but the most important is the sodium-potassium ATPase.

During our transport class, you remember we discussed the role of sodium-potassium ATPase. Basically, it removes 3 ions of sodium, right? It removes 3 ions of sodium and, in turn, it accepts only 2 potassium ions inside the cell. So, cells basically want to remove excess sodium from the cell, and this process happens via the involvement of ATP because ATP is important or through the use of energy. So, this is the primary active transport process that requires ATP or the involvement of energy, and ATPase is the enzyme that plays a particularly crucial role during this process. So, the sodium-potassium ATPase pump is the primary, very important ion pump.

Apart from that, you will see the sodium-glucose co-transporter pump; you will also see the sodium-amino acid co-transporter pump. And these are mostly secondary active transport pumps. That means both the sodium glucose transporter pump and the sodium amino acid transporter pump are dependent on the primary active transport pump, which is the sodium-potassium ATPase pump. I will explain how it happens, and if you remember, in the cell transport class we also discussed, but let's see in the next slide how these things happen. Also, what are the various substances that generally get reabsorbed, right? So, under normal conditions, you will see that glucose, lactate, and amino acids will mostly be reabsorbed back into the blood, with about 100% of these molecules reabsorbed.

What about sodium? Sodium is also reabsorbed during the process of co-transport with glucose and amino acids. Bicarbonate is very interesting; we will discuss it, and you will see how bicarbonate reabsorption happens, but mostly just try to understand that bicarbonate reabsorption goes through a complex process where it combines with the secreted protons to form carbonic acid. So, blood protons come from carbon dioxide, which then adds up with the secreted protons to form a complex, and that complex eventually gets converted back to carbon dioxide and water. So, the intercellularly generated additional bicarbonate ion that stays inside gets kind of reabsorbed back into the blood. We will see how the process works, but this is another important kind of reabsorption process, and then water—water is how the body tries to limit water loss.

So, the body tries to reabsorb as much water as possible; about 65 percent of the water gets reabsorbed. Then potassium, calcium, magnesium, and chloride—about 50 to 55% of these ions, like potassium and chloride—get reabsorbed back. And finally, lipid urea is reabsorbed back into the blood. It tries to, of course, reabsorb as much as it can, but there is a significant amount that is not reabsorbed. Now, let us see one by one how things work.

So, we will start here first with the sodium-potassium primary ATPase pump. So, what we said during the sodium-potassium ATPase pump is that these are cuboidal cells. So, these are cuboidal types of cells which also have hairpin-like brushes that try to remove excess sodium ions from themselves. So, what it is trying to do is remove 3 sodium ions from inside the cells to outside, and in turn it accepts only 2 potassium ions, and by this process it maintains the salt balance of the cell; importantly, you should remember this process also requires the

involvement of ATP or energy. Now, just think about if we are continuously having this primary active transport where more and more sodium is going out of the cell; then what will happen? Let us consider here as if we have cells and this primary active transport is happening in multiple cycles.

So, what are we removing? 3 sodium ions, and we are accepting only 2 potassium ions inside. But if this process continues for maybe 100 times or 1000 times, what will happen? The sodium concentration inside will decrease because we are removing more and more sodium ions from the cell, and then outside of the cell; what will happen to the sodium ions? The sodium ion concentration outside will become high. So, this is exactly what happens after a few rounds of the primary active transport process: the sodium concentration inside becomes very low, while outside in the proximal convoluted tubule area, the sodium concentration becomes high. And that means it creates a concentration gradient for diffusion. So, what will happen is it creates a concentration gradient where sodium ions from outside, when it is high, come in as a process of simple diffusion from high to low concentration.

Interestingly, when sodium is coming inside in the process of simple diffusion, it acts like a kind of piggyback system. So, for example, consider that sodium is coming inside or moving in one direction; it helps some other molecules also come inside with it. What are some other molecules that it helps to come with? For example, glucose, lactate, and amino acids. So, all these molecules, like glucose, lactate, and amino acids, can co-transport with sodium. So, you remember that during the initial glomerular filtration rate, glucose came in and then sodium came in.

Amino acids came in. What happens during the sodium diffusion process is the same way that amino acids, glucose, and lactate undergo the co-transport process, which is a form of secondary active transport. So, both sodium-glucose co-transport and sodium-amino acid co-transport are secondary active transport processes because they do not directly involve the participation of ATP; rather, they are dependent on the primary active transport of the sodium-potassium ATPase pump, which is why they are called secondary active transport. So, once the amino acid or glucose comes inside the cells, what happens is that the glucose concentration slowly increases, and similarly, the amino acid concentration also increases. Then, they exit through a simple diffusion process from the cuboidal cells back into the blood. Similarly, the glucose concentration builds up here, and using various glucose receptors like the GLUT receptor, this excess glucose enters the blood from the cuboidal cells of the proximal convoluted tubule.

So, in this process, glucose, amino acids, and lactate almost get 100 percent reabsorbed. So, hopefully it is clear that all these molecules and ions, including sodium, glucose, and amino acids, along with lactate, are being reabsorbed mostly via the process of secondary active transport. Hopefully, it is clear. Let's take the next few things, right? So, for example, how the reabsorption of sodium occurs. We already told you, right? Initially, the primary active transport of sodium occurs, which causes the sodium concentration to become low inside cells and high outside, or the sodium concentration goes high outside, and wherever it happens, more sodium will come inside through diffusion.

Once diffusion occurs, the sodium concentration inside will slowly build up, which will further trigger the primary active transport again. So, this is basically a homeostasis process in which the diffusion of sodium happens, and then once the sodium builds up inside, the primary active transport removes the excess sodium out of the cell. So generally, sodium goes out of the cell.

And when, very interestingly, sodium goes out of the cell, which is about 65% of all sodium, it also carries water along with it, which is called obligatory H2O or water reabsorption. So, water basically has a high affinity for sodium.

So, wherever the sodium moves, water follows it. So, as we can see, about 65 percent of the sodium generally comes out of the cell using the process of primary active transport, and while this sodium moves across, water molecules also follow the sodium, and about 65 percent of the water molecules come out from the proximal convoluted tubule back to the blood capillaries. Hopefully, it is clear. Then you can see that we have covered water and sodium. Then the most important one is about how bicarbonate reabsorption happens.

So, let us try to understand here how bicarbonate reabsorption happens. This is very important. So, you see that inside the blood, after cellular respiration, it can generate a lot of carbon dioxide. This carbon dioxide, because it has a high concentration or molecular deposition here, can easily come inside this proximal convoluted tubular type of cells. And when they come inside, a very interesting thing happens because cells also have water; this particular enzyme, carbonic anhydrase, can convert carbon dioxide and water to carbonic acid.

So, what happens again? Let us clear it up. After cellular respiration, carbon dioxide gets deposited in the blood that can diffuse inside; inside the cells, water is present along with a particular enzyme, carbonic anhydrase. So, this is like an enzyme called carbonic anhydrase. This enzyme converts carbon dioxide and H2O to carbonic acid, okay. So, hopefully it is clear, and now once the carbonic acid forms, it can easily dissociate into two things.

One is a proton and one is a bicarbonate ion. So, carbonic acid can stay in a balanced condition; it can be converted to or dissociated into one proton and one bicarbonate ion. Now, you remember that sodium was more outside, right? Now, sodium can enter by the process of diffusion. What happens when sodium comes inside is that the hydrogen ion, or H plus proton, which was initially generated by the dissociation process of carbonic acid, comes out of the cell by a secondary active transport process called antiport. In the last slide, we discussed the secondary active transport symport process, such as sodium-glucose and sodium-amino acid transport, because both sodium and glucose were moving to the same side.

What was that? Because both sodium and glucose, or the amino acids, were going from one side to the other, but in these cases, you see sodium is going from outside to inside of the cell, while the proton ion generated inside the cell is coming out. So this process is called sodium hydrogen secondary active antiport transporter; okay, so this is called sodium hydrogen secondary transport antiport type of transporter or the process because the direction is different. Now, the hydrogen, as it comes outside near the proximal convoluted area, combines with the bicarbonate that was filtered via glomerular filtration, so our urine, or the part of this proximal tubule, has a lot of bicarbonate outside that gets combined with this proton and becomes carbonic acid. So, the proton that gets dissociated inside the cell comes out by the antiport mechanism, and this H plus, along with the already existing bicarbonate that came from the glomerular filtration, gets conjugated together and becomes carbonic acid. Now, very interestingly, the cell wall also has a carbonic anhydrase type of molecule or enzyme.

So, as you know, like you remember what can happen if the carbonic acid comes close to the carbonic anhydrase enzyme, it gets converted back to carbon dioxide and water, right? It is very interesting. So, the proton initially comes out, gets conjugated with the HCO3 minus, and becomes H2CO3, or carbonic acid. H2CO3 is dissociated into carbon dioxide and water

molecules by the action of the carbonic anhydrase enzyme, and this carbon dioxide and water basically come out via the proximal convoluted tubule into the urine. But then you will ask me how this bicarbonate reabsorption is happening, right, because you just told me that carbon dioxide is coming in from the blood and eventually carbon dioxide and water are going out through the urine. So, how is the bicarbonate reabsorption happening? You see this leftover bicarbonate here.

What was initially dissociated from the carbonic acid left over bicarbonate, because a lot of bicarbonate molecules are now being generated here; the bicarbonate concentration goes higher and higher inside these tubular cuboid-type cells, and then through a diffusion process, this excess carbonic acid or the excess bicarbonate ion comes out of these cells and gets reabsorbed back into the blood. So, what happens? Whatever the leftover bicarbonate ion due to the excess accumulation of this bicarbonate, it gets diffused out of the cell back to the blood. How much? About 90 percent. So, 90 percent of the bicarbonate gets reabsorbed back into the blood in this indirect way.

So, you fully understood it. Then finally, lipid and urea, you know, like lipid urea, these are like, these are what? These are non-polar types of molecules, and because they are lipid-soluble molecules as well, our cell membranes are made of glycolipids and a lot of bilayer membrane lipids. And because they are lipid soluble, both lipids and urea can easily pass through those cells via the lipid soluble component. So, all these lipids can easily come out by that process. And then what is the rest of the thing like chloride ions? Chloride ions can also come out from the cell and get reabsorbed by the sodium chloride symport secondary active transporter. You can see that co-transport secondary active transport can happen in the same way as glucose and amino acids.

So, chloride ions also mostly get completely reabsorbed. And then finally, like calcium, magnesium, and potassium, these ions here—calcium, magnesium, and potassium—create a paracellular junction between the two cuboid-type cells. These are some sort of tight junctions. So, these ions—calcium, magnesium, and potassium—can actually crawl in from the small tight junctions, and about 50 to 55% of these important ions can get reabsorbed into the blood. So, water is about 65%, sodium is also about 65%, and they get reabsorbed.

And then glucose, amino acids, and lactate are almost 100% reabsorbed. Lipid urea can also be reabsorbed by 30 to 50%. Then about 90% of bicarbonate can be reabsorbed. Chloride ions can be reabsorbed at almost 80 to 90%. And then finally, the calcium, magnesium, and potassium can also be reabsorbed by about 50 to 55%.

So, you can see this is the process of how the body is almost retaining the majority of the ions, right? Finally, you remember I told you that some of the very small proteins, like insulin and hemoglobin, if they can pass through this initial glomerular filtration, what will happen to them. You see, they have some specific receptors, like protein receptors for insulin and hemoglobin, and they can get inside the cells by the process of endocytosis. Once they come inside through this receptor-mediated endocytosis, they can mix with the lysosome and undergo lysosomal degradation. So, whenever there is lysosomal degradation, this protein will get chopped up and degraded, and smaller components like amino acids will eventually be exocytosed from the cell. So, this way, these amino acids can get reabsorbed back into the blood if any insulin and a small amount of hemoglobin can enter; they get degraded and reabsorbed by the process of endocytosis, followed by lysosomal degradation and exocytosis.

Finally, we will end with the secretion mechanism. Okay, so what different types of secretion can happen from the blood to inside the urine? There are like three things we will mostly discuss. One is glutamate metabolism, which basically secretes bicarbonate. So, through glutamate metabolism, what gets secreted? Bicarbonate. From where to where does bicarbonate get secreted and reabsorbed? From the blood into the blood.

And then proton secretion can occur. Protons are generally exchanged for sodium ions. You remember during secondary active transport, aiding bicarbonate reabsorption and pH balance. Then different types of drugs and organic compounds can also be secreted. For example, if you take some drugs like penicillin or any other drug, an excess of drugs after metabolism, liver metabolism, if it stays in the blood, can be secreted into the urine and come out through the urine. So, mostly we will see this bicarbonate secretion, proton secretion, and drug secretion.

Let us see how things happen. Let's start with the drugs. So, penicillin or other types of drugs, for example, will mostly be metabolized by the liver, and our body will use specific areas for certain drug actions. But if certain drugs are still intact, maybe with a very high dose, some of the molecules are still there and they are passing through the blood; because some of these drug molecules are sort of high in concentration, they can diffuse inside. But this type of process, although we are saying that they can diffuse inside, still needs a process of energy utilization. They cannot come only by the concentration gradient, unfortunately.

They will require the involvement of ATP. So, basically, they require the energy. And these drug molecules from the blood will first come inside these cells, and eventually they will pass to the proximal convoluted tubule and then through the urine. Hopefully, it is clear. The bicarbonate, HCO_3, this we have already discussed, right? How this happens is when the hydrogen secretion occurs, right? So you remember that from the blood, the CO_2 will come inside, and the CO_2, in the presence of water and carbonic anhydrase, what does it convert to? It converts to H_2CO_3, which gets dissociated into H plus and HCO_3 minus, and eventually, the H plus enters the urine via the antipode mechanism. So, this is called the hydrogen or proton secretion, although it is an indirect secretion procedure, as you can see, because H plus is not being directly secreted from blood to the cell.

Via a process of dissociation and conversion, you can see that the proton is eventually getting saturated in the urine. The same applies in the case of metabolic acidosis. So, for example, in cases of pH, if the blood pH goes below 7.3, like if the blood experiences some acidic condition due to metabolism, what happens basically is that the glutamine-rich cell has a lot of glutamine-type amino acids and molecules, right? So, this glutamine in the presence of acidic conditions gets converted to ammonia by a process of deamination, so it gets converted into ammonia and bicarbonate, and this ammonia is very toxic to cells; therefore, cells will not keep this ammonia inside, and the ammonia will eventually come outside of the cells, but they also require ATP. So, they also require the involvement of energy for this ammonia to come out, and ammonia can also dissociate into ammonium ions (NH_4^+) that can dissociate into ammonia and protons, which will eventually be excreted in the urine.

Ammonia is very toxic. It is one of the most toxic substances for the cells, for the nephrons, and for the body. So, we really need to remove all ammonia from the cells. And you can see one thing: through this process, the cell is also generating bicarbonate. This bicarbonate ion will eventually diffuse into the blood, and do you know what this bicarbonate will do? This bicarbonate ion will try to increase the pH back to a neutral condition. Initially, during acidosis, an acidic environment is created that triggers this chain reaction.

Eventually, bicarbonate forms and exits the cell back into the blood, which helps maintain pH balance. This is how pH regulation can occur, and it demonstrates that this is a very important process through which tubular secretion can happen. So, these are different ways in which various molecules, like protons, ammonia, and even various drugs, can be secreted from the blood back to the urine, either in a direct way or in an indirect way. So, it is very important that you go through the secretion mechanism of glutamate, protons, and other drugs. Finally, do you know that the proximal convoluted tubule has a brush border of microvilli that dramatically increases its surface area and makes it highly functional? The brush border, made of thousands of teeny finger-like projections, significantly enhances this absorption property.

So, that is why it is very important to understand that each of our body components has a specific type of cell type. So, because a lot of reabsorption processes are required here, the cells create highly surface area-based cells that can improve absorption at a rapid rate. Hopefully, you enjoyed the class on the proximal convoluted tubule, and we will meet again in the next class to see how the next phases of the kidney urination process occur, which take place in the loop of Henle. Thank you again.