Human Physiology

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Lecture -20

Hemodynamics and Regulation-Part4

Now, we are going to another very interesting chapter. I have talked about it several number of times. Several on several occasions and you will keep on hearing about this from me *ad nauseam* - such an interesting phenomenon. What am I talking about? What am I talking about? What am I talking about? Nitric oxide, nitric oxide, it is a gaseous molecule, nitric oxide. What was the first clinical evidence that there may be something like this? Nitroglycerin, what was it? Nitroglycerin, which you have been using for 100 years – nitroglycerin. Using it for giving instant relief to a patient of angina pectoris - like situation without knowing how it works. Now, we got that knowledge around about 1990, so very recent only 30 years back we started from 1986 onwards, there was intense research and by 1992, the things were pretty clear. So, that is the nitric oxide and nitric oxide is there are different kinds of nitric oxide generating enzymes, there is one neuronal nitric oxide, there is one endothelial nitric oxide, there is one inducible - different forms – we will not worry about it now. It is released by the enzyme which we call as nitric oxide synthesis, it is an enzyme it is a huge molecule.

So, that is a huge molecule, I always put these images because they look so beautiful. Not that I understand much there they look nice just ribbons and cords and ribbons. Do you know much about it? Great. Now, we know what - I will do is - I will take a tube, hello listen to this, I take a tube and I will allow just water to flow through it at a particular rate whatever pressure at a particular rate the water is moving. So, is water simple language is it rubbing on the inner wall of the pipe or the tube yes or no, I mean you do not have to think as if it is a very profound question. It is a very simple question. Is water rubbing on the inner wall? Rubbing on the inner wall.

Now, what I will do is I will just hold the tube from outside and press it slightly. So, will the rub be more or less? More. Rub will be more. Now, I will not use the word rub, I will use the word shear stress - shear stress sounds good you know, shear stress what is it? Shear stress. Now, that is why biology - I mean how biology never ceases to amaze you at every stage you study biology you wonder how is it happening? Because the endothelial cells, which are lining a blood vessel, whether you are in heart or in capillary they are all endothelial cells which have got the privilege of coming in direct contact with the blood are you with me? Those cells have mechanoreceptors and they are sensitive to shear stress.

Hello, so you are in a endothelial cell look outside you see the blood is flowing - that is fine flowing at a normal speed. Wait I suddenly find that the blood is flowing at a higher rate and it is rubbing on me with a little more I know it are you with me? Because I have mechanoreceptors those mechanoreceptors as long as the blood was flowing at a particular rate I was fine, but the moment it started, I started experiencing what stress? Shear stress. Shear stress. So, here the author has drawn a single endothelial cell there are millions and millions across our entire circulatory system and on the apical side, means on the side which is directly coming in contact with the blood - there are mechanoreceptors, which can either sense the increase in the shear stress or there are additional receptors which can also be excited by a range of chemical agents which are travelling through the blood and those agents are written on the top at the right. So, tell me what can you please read for me what are the agents the author is talking about? Bradykinin.

Bradykinin. Substance. Substance beyond even insulin who thought of insulin, but experiments show that they do and there are half a dozen more substances are you with me? Means the blood that is flowing through a tube can talk to the tube and in response the tube can send messages in terms of chemicals. The tube can receive information in form of either shear stress or in terms of these chemicals which are travelling through the blood and what will the endothelium do in turn? Well, if you are in the endothelium answer my question. If you are sitting in the endothelium and if you start travelling radially from the endothelium towards the outer edge of the blood vessel you will have to pass through the smooth muscle layer.

Hello, you will have to pass a message, there you give a message that smooth muscles you relax, you relax so that the blood vessel relaxes so that the blood can flow with an earlier speed so that the shear stress is reduced and it has attained original value. Are you with me? Now that agent which is released by the endothelium is called as nitric oxide, one of the most important relaxing, vaso- relaxing agent. Now let us see how it works. Did you understand the frame that I have been trying to communicate to you so far? So, we are now look at the image at the top. The author has shown the inner tube, the inner tube is the endothelial cell and there is a lumen and through the lumen the blood is flowing and there is outer tube, the outer tube has the smooth muscles.

Now the blood is flowing and may be because there is an increase in the shear stress or may be because some of those agents or there are more agents there I want you to read. So, earlier earlier list gave us some compounds and this gives us more compounds. They have been demonstrated to show an effect. So, what effect - when these compounds either come to the endothelial cells or when endothelial cells experience more shear stress in the endothelial cells the nitric oxide synthesis is activated and I want you to remember this it converts what is written here please.

Arginine. It converts arginine into what please. Arginine. And what please. Nitric oxide. Nitric oxide.

So, what is the source for nitric oxide. Arginine. Arginine within the endothelial cells will be converted into citrulline in the presence of nitric oxide synthesis. And now, so where is this action happening? It is happening in the endothelial cells. But now comes the beauty of nitric oxide it is a gaseous molecule it can dissolve and there is nothing to stop it.

No plasma membrane, no polar, no hydrophobic, no hydrophilic, nothing it can just go, nitric oxide can just go, go from where endothelial cells into the smooth muscles. In the smooth muscle it combines with it combines with another molecule which is called as guanylyl cyclase. What does it do? So, what is guanylyl cyclase? It is an enzyme. Where is it sitting - in the smooth muscles. We are in the smooth muscles now. Are you with me? In the smooth muscles you will have guanylyl cyclase.

The guanylyl cyclase has a site where nitric oxide can combine. So, nitric oxide now has become a ligand. Are you ok so far? So, there is a very normal term not in strict sense, but approximately you can say that guanylyl cyclase is a receptor for nitric oxide. People freely use that phrase that guanylyl cyclase, what did I say? Guanylyl cyclase serves as a receptor for and then if it does then it acts on cyclic GMP. This acts on GTP is converted into cyclic GMP and cyclic GMP is converted into what acted upon by protein kinase A.

And finally, finally what is not given here is that cascade of bichemical events, cascade of events which is triggered by nitric oxide. It finally, leads to reduction of calcium ion concentration in the smooth muscle and once the calcium ion concentration goes down, the muscle has no alternative but to relax. Is it very clear? I am sure you have all heard of an agent called as Vigra which is used by male for certain penile erection dysfunction or impotency - Vigra. What is the name? Vigra. How does it work? How does it work? Now here the author tells us about the pharmacology of Vigra.

What Vigra does? Vigra is a commercial name. I want you to remember the scientific name. What is the scientific name? Sildenafil. Say that again. Sildenafil acts by inhibiting cyclic GMP specific phosphodiesterase type such and such an enzyme that promotes degradation of cyclic GMP.

So, this enzyme is no more there. So, the degrading effect is not there. So, then the effect of nitric oxide continues for a longer time. Are you with me? So, this is an interesting way by which you not only about the about how the nitric oxide comes, but yeah. Sir, can the nitric oxide also diffuse it? It can go everywhere.

Nitric oxide can go anywhere, but unless it finds guanylyl cyclase it cannot do anything. It has to have a receptor and it is destroyed rapidly. Vigra works in whole body or? At higher concentrations, it will work also on heart. It is selectively known to act on certain tissues. Therefore, it is it has been approved for clinical use.

It is a Pfizer product. Just this for general interest - Nobel prize what year 1992. What am I doing right now? I have selected some very interesting cases from our physiology which play

an interesting role in regulating the blood pressure. Are you with me? And we started by using, by studying, about adenosine and like molecules then we went to nitric oxide. And now we are going to a slightly higher level. Now, what do you mean by higher level? What we did we have what we have done so far more or less local you know.

A cell will give rise to adenosine. Adenosine will act on an arterial smooth muscle which is 1 mm away, 2 mm away that is all. The adenosine is not going to last. There are enough there are enough enzymes in the extracellular fluid which will chew away or break away adenosine.

These are also called as tissue hormones. They have a very short bio half-life and they are readily destroyed. Now, we are going to higher level. Let us see what you will understand what I mean by higher level very shortly. So, you know what this is? What is this? The nephron.

In the nephron you can see the, what can what can you see? The blood vessels. What can you see? The blood vessels right. Supposing for x y z reason there is fall in blood pressure. And we instantly know that one organ that does not like it at all.

No organ likes it. But one organ that does not like it at all is what? Kidney. Kidney. Because kidney says no below 50 mm Hg I cannot work. So, 50 mm Hg pressure has to be there. So, we are trying to see what is the role of kidney.

We have also seen how kidney - a Bowman's capsule regulates its own blood pressure. And if there are 50000 Bowman's capsules, each one is doing its own business. Now, we will see how the blood pressure is regulated at a higher level at the level of entire physiology. And that happens in a very interesting way.

Follow the story. We are talking about the Bowman's capsule. And why this is important? This unit this is a nephron and this where this the ultra-filtration is going to happen. And better we better have 50 mm Hg pressure of the blood more than that. Now, if this blood is going this way therefore, I will call it an afferent arteriole.

Bowman's capsule. Glomerulus actually, glomerulus and the blood will flow out into the efferent vessel. Now, for some reason the blood pressure has fallen. Some reason. Well, you have donated blood, blood pressure has fallen. Of course, there are many compensatory ways but let us focus on this.

The kidney will immediately know it because surrounding on the just as the afferent arteriole is about to enter into the Bowman's capsule, the tube as it just is about to enter. There is a layer of cells. There is a layer of cells and it is called as juxtaglomerular cells. Juxta means nearby.

It is near the glomerulus. Therefore, what is the name? Juxtaglomerular cells. And these juxtaglomerular cells have again mechanoreceptors. So, if there is a fall in blood pressure the mechanoreceptors get excited and the juxtaglomerular cells or complex also gets excited and it starts releasing and it starts releasing a protein. Some people like to call them as hormones, some people do not like to call them as hormones, that is okay.

But everybody calls it as renin. What do you call it as? Renin. Renin coming from renal and it is a protein. Renin. Are you getting the language? Renin.

It is a large protein molecule. Again another of my fascination for the structure of protein. This is a renin molecule. Where does it go? It goes in the blood. Where does it go? In the blood. In the blood it acts on a protein which is called as angiotensinogen.

Now it becomes more interesting. It acts on what? Angiotensinogen. So, you have the fall in the blood pressure. Renal perfusion pressure. Perfusion pressure will determine the rate at which the ultra-filtration is happening. So, when it happens and the pressure goes downward - then in response to that the juxtaglomerular cells are releasing the protein named as renin.

Where will the renin go? In the blood. In the blood. It goes in the blood. In the blood it contains, it encounters a molecule, a large protein molecule called as angiotensinogen. Say that again. Again it is a large protein molecule that is coming from liver.

Where does it come from? It comes from liver. And then under the influence of angiotensinogen, under the influence of renin, angiotensin is a big molecule. From one end it cuts away a small molecule which is 10 amino acid long and that small molecule is called as angiotensin-I. So, angiotensin-1 is coming from angiotensinogen. Why it is coming? Because it is acted upon by renin.

Now this angiotensin-I, it is in the blood. Everything is happening. All these actions are happening in the blood. It flows with the blood, flows with the blood, flows with the blood and as it flows through the lungs, as it flows through the lungs, okay, the blood vessels in the lungs are equipped with yet another enzyme which is called as angiotensin-converting enzyme. What do you call it as? Angiotensin-converting enzyme.

A-C-E say that again. A stands for what? Angiotensin. C stands for what? Converting. E stands for what? Enzyme. It will be abbreviated as what? ACE. okay.

Now under the influence of ACE angiotensin-I which is made up of very small molecule of 10 amino acids. How many amino acids? 10 amino acids. And angiotensin-I is relatively an inactive molecule, does not do much. But when it is acted upon by ACE, it cuts away 2 amino acids and how many amino acids remain? 8.

I will call that as angiotensin-II. What do I call it as? Angiotensin-II. Angiotensin-II is one of the most, most, most powerful vasoconstricting substance we are aware of. Means what? It

will act on the smooth muscles of the blood vessels and bring out vasoconstriction. Extremely - one of the most powerful substance is angiotensin-II, okay.

Now before I close I just want to leave you with a thought. ACE inhibitors, look at the language, ACE inhibitors are very widely used for conditions like hypertension. Makes sense? Makes sense? ACE inhibitors, what are they called as? Say that again. Say that again. So if you tomorrow meet a person who is suffering from high blood pressure, okay, then you are supposed to ask him 4 questions. Which one are, which one of this are you taking? Okay, now you answer, what are the 4 chemicals I am talking about? Calcium antagonist, beta-blocker, nitroglycerin and ACE inhibitors.

And actually what the doctors do is they try this, now it does not work, let me try that. This is all, this is all what they keep on doing, shuffling between these 4 extremely important tools for the treatment of hypertension, okay.