Human Physiology
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Lecture – 34
Excretory system : Regulation of Osmolarity and counter-current mechanism - Part 3

This is a very good diagram. Just focus on this - we will solve all the questions. Let us see we are talking of the capillary ok, we are talking of the capillary. In capillary, normally in any capillary, anywhere, what should be the osmotic value? 280. 280 good 280, 300 ok. But now why is author indicating 700 here? Vasa recta. Vasa recta we are going down ok.

So this is this is this is clear ok. Now along with that, along with the blood ok from this side along with that the author is bringing what? The hormone here? Vasopressin. Vasopressin will get out of vasa recta, it will get on the interstitial fluid, it will act on the tubule that is going down, ok. And there it encounters a receptor ok. Can you see this receptor? Where is it sitting? It is in the plasma membrane what do you call that receptor as? Vasopressin.

Vasopressin receptor. Now this is again typical peptide interacting with this receptor - 7 transmembrane protein - hello? Ok. So this vasopressin is the ligand and as a result of that - this is G protein coupled protein - it will stimulate adenyl cyclase, it will give rise to cyclic AMP. There is a signal and finally the signal goes to the synaptic vesicles. These are the vesicles within the cytoplasm ok. And sitting on those vesicles is the what can you read there? Aquaporins. Aquaporins. Now under the influence of the hormone, these will be, what? Trafficked. The cytoskeleton system will be excited and those vesicles will move move move move move and finally where have they settled? Apical or basal? Apical.

Apical. Now suddenly for the water ok, the aquaporins are available ok. So through this aquaporin, water will get in ok. Now this is I will say inducible aquaporin who induced it? Vasopressin. Vasopressin ok at the apical side, on the basal side, there is another aquaporin which is constitutional. So it is always there so the water will come in and the water will get out and the water will get into the bladder. Have you followed the entire sequence of events which are triggered by what? Vasopressin.

So the blood is here, the blood is here, the vasa recta is here and what will come out - the vasopressin will come out ok. And can you see that green receptor going 7 times up and down ok. We have some more detail - what is it called as can you tell me. What is the meaning of AVPR2 can somebody tell me? vasopressin type 2 receptor. This V1 this V2 this is what type? This is V2 ok. Above that can you see that tiny what has author written there? Aquaporin.

Aquaporin. Aquaporin 3. You know in the earlier figure we had seen Aquaporin 1, 2, 3, 4, 7 we had seen that the author specified what kind of Aquaporin what kind of Aquaporin is constitutionally sitting on the basal side of the membrane? 3. 3 it is there ok alright. So then arginine vasopressin combines with the receptor - G protein coupled adenyl cyclase - cyclic AMP, cyclic AMP acting on the vesicle, vesicle, vesicle then microtubules and the actin filament it will move there and then Aquaporin 2. Again Aquaporin 2 will be introduced here, this is inducible ok. And this will allow the water to get and supposing you have - you take water ok. As a result of that, now let us go the other way round. We have taken in water so those cells of secreting vasopressin are now inhibited. As a result of that, arginine vasopressin level in the blood has gone down. As a result of that, you do not get you do not get that stimulation anymore ok. Shortly within 10 minutes those vesicles those vesicles will be taken in ok and no more Aquaporins are available for transport of water from the lumen to the inside. Are you with me? So for this system to operate, they will continuously need signaling from arginine vasopressin are you with me? Because there is no point in keeping the Aquaporin there ok. Once the osmolality has been restored - make sense? Go back going back to the very important point. What are the factors that are responsible for building up the high osmolality in the medulla? We have given a lot of credit to the thick segment, thick ascending segment, and we said in that in the wall there are lot of lot of transporters and because of which sodium sodium sodium sodium - so we keep on talking about sodium, ok.

Author tells us that the contribution of sodium and along with that other ions is about 60% not 100%. What is our target? I want to understand what are the factors which are responsible for building the osmolality to 1200. My candidate number 1 is sodium does it give me 1200? No it doesn't give me it doesn't give me 1200. It gives me about 60% of that. Then which is the other important character I am missing. The other important character is - strangely enough - is it urea. Urea which we normally consider as a useless molecule which needs to be thrown ok. Time has come for us to slightly change - change our concept about that molecule, ok. Within limits, urea is a useful molecule that contributes to building up the osmolality, high osmolality in the medulla. Did you get the message? And it is so important that it contributes almost 40% of the osmolality in the medulla. It is because of urea - it is something like this - the kidney has “thought” - the kidney has “thought” that I am here to separate the urea good. Can't I put it to some use in a restricted way? Urea may be otherwise an excretory product and needs to be thrown, but it is a solute and that solute is in a sense useful because if I want to increase the osmolality in a particular area that molecule is very helpful, ok. Forget about this I will tell you a story. Forget about all this - you know shark shark shark shark the shark lives in the sea. Sea water fish - it is a cartilaginous fish. Now osmolality of sea water is very high. We all know it is salt salt salt everywhere. Osmolality is about 1000 1000 1000 milliosmotes/liter. Sea water is 3 more, 3 times stronger than the osmolarity of your blood. Your blood is 300 - it is 1000 ok. So every fish is continuously being subjected to dehydration because their osmolality is 300 in fish and outside is 1000. They are continuously losing water. You are in water but you are dehydrated. Water, water everywhere not a drop to drink. But in shark the osmolality is 1025 1050 or 1075, so the osmolality of shark blood is even stronger than that of sea water. So that guy has no problem ok. It can survive very well, ok. Now you can ask why how the animal has been able to

maintain such a osmolality. The answer is urea. Urea in the blood is very high so the osmolality of shark blood is very high, so the osmolality of shark blood is very high - urea concentration in the blood of a shark is 100 times more than your or my blood. So you can ask another question how does that guy tolerate that urea, ok. That is another question. We will talk about it in animal physiology II. If you are still there, ok. But why am I making this point? I am making this point because I want you to appreciate the beauty of nature, ok. Nature is trying to find out a solution. If you can find any ok. So so urea molecule actually - it is – well every cell generates ammonia - that ammonia - you can excrete ammonia - your liver can convert what - no I made a mistake - I have corrected. It the joke is costly because I have lost my theme of thought such words always create a problem. Liver can convert ammonia into urea. Ammonia to urea ok. So the nature has thought, why cannot I use that molecule for taking my osmolarity so high, that I am not really worried about the osmolality of sea water. Having conveyed that point, I will come back to this point. So what is urea - let us see now ok. So the kidney handles the urea in such a particular way that urea that within the medulla, the urea contributes to about 40 percent 40 percent of the osmolarity. So urea plus sodium all put together is about 1200 - thus enriching the osmolality of medulla to about almost 1200 milliosmoles. How does that happen? just follow - first of all look at the thick line look at the thick line look at the image look at the thick line that is the part where in the urea is blocked and it cannot go out. Are you with me? Is it dependent on aquaporins? No aquaporins. This is for water, this is for urea, ok. And its profile is not exactly like aquaporins. No it is a different profile so this part of the nephron, where you must remember as to where urea can get out of the nephron and where urea cannot get out of the nephron. Did you get the image there? From that thick line urea cannot get out of the nephron are you ok so far? Ok good. Now the ultra filtration is happening. Now the author has given an image - given the number 4.5. Now what is this 4.5. Very simple. What is the osmolality of blood 280 – 300. Whatever? Out of that, the contribution of urea is 4.5. You got the language. May not be lot. Because of sodium, lot of calcium very little because of potassium, because blood potassium is very low. All put together I am not worried about it. I am only worried about urea and urea contributes to how much 4.5. Are you good so far. Now as you go down it becomes 7, ok. Water is absorbed, other things are absorbed - 7 hello. Are you with me. As you go down it becomes 15. Why because urea goes, water goes, but urea does not go as much as water goes. Therefore it becomes 15 it becomes 15, ok. Now just do not worry about these arrows I will come back then you go here, ok. As you go here, ok, then the urea cannot go out ok. And then and then and then and then as you go by here you have urea which is about same as that was filtered and then you go here and go here all other things are being absorbed ok by the time you come here the concentration of urea has gone to about how much 300 milliosmoles. now this part of the medullary collecting duct is equipped with urea transporter - something like aquaporin. But a different molecule. Urea transporter. What will it do? It will allow the urea to come out now are you in the cortex or in the deep in the medulla? You are deep in the medulla. You are right. So deep in the medulla - the kidney and urea concentration is very high because of the transport it flows everywhere in the medulla and these cells in the loop of Henle. They have got the capability of picking up that urea and secreting it in their lumen. So you have a urea cycle, so where as some of the urea some of the urea is being thrown out, some of the urea is being re-circulated in this part of

the kidney. That adds to about 40 percent strength to the medullary fluid. Very interesting point that is covered by arginine vasopressin and I will talk about it in this very interesting slide. Please focus on this. Entire world knows that arginine vasopressin comes, it acts on those cells. It induces the aquaporins - aquaporins will go on the apical membrane - water will be absorbed. What is less known about the property of arginine vasopressin is that. It also facilitates the reabsorption of urea because if urea is not there then you will lose that 40 percent. Hello, are you with me? Urea is contributing how much 40 percent. If urea is not there - you will lose 40 percent that is not a good idea. So if you are a land animal, you are very often subjected to dehydration and then you have to have very powerful mechanisms of reabsorbing water and what is the mechanism of a reabsorbing water? You have to make sure that your osmolarity of the interstitial fluid in the medulla is high. That is the only tool you have. If that osmolarity goes more and more and more you can absorb more and more water and you have more efficient kidney and the extreme example of that is the Australian mouse. Why is that the mouse is capable of generating such a strong urine - because it is capable of generating interstitial fluid in the medulla whose osmolylity is 10,000. Therefore, it can absorb, are you with me? So capability of the kidneys to reabsorb water from the fluid that is being thrown out of the body will depend on the osmolarity of the how much of osmolarity can you generate. Let us see, we are again looking at the same cell. What cell - medullary cell of what collecting tubule. We are looking at the basolateral membrane and here is the receptor - the same 7 transmembrane receptor for arginine vasopressin - adenylyl cyclase - cyclic AMP and this mechanism - and then finally your vesicles. These vesicles have again very large protein molecules they are urea transporters. What are they urea transporters? Like aquaporins they will also go and sit in the apical membrane and they will facilitate the transport of urea. What are you really trying to do? You are trying to retain the urea into the medulla. When urea is retained it will increase the osmolarity - once you increase the osmolarity - it adds up to your power of reabsorbing water and eventually conserving water. Am I done there hello are you good.

Since vasopressin can stimulate urea reabsorption, can under dehydration, the osmolarity of medulla increase even beyond 1200. No it does not that is the limit. We believe that the human kidney can go from 1200, 1300, 1400 but that is the range it cannot go beyond that. So during dehydration level it slightly fluctuates from - these are individual variations when we say 1200 to 1400 they are individual variations. So it more or less remains like. Like any other thing like any other feature in your physiology there we are always talking about a range here.

And in case - we have to make dilute urine - there is low vasopressin in the blood. So does urea transport also decrease?. Absolutely. The amount of urea in the medulla is being governed by arginine vasopressin. Governs two things - absorption of water and making sure that urea is retained. So when vasopressin goes down - both the functions will relatively go because we do not need them now because you have had water. Whenever there is a challenge on your homeostasis okay, our physiological response - just now I spoke about 10 minutes back - our physiological response is by two ways. Number one is a physiological response which we seen and other was behavioral response, okay. How is behavioral

response generated? Well the information is processed in the brain and then the brain triggers the thirst mechanism, okay. The thirst mechanism will do lots of things. In our mouth our saliva is continuously being secreted at a particular rate, okay. As long as the rate is normal, okay, our mouth is not dry. But when our body starts dehydrating the rate at which our saliva is being secreted in our mouth goes down. Saliva is still there, but the rate at which it is coming - it goes down. It generates a feeling of dryness - generates what dryness. My throat is dry, okay. Is it really dry? No. Saliva is still there. Okay. But it is not coming at the same rate Then it is dry, okay. It will trigger it will trigger what? What? Then what will you do? Start start start looking for water okay and ingest and ingest water.

Recent studies show that osmoreceptor are also there in our throat, okay. And in the esophagus and in different parts of our alimentary canal. Osmoreceptors are there, we do not know much about it, okay. So do not ask me questions, I do not know. You see even there is loss of blood - accident loss of blood okay - there is dryness is mouth, okay. is there a change in osmolality. No. Even the loss of blood can generate thirst - let us see this very interesting. The plasma osmolality we are normal we are somewhere here okay. We have arginine vasopressin in the blood, okay. As the osmolality goes here here here here here what happens to the vasopressin can you see this vasopressin in the blood, okay. So you are collecting vasopressin when you are fully hydrated now you are dehydrated dehydrated - vasopressin goes here and some here. What does this indicate – the intensity of thirst is going up. And at the top you can see what hormone? You are able to see the structure of what hormone? There okay. You can actually count that there are okay. See this is a very rare case in the in human beings where as a result of the damage or some other reason to the posterior pituitary, the patient is not capable of secreting sufficient amount of arginine vasopressin. What will happen can you guess? Lots of urine obviously? Correct. Lots of dilute urine okay. Now the patient has no control because his kidney cannot absorb water. So the only thing the poor patient has to do is to keep on drinking water and formation of large amount of dilute urine. This condition is called as diabetes insipidus. Correct. What do you call it as - diabetes insipidus. Which diabetes refers to the problem with the urine if it is sugar it is mellitus - if it is water it is insipidus, okay.

Now we are grateful to the technology - biotechnology product. What do you call it as? Desmopressin. This is a chemical name okay. This is like arginine vasopressin, okay. and this can be used for the treatment of the patients okay. Just a couple of slides I will complete my today's lecture. I will ask you a simple question. Fill in the blank tell me the name of a hormone that will help us to conserve sodium.

Aldosterone. Very good. Aldosterone before aldosterone what will come? Angiotensin. Very good. Now we will go to the other end. You have taken too much of salt and what is the other end you have taken too much of salt so how would how would the physiology respond? You remember something. We had seen that graph in which you have you have increased your intake of salt 10 times. You remember from 30 to 300 okay and so how does the body deal with excess of salt. The answer to the question is you take salt okay.

Osmolarity of blood goes up. As a result of that the blood draws water from the rest of the body are you with me? As a result of that the blood volume increases that blood volume increase. The blood volume is sensed - the blood goes back into - follow the chain of events. Blood goes back into the right atria - right atria stretches - more stretches it realizes - in my words - it realizes that there is per bit more blood is coming, okay. It responds to this kind of stimulus. It responds by generating hormone and what is that hormone called as please read for me. I mentioned about it once in the past what do you call it please atrial natriuretic peptide. Is the is the term self-explanatory atrial natri- is sodium okay - and diuresis refers to excretion. So this is a peptide hormone that is coming from the right atrium okay and of course it is a hormone gets into the blood it acts on the kidney okay and what it does is - you remember we talked about ENAC do I make sense? what is ENAC -epithelial sodium channel. Correct? can you read can somebody please read for me the statement that is written in blue font. ANP inhibits ENAC located in the collecting duct. What was the normal what was the function ascribed to ENAC? Sodium reabsorption okay. Now what is ANP doing? Inhibiting which means what will happen to the sodium - it will be excreted, okay. This is one of the other functions. All put together - this is this is your physiological response to make sure that when you have taken excess of sodium okay you need to get rid of it. And atrial natriuretic peptide accomplishes that function by inhibiting those systems with which we reabsorb sodium, okay. I think there are couple of slides I want you to read on your own. This tells us as to how the peptide is released – and how hormone works.