Human Physiology
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Lecture – 39
Respiration - Part 3

Now I am talking to you, to you, I am talking to you, what was her question? Her question, yeah, and the answer is actually very simple, I will not give you the answer but I will let you work out the answer by showing you a couple of slides, what is this slide? So as you go towards the gravitational pull the alveoli becomes smaller and smaller and the blood becomes more and more, are you with me? And if you go further, further down okay then comes a stage when the ventilation is very weak and it is all blood flow particularly in the standing position, are you okay so far? Now remember this thought and then think of this thought, what is this thought? In a particular alveoli if the ventilation is not enough what will happen to the blood supply of that alveoli? So that is what happens exactly to those alveoli which are down deep down. They have lot of blood, no air - as a result of that blood supply to those alveoli goes down therefore that goes down, got the answer? Great, very simple okay, yeah. Okay so we know this slide. And what is the message we want to get here? Yeah you are right, Bohr effect, what is it? Everybody - what is Bohr? Then put some life in your life okay, so what do you want? Bohr effect okay, why Bohr effect is important? Why Bohr effect is important? Because okay - what is Bohr effect? Okay - let us go one step backward, what is Bohr effect? Bohr effect - tell me that carbon dioxide can influence the affinity of hemoglobin to oxygen okay. Let us say you are in an RBC okay good - what about that - your RBCs are flowing along with the blood, where are you coming from? You are coming from lungs, go to the heart, go to the left ventricle, go to the tissue okay. You are rich in oxygen, oxygenated, partial pressure is about 95 mm Hg. You are okay? And then you go to the tissue and as you go to the capillary and outside partial pressure of oxygen is much less okay, so you start not only giving out your oxygen but you also start absorbing carbon dioxide yes or no? Now when that carbon dioxide gets into the RBC, it gets into the plasma, it gets into the RBC, what happens to that carbon dioxide? I will tell you two, three slides down but one of the things definitely happens is that CO2 plus H2O, carbonic anhydrase, carbonic acid, H+ ions, bicarbonate ions okay. Those H+ ions - they combine with hemoglobin okay. Hemoglobin is a very large molecule, it acts as a buffer in many places it can combine with this H+ at many places it can combine, okay. And when that is happening, the hemoglobin molecule already had lot of oxygen that it was carrying okay. Now its affinity for oxygen gets less - which means it will more readily give away the oxygen, are you with me? So this hemoglobin molecule has many tricks, wonderful tricks, and those tricks are with reference to manipulating its oxygen affinity depending on the need of the tissue – this means what? If you are flowing through the lungs and suddenly you realize there is lot of oxygen around, then what would you do? You are in RBC, you are going through the lung and you are right in the alveoli and you suddenly realize that there is plenty of oxygen okay, plenty of oxygen. As soon as you are there in the alveoli because of the partial pressure you start losing your carbon dioxide from the RBC into the lumen of the alveoli okay, means what? The carbon dioxide that you had picked up in the tissue you are losing now, the moment that happens - hemoglobin goes through another stage, now its affinity for oxygen goes up. Look at this - I mean it is not science, it is much more than science, look at the beauty of the molecule, the moment it is in the tissue pick up carbon dioxide okay, reduce affinity for oxygen give away, you go back to the lungs opposite happens, give out carbon dioxide, increase your affinity, pick up as much oxygen as possible and take it to the tissues. It is not a dead molecule okay, whatever comes I will give, whatever does not come no, no, no. It is a wonderful trick. Now this is just one of the tricks, the molecule has amazing number of more tricks. Okay. So what you really need to start loving this molecule called hemoglobin okay because it is like a magic. Just like a magic okay and another few slides I will introduce you to some of these tricks which this molecule can do and of course this we have done last time, what is it? Okay so carbon dioxide, we are in the tissue, the carbon dioxide - as a result of H+ ions, as a result of acidity - see we are still talking of Bohr effect, as a result of that - so if this curve, the middle curve what is it, you know very well, oxygen dissociation curve okay. If you have forgotten about oxygen dissociation curve, your blank faces tell me that I am right okay. We are talking about it, what are we talking about it - when the partial pressure of oxygen is 100 which means you are in the lungs okay. When you are here 100 ml of blood is carrying how many ml of oxygen? 20. Very good, you have not forgotten, I am so happy, 20 and when that is the scenario, what is your level of saturation? 100 percent.

100 percent, good. When you are flowing from the lungs okay, when you are flowing and then you go to the tissues and when you are in the tissue, you are giving away the oxygen. As a result of that you are here. As a result of that you give much, you give how much of oxygen? 5. 5, very good, okay. And the partial pressure will fall to about 40, partial pressure will fall to about 40, are you with me? And we have seen - by the tissue - 40, go back to the lung - 100, go to that, see what you got, we have done it 100 times okay. But supposing there is too much carbon dioxide for some reason - you have done too much exercise, okay. The tissues are generating lot of CO_2, as a result of that the pH is shifting from 7.4 pH. As a result of excess of exercise, excess of carbon dioxide, the pH has dropped to how much? 7.2.

As a result of that the oxygen dissociation curve which was here now has moved, moved means what? At the partial pressure 40, it has so much percentage but had it been, when it was 7.4 it was so much, are you getting the difference, we are looking at the curve, just go vertically from here okay and what is the difference between this point and these two points? Just go there and you will see how much of oxygen, how much of saturation is there? You can translate into ml of oxygen okay, means the more the acidic, the lower the pH okay, its affinity for oxygen will go down. I will tell you an amazing experiment, not experiment, it was, it really happened, I will paint the scenario for you and leave it to your common sense to unfold the rationale behind it. There was this guy who was skiing somewhere in the Alps or somewhere and there was an accident and he was covered with snow, by the time they recovered him, his body was of course you can imagine - very cold, I do not know whether temperature was 15 but the fellow did not die and the heart was still beating. Are you okay so far? So they immediately rushed him to the hospital and what the doctor did was, he withdrew the blood okay, withdrew the blood, maybe 250 ml, 500 ml whatever is possible. What was the temperature of the blood, it was say, I do not know but 20, 22 degrees Celsius, are you okay, the whole body was cold and he should have died by now but he did not die. They took the blood outside, they warmed the blood to 37 degrees and they put it back - and the fellow survived. Can somebody give me the rationale. The moment he went there, see look at this temperature, look at this slide okay, as the temperature goes up, what happens, the curve moves to the right, means his affinity goes down okay, so when his body was presumably at 20, the curve was here, so what was his hemoglobin, it had lot of affinity, lot of affinity means it is not giving away oxygen. So hemoglobin is rich in oxygen but he is not able to part with it because of the temperature. What did the doctors do? Take it out, take it to 37 degrees and put it back. Now this hemoglobin - now because it is at 37 degree, it could easily give rise to, so artificially the doctor moved, doctor moved the dissociation curve from here to here somewhere and the patient survived. Why did I tell you the story, to give you the impact of the, of what, the property of hemoglobin to associate with oxygen is also dependent on temperature.

Now that also makes sense you know - because if you are doing vigorous exercise in a gym, the temperature of your body or the skeletal muscles literally goes up by 1.5 to 2 degree Celsius which is huge, obviously you are doing exercise, the temperature goes up, okay. The dissociation curve moves to the right which means the affinity of hemoglobin for the oxygen has gone down which means more oxygen is available for your muscles to use up. You follow the entire chain of thought, yes or no, great. So this is yet another example. In the normal conditions, when the blood is returning to the veins after passing through the capillary, basically 60 percent of the hemoglobin molecules are still bound to the oxygen and they never release that oxygen. Oh yeah, yeah, yeah, lot of, lot of, I mean never some molecules may, some molecules may, yeah you are right okay. Yet another, what are we doing? We are still looking at the hemoglobin molecule okay, very old molecule, literally very old molecule.

Now we know that this molecule shows the phenomenon of cooperativity. Now as students of enzymology, have you read about cooperativity? Okay, good. That simplifies my job. So this molecule also shows cooperativity, means what? Means, so let us imagine a molecule of hemoglobin, it has, let us presume that it has completely lost all the four molecules of oxygen, completely deoxygenated. Now you can always ask a question, no, no - this is 75 percent should always be there. I will tell you, well there is another guy who has all the four, one this guy does not have, okay.

So, he does not have, it is completely deoxygenated, there are no oxygen molecule on that. And where is it? It has now arrived in the lungs. Okay, now the first molecule of oxygen combines, there are four, alpha, alpha, beta, beta, hello. I am talking about four subunits of what - hemoglobin, two alpha two, it is a tetramer, four proteins coming together, each protein is about 141 or 45 something amino acids, residues. So, one guy combines with O2. When it does this, this 1, 2, 3, 4, alpha 1, I am talking alpha 1, okay, it has combined with oxygen, the whole molecule undergoes a structural change. When it undergoes a structural change, one, it influences, it actually physically changes the structure of the other.

When it changes the structure of the other, the other guy, the other guy's affinity for oxygen goes up. And then the third and then the fourth. And the fourth has, I want you to read this line, what does it say, loudly? The affinity of what? For fourth oxygen molecule, now you know what I mean by fourth oxygen molecule, what is it? Is approximately 300 times that of the first. Look at the affinity, look at the way the hemoglobin - the affinity is combined, it is four times more. I am sorry, I made a mistake, the fourth one, how many times more affinity? 300, huge amount, is it not an amazing molecule? So how it will, how rapidly it, nice animation.

Can you see the four units there, four proteins there? Okay, at the centre somewhere there is a porphyrin ring, at the centre - which is not shown here. At the centre of the porphyrin ring there is iron, that iron is the red one, can you see here? The author has shown only red one here. Are you okay so far? That iron is there, at the centre of the porphyrin ring, there is porphyrin ring here, centre iron is there. Are you with me? And then this alpha protein is there, I am talking about this one protein, alpha one protein. Now at some position, I do not know the exact, I do not know, it is there in literature, there is a molecule histidine. And that histidine molecule hooks on to this iron.

This porphyrin ring in one plane, okay and then there is that, that those, that helices that you see, in that helices one of them is histidine, that histidine molecule has a, has a pentameric ring there. This histidine molecule, okay, this histidine molecule is, is combining, on one hand it is connected to the iron, are you with me? And on another hand it is a part of the, it is part of the alpha helix, which is a part of the alpha one part of the hemoglobin of the whole molecule. Are you okay so far? The moment it combines with oxygen, who combines with oxygen? This iron combines with oxygen, okay. It is oxygenation or oxidation? Oxygenation. As a, as a, as a result of that, this histidine pulls the iron.

As a result of that, the entire molecule undergoes a change something like this. When that undergoes a change, that undergoes a change, that undergoes a change, that undergoes a change and as a result of that, the affinity goes on increasing the lastness far, far more affinity. Are you with me? Details are amazing, they are there in the literature, people have extensively worked on it as to how exactly it happens. You can, you can read more about this. But this is a phenomena of cooperativity and this was extensively studied by this scientist called Hill.

Hill and then he used lot of mathematics to model this and he said that okay, if there is no cooperativity, what do I mean by no cooperativity means oxygen combines in the one, it does not influence the second, combines with the second, does not influence the third, does not, no cooperativity, Hillís coefficient is called as 1. And then, and then it, the first one combines has some impact, some impact, some, so the Hillís coefficient is 2, 3, 4, 5, 6. So, he has taken it to when it is very high, he calls it as 6 by his mathematical calculations and he says that the, the Hillís coefficient for oxygen binding of hemoglobin is about how much? 2.

2 to 2.3. Now, now studying his coefficient is a very specialized area in physical chemistry about which I do not know. But if you are interested, you can read more about it. But this is just to introduce you to the concept of how to quantify the, he has, he has been able to quantify the affinity of hemoglobin molecule towards oxygen, first one compared to second, second to third and third to fourth. Now, let us see as to, okay, we are here, where are we in the tissue? Okay. We will try to find out as to how, again we are there to understand the Bohr effect.

For that let us, let us look at the RBC and where are we in the tissue? Are you okay? So, where, what am I, where am I, I am in the, I am in the capillary here, there is interstitial fluid and there is a tissue and that tissue is continuously generating what? Carbon dioxide. Okay and which way the carbon dioxide is flowing you can see that. Okay. Now, let us look at the, let us go from the top.

Okay. So, there is carbon dioxide, there is some, the carbon dioxide comes from the cell, it goes in the interstitial fluid and from the interstitial fluid it gets into the cell. Carbon dioxide and oxygen both are lipophilic molecules, they have no problem, they can just go where they like and who drives them it is the partial pressure. Okay. So, because the partial pressure of carbon dioxide is high here, it is going into the blood and plasma and some of them is some of the carbon dioxide remains dissolved in plasma, some.

Okay. So, far it is carbon dioxide, plasma is water, it is going to oxygen, carbon dioxide is going soluble in water, it is just going to dissolve some of it. The second is some also happens is carbon dioxide, carbon dioxide plus water gives rise to what acid it is, H_2CO_3 is what? Carbon dioxide. Okay. But author has written they are slow, why slow because in the blood there is no carbonic anhydrase. Now, these are the things you have to remember.

In the, I made a mistake in the plasma, in the plasma, in the plasma there is no carbonic anhydrase. Therefore, it is slow and therefore, you will get all this HCO_3 and H^+ ions but it is a very slow reaction. Exactly opposite to that the RBCs are abundant, have an abundant supply of carbonic anhydrase. Remember, these things you have to remember.

So, RBC in addition to a protein called as hemoglobin is extremely high in the concentration of carbonic anhydrase and as a result of that, the CO_2 that enters into the RBC combines with water carbonic anhydrase H_2CO_3 bicarbonate plus H^+ ions. Okay. Some of the H^+ ions they combine with hemoglobin to give, it is hemoglobin the molecule that is bound to large number of H^+ ions. Are you okay so far? Are we okay so far? Okay or no? Are you fine there? Okay.

Now, now let us see. Some of the carbon dioxide enters, enters. Some of the carbon dioxide directly combines with hemoglobin. Carbon dioxide has different roots.So does hemoglobin have affinity for carbon dioxide? Yes, it does.

It does. Can it combine? It does. And as a result of that you have a compound which is called as carbaminohemoglobin. So, where is, where are you getting the formation of carbaminohemoglobin? This carbon dioxide will come into the RBC. In the RBC the hemoglobin will combine with hemoglobin and called a carbaminohemoglobin.

Are you okay so far? Okay. Now, but hemoglobin is already there. It is already oxygenated. It is coming from the lungs. Okay. That will give rise to oxygen and this oxygen will be, look at the thickness of the arrow.

Abundance of oxygen will be released by the hemoglobin of the RBC. It is getting out of the RBC, getting out of the capillaries and it is being supplied to the cell. Look at the, appreciate the thickness of the arrow. And there is a small concentration of oxygen that is dissolved, very small, about 2, 3 percent that can also go depending on the partial pressure from the plasma into the cells. Are we okay so far? You have to remember this one.

Now, listen to this. Carbon dioxide is being transported by the blood from the tissues back to the heart and then to the lungs in three different forms. How many different forms? Three different forms. And the three different forms are given here. Number one, carbon dioxide is being carried as carbon dioxide.

Look at the top. Look at the top there. Carbon dioxide being carried as carbon dioxide. And this is of the total amount of carbon dioxide being carried. How much this contributes to? 7 percent.

7 percent. You are good. Then some of it goes as carbaminohemoglobin, carbaminohemoglobin where CO_2 is combining with hemoglobin and that contributes about how much? 7 percent. And a huge amount, huge amount goes as bicarbonate. So how is carbon dioxide being carried? Major, 70 percent is being carried from the tissue to the lungs in the form of what? Bicarbonate. And it contributes to how much? 70 percent. 70 percent of oxygen is being carried in the form of, now you need to remember these three forms.

Are you done so far? The three ones. So what do you have in the cell? Lot of bicarbonate. Lot of bicarbonate. Bicarbonate has a charge. As a result of that charge can it flow out of the plasma membrane? No.

No, it cannot. So what cell does is, I will tell you the reason, rational afterwards. What the cell does is, cell rapidly exchanges the chloride ion which is negative, bicarbonate ion which is negative, so there is no net charge transfer. And an exchange happens and that exchange is such that the chloride ions go out and the bicarbonate, I am sorry the chloride ions come in and the bicarbonate ions go out. We are looking at an RBC.

Bicarbonate is generated. Why is the bicarbonate generated in the RBC? Because CO_2 came. Hello? CO_2 came. CO_2 water carbonic anhydrase and bicarbonate ion is generated. Huge amount of bicarbonate is generated within the RBC. Are you okay so far? Now that bicarbonate ion moves out, that bicarbonate ion is moved out of the cell in exchange for chloride ion one to one.

And because the chloride ion gets in and because the bicarbonate ion gets out, this phenomena is called as chloride shift. What is it called as? It is going to happen where? In the tissue. Why in the tissue? Because there is carbon dioxide. I will go back now again. The tissue will give rise to carbon dioxide, it will enter into the RBC.

Okay, carbonic anhydrase, carbonic acid, bicarbonate. Now we are exchanging. Bicarbonate is going out and chloride is coming in. As a result of the loss of bicarbonate, okay, there is slight shift in the pH of the RBC towards acidity. Hello? As a loss of bicarbonate ion, there is slight shift of the content of the RBC towards acidity. The moment it goes towards acidity, the affinity of hemoglobin for oxygen goes down, oxygen is released.

Yet another trick that the molecule shows with reference to ensuring that when you are in the tissue, you release the oxygen more rapidly or more readily. Are you getting the argument? And this is the, now how does this happen? Answer to that question is, I will not give, I am asking you. Are we talking about the exchange of chloride and bicarbonate for the first time in this class? No, very good. When did we do it? What kind of cell did it? What kind of cell did it? Intercalated cell.

Intercalated cell. Intercalated cell. I just put that to remind you. That is a kidney cell. So it is the same protein, same protein which is there in the kidney, is the same protein in the plasma membrane of the RBC. That was in the plasma membrane, this was doing the function of anion exchange.

So, it is called as anion exchanger. That protein is called as what? That protein is called as anion exchanger and this is how the protein looks like. And author tells us that the, it is also called as, read the first capital word, Band 3 Anion transporter. That is the language biochemistry people have given. I also know the anion exchanger 1 or band 3.

That is the, read the last paragraph please for me somebody. AE1 is an important structural component of the erythrocyte cell membrane. It is in the cell membrane. What does it say? Making up to 25 percent of the cell membrane surface. That is how if you look at the surface of the plasma membrane of the RBC. 25 percent of that is occupied by what? It is a very important player.

And each cell, each red cell contains approximately, look at the number. What does it say? 1 million copies of anion exchanger. So that protein, we will have, we are going to have about 1 million copies of that protein on a single RBC. Which will bring about the exchange, the chloride shift or exchange the bicarbonate to the.