Human Physiology
Prof. Nishikant Subedar
IISER-Pune

Lecture – 21
Hemodynamics & Regulation - Part 5

So, what are we, what are we talking about? We are talking about fall in blood pressure, an example fall in blood pressure, ok. It is sensed by the mechanoreceptors which are located in the afferent arteriole as it enters the Bowman's capsule, ok. And since there is fall in blood pressure, ok, the change in the, the change is perceived by the mechanotransduction, ok. And that is passed, that information is passed on to a type of cells which we called as what? Juxtaglomerular cells, near the glomerular, juxtaglomerular cells and the juxtaglomerular cells in turn respond how? By releasing a, releasing a, releasing a substance, substance as if it is something great. What is the name of the substance? Renin. So, if I call, if I call kidney as an endocrine gland, ok, then fill in the blank, the hormone secreted may also be called as? Renin.

As? Renin. Renin. As what? Renin. Renin, ok.

So, renin may also be, not that everybody does, but it is ok. Can be considered as what? Endocrine. Endocrine, a hormone, ok. Good. And that renin acts on a substrate and that substrate is called as what? Angiotensinogen. Angiotensinogen which is a very large protein molecule which is there in the blood secreted by what organ? Liver.

Secreted by what organ? Liver, secreted by what? Liver. Liver, what is the action of when the renin acts on the substrate angiotensinogen, it cleaves a tiny fragment of small peptide which is about 10 amino acids long and that one, that tiny fragment is called as what? Angiotensin I, One, ok.

And then as it, as it flows along with the blood and passes through the lungs it is acted upon by an enzyme which is called as what? ACE. Tell the, tell the full form? Angiotensin converting enzyme. Abbreviated as? ACE. This is. Good. And under the influence of that enzyme angiotensin I is converted into? Angiotensin II.

How many amino acids? Eight amino acids. Eight amino acids and why are we so much worried about angiotensin two? It is a one of the most powerful vasoconstrictors encountered in biology therefore we need to focus on small molecule and we will visit this molecule again and again and again and again. So here are the two structures you can see angiotensin I, angiotensin II and there you can see the capillary bed work at arterioles. You can see the smooth muscles there, you can see the smooth muscles there and on the smooth muscles will they have receptor for angiotensin II? Yeah, they will. And when they are activated, those smooth muscles will undergo constriction and thereby increase the increase the blood pressure. Just an example.

Alter the pressure in mm. What have we done? Well you have withdrawn. Not a great experiment. There is an accident and there is hemorrhage. There is hemorrhage and as a result of loss of blood there is a fall in blood pressure and from 100 which is mean, 100 approximately we are taking mean of what? Whatever is 80, 120 whatever we have calculated it is about 100 and as a result of loss of huge volume of blood the blood pressure has fallen where in this particular case the mean blood pressure is 50 which is not a great idea, it is a bad idea from the point of view of what organ it is a bad idea? It is a bad idea.

It is a bad idea. Okay. And then if you if, you as a result of fall of blood pressure - it will set of a chain of reactions which will again begin at the level of juxtaglomerular cells. Hello? And then renin and then angiotensin I and then angiotensin II and then it goes everywhere and acts on the smooth muscles, okay and the entire blood vascular system shows the profound constriction and as a result of that the blood pressure may be taken from 50 to 80 or something I mean, okay. So this one slide tells us the profound impact of angiotensin II - how the organ kidney, okay which is very interested in making sure that I get the blood supply at a proper pressure and when I note that I am not getting enough proper pressure I take the necessary steps. What is the step? Release renin.

Do you get it? Do you get it? So what is the entire mechanism targeted as? Kidney wants to make sure that I must always get blood pressure which is which is 80, 90 whatever ideally 100, okay but for that - so you got the message. So yeah. Do all blood vessels not have the receptors? No, no, no. All of them do not have but majority of the venous system smooth muscles there they have. It is not uniform distribution, it is uneven but for that you will have to go into details and but it is not even, it is not even.

I can talk about it later but not at this stage. But your question is absolutely bona fide, it is different, okay. We were just reading about ACE for a very long time, okay then ACE suddenly became very popular and very important, okay since COVID came, okay because it was realized that - where is ACE sitting? ACE is sitting in the lungs, okay in the blood vessels of the of the lungs, okay. It was realized that COVID virus, okay enters our body through the ACE enzyme, okay. So although we have been calling ACE as ACE, okay enzyme for a very long time, since 2020, people have started calling it as a receptor for COVID virus.

Molecule is the same, what is the molecule ACE? We consider it as what? Enzyme, of course it is an enzyme, okay. But we have also started looking at the same molecule as what? Receptor, receptor for what? COVID, yeah. So just read this interesting paper which came into prominence, okay, okay. And then of course we discussed about this also, we need to briefly talk about captopril, okay. It is a drug, where is it? It is available in the market and people take it for the treatment of what? Hypertension and related conditions, okay and so -

this is our fourth strategy for addressing the issues with reference to and this is just one of the, this is what? ACE inhibitor, what is this? This is this is ACE inhibitor, okay. A typical treatment plan for hypertension will often include what and what and what? ACE inhibitor and calcium antagonist.

Good, so what am I doing? I am slowly going from, if you see what we did yesterday and what we are doing today. We first looked at those molecules which are released by the cell and which act in the vicinity or in the neighborhood, okay. And then we started talking of the molecules which act a little remote, comes from renin, acts on angiotensinogen which is somewhere and now we are talking of yet another very interesting hormone, a hormone which has a profound influence on vasoconstriction and this particular hormone comes from the hypothalamus. So what am I looking at? This is the human pituitary gland, what is it? Human pituitary gland, so from this point onwards, hello, from this point onwards, if you go couple of inches inside you are going to this, get that organ which we call as pituitary I am sure you have heard of, about half a gram in weight, very tiny, very interesting range of hormones, okay. Now this pituitary gland has two parts, anterior part and posterior part. I am not here to talk about the endocrine importance of the pituitary gland about which I will talk in due course of time. Right now our purpose is to focus on just one hormone and that hormone I am sure you have heard of is called as vasopressin, say that again, say that again, vasopressin, okay it is a nonapeptide, it is a peptide hormone made of 9 amino acids and interestingly it is secreted, it is secreted by the posterior pituitary gland but not synthesized there, not, NOT, not synthesized.

Where is it synthesized? It is synthesized in certain neurons and those neurons, so here I have the pituitary gland and this is the part of the brain and that part of the brain is called as hypothalamus. What do I call it as? Because it is the lower part of the thalamus, so hypothalamus located below thalamus, hypothalamus and in the author has shown two neurons, in reality there are hundreds of neurons and those neurons have the necessary machinery mRNA and endoplasmic reticulum and Golgi complex and they synthesize this peptide hormone which is a large molecule then cleaved and finally you have arginine vasopressin which is a peptide hormone consisting of 9 amino acids that molecule is trafficked along with the axons, can you trace the axon from the hypothalamus into the posterior pituitary gland please, can you trace that axon? Great, and so the vasopressin hormone travels along with the axon, axonal transports mediated by cytoskeletal system and then it comes into the posterior pituitary gland and in the posterior pituitary gland it directly communicates with the capillary, can you see the capillary there? And if that neuron in the hypothalamus is excited and that neuron starts firing action potential then the action potential will go from the cell body all the way along the axon and finally when the action potential arrives here then it will release by exocytosis vasopressin and where will the vasopressin go from there? It will go there from there it will get into the? Capillaries. Get into what? Capillaries. Capillaries, so here we have a product which is synthesized by a neuron which gets into the blood therefore I am going to call that molecule as a neurohormone, what will I call it as? Neurohormone.

Why neurohormone? Because it is coming from a neuron, why hormone? Because it is going in a blood and so we have the neurohormone that is now being poured into the therefore I can also call the posterior pituitary as, let us see if you make sense of this neurohemal organ, hello, what did I say? Neurohemal organ. Hemal refers to blood, neurohemal organ, so the hormone goes from the neuron into the blood and from there from the blood it will go everywhere. Now why would this happen? This would happen because vasopressin is released in our system under two circumstances, one, when there is sudden loss of blood, you will get lot of vasopressin and secondly if you are dehydrated, dehydrated, you are moving out, sun, you sweat and do not get water to drink, when that happens for some time, two things happen, your throat gets dry that initiates behavior and you start looking for water, if you get water you will ingest water, that will happen and simultaneously your physiological response is that those cells in the hypothalamus will start releasing arginine vasopressin will release into the blood and it will get into the blood, it will act on the kidney and it will trigger a very interesting function of reabsorption of as much of water as possible from the urine, so that the urine becomes more concentrated and you are conserving water in your blood, I will talk more about it when we talk about the excretory system. But I am going to talk of yet another very important function of the vasopressin molecule, it is also known as vasopressin, it is also known by another name, can somebody help me out? ADH. ADH, anti-diuretic hormone is same, so when it acts on the kidney I will call it as anti-diuretic hormone and when it acts on the, so arginine vasopressin, you can ask why, why arginine, why arginine? Arginine because that, look at the structure in vasopressin there, can you see that there, can somebody tell me how many amino acids are there? 9.

9, it is a nonapeptide, can you look at the 8th peptide what is the 8th peptide? Arginine. But you will say there are so many peptides, so many amino acids why am I worried about arginine, why do I call it as arginine vasopressin, interesting question. So the question is, in all mammals, all mammals it is arginine vasopressin, but in pig that arginine is replaced by lysine, therefore in the pig this particular molecule you will be called as what? Lysine vasopressin.

Lysine vasopressin. Vasopressin, but in humans and all the mammals it is what called as what, therefore that word arginine has stuck there for good, so therefore we call it as arginine vasopressin, okay. So that arginine vasopressin when it comes from the pituitary, it will act on the smooth muscles of what blood vessels, of what of some of the major veins and also some of the major arteries, what will it do? Vasopressin. Vasopressin, vaso- is blood vessel, pressin is press them, increase the constriction and now to go into some few details, a few details this is, this is a peptide hormone, it also takes a signal to the target cell by way of 7 transmembrane G protein coupled system - are you with me? Okay so what do I do? I just go to the smooth muscle of the blood vessel, okay, Tunica media, hello Tunica media, have you forgotten already? Okay, externa media, interna, okay, interna is same as endothelia layer. So I take a smooth muscle cell from there, look at the plasma membrane and in the plasma membrane I am going to find many receptors but I am also going to find a receptor for what? Arginine vasopressin and that receptor I will call as what type? Look there tell me, what is written there? V1 receptor, where will I find it? V1 receptor, now I go to the kidney, in the kidney I go to the nephron, in the nephron I go to the collecting tubule, if you remember, fine. otherwise I will tell you, you go to collecting tubule, I will take a cell from there, from the cell I will take a plasma membrane and there also I will get a G protein coupled system where arginine and vasopressin can bind but I find that this receptor is different from that receptor and I am going to call this receptor as what? V2. V2, okay, so the action of arginine vasopressin on these two organs is via two different receptors and therefore we call them as V for vasopressin, V1 and V2 receptors, very interesting.

This is just to impress on your mind the profound importance of vasopressin in influencing the blood pressure. So let us see, there is loss of blood, hemorrhage refers to what? Loss of blood, okay, and we are trying to standardize hemorrhage per ml per kg, how many ml, so 5, 10, 15, 20, there is more, more hemorrhage, okay and as a result of that, the pressure, whatever it was in the beginning, I will call as 0, that may be if it is human it will be about 100, I will not call 100 as 100, I am calling 100 as what? 0. 0 and I find that as there is a loss of blood, it will result in the what? What? Loss of what? Loss of pressure, I can see the loss of pressure from 0 it has gone to almost minus 20, 40, 60 and then I can correlate it with what? Vasopressin release, okay so there is a clear correlation as pressure goes on falling, vasopressin goes on releasing and therefore, what will the vasopressin do? It will release the, okay what will vasopressin do? As a result of the action of the vasopressin on the smooth muscle the total volume available for, the total volume available for your 5 liters blood, hello, you are healthy, okay how much blood do you have? 5 liters, where is it accommodated? It is accommodated in your closed cardiovascular system, okay and as a result of hemorrhage, okay you are losing blood so the blood pressure will fall, okay. As a result of the effect of arginine vasopressin - because now the volume is reduced, the pressure will be maintained, okay so you are still good doing good, okay although you have lost, although you have lost blood because our vascular system has got, the elastic vascular system is okay you are good with 5 liters, I will accommodate 5 liters but if you have dropped down from 5 liters to 4.5 liters I will constrict the entire blood vascular system so that my blood pressure still remains okay.

Yes, I do not know, I do not know you have to read, read it and tell me, I do not know, good question, good answer both equally relevant. Just see this, it is this almost locally acting substance but it is very important, you know if there is a wound, okay if there is a wound, our physiological system must come to our rescue and one of the major problems is loss of blood, okay to stop that loss of blood from, to stop the blood from, okay. What the hormone is released from the endothelium cells therefore the name is called as endothelin, endothelin and it constricts the tiny, tiny blood vessels not the large ones but the tiny, tiny ones, what is the aim? Just to make sure that if the blood vessels constrict, okay you will prevent the loss, okay. So this is yet another substance which is again a peptide and which plays an interesting role in, okay. Now we will go to the, we have already done this once, we will do it once again, why? Because at the highest level, we are, you see we are talking of different levels of control, okay we have seen the local level, we have seen the endocrine level, the hormonal level and we are seeing ultimately it is the nervous regulation of the circulation which we have already seen and we know that there is a what? Autonomous nervous system divided into sympathetic and parasympathetic, sympathetic is also called as thoraco-lumbar, what is it? Thoracolumbar, why? Because the neurons are located in the thoracic and lumbar region. The preganglionic neurons - they give rise to preganglionic fibre, preganglionic fibre will talk to the postganglionic neuron, the postganglionic neuron will give rise to fibre and it is the postganglionic neuron which will terminate where? It will terminate in 100 places but right now because I am talking about circulatory system, I am talking about what? I am talking about the end, the terminals of the postganglionic fibre on the heart and on the red ones and, what are those red and blue tubes there? Arteries and veins, okay. And so we have the arteries and veins being supplied by what? By what? By the sympathetic nervous system and we have already seen, seen what? We have already seen that via, by acting via the alpha-1 receptors, okay, in your visceral organs there will be constriction and if you are running somewhere, okay and then via the beta 2 receptors dilate there, so it is managing the traffic of blood from one organ where it is not as much required to the organ where it is required. Now, will the sympathetic postganglionic fibres supply the capillaries? Get the question? Do they supply the capillaries? The answer to that question is no, they do not supply the capillaries, they supply the earlier part of the capillaries and they supply the later part of the capillaries, because capillaries per se do not have smooth muscles, never forget that. Capillaries have no smooth muscles, no and the target is smooth muscles, so what is the point in going to the capillaries? So to emphasize that point, of course the blood is, the oxygenated blood is coming, coming, coming, may arterioles, metarterioles and then it is entering into the capillary, capillary, capillary and then venule.

So in this part you will not have any innervation, nerve supply of the parasympathetic nervous system but before and after. Okay and then depending on the type of receptors then, you will get the response of contraction or dilation or whatever, whatever it is. I put this slide just to have a profound effect of what can norepinephrine do to your vascular system, profound effect. Well very simple you take a dog and inject, inject but before injection make sure that you are monitoring the blood pressure and you inject and you inject and you find little change, not a great change. But you say such a powerful molecule, why am I not getting a great change? You are not getting a great change because the moment you give norepinephrine and you start seeing the effect, the compensatory mechanism start operating, okay and you do not see a great change, okay because physiological systems are continuously monitoring your blood pressure and giving out necessary corrective signals. I want to stop the corrective signals.

What I do is I will inject an anesthetic like substance in the spinal cord, okay. So are the compensatory, what have I done, what I have really done is I have now killed the compensatory processes. So the moment I kill these, so this is the mean blood pressure of about 100, are you with me then? And then the moment I give an anesthetic like substance in the spinal cord, what happens to the blood pressure? It falls, it falls, okay. And then when it has fallen, then I give an injection of norepinephrine. So what I see is an effect of norepinephrine which is not, which is not camouflaged by, which is not hidden by any compensatory mechanism, I see naked effect of norepinephrine and it is profound.

And it remains for another interesting thing, just look at the x axis and tell me how long do you think the effect of norepinephrine is lasting? 5 seconds, 5 seconds, how long? 5 seconds. Because, because there are enough enzymes even in the blood to break down the molecule, therefore one point I want you to remember, remember, is that the biological half-life of norepinephrine is 5, 10, 15 seconds, 15 seconds. What is the biological half-life of insulin? Very good, only one answer, how long? Six minutes and what is the biological half-life of norepinephrine? 5 to 15 seconds, that is all. Which one? This, this, no, no, this is because it is broken down, you give norepinephrine, you give, you get the effect but epinephrine is so rapidly broken down.

Does it fall apart because of the loss in pressure? Oh, no, no, you have everything, the responses, the response, I mean, you see you have given norepinephrine, okay, because you gave norepinephrine to an intact animal, okay. So it should stimulate the entire cardiovascular system and increase the blood pressure. But at the same time then there are compensatory mechanisms, it means it may be because, okay. The information may go to the medulla oblongata, from the medulla oblongata it will, the information may come down via the vagus, it will go preganglionic, postganglionic acetylcholine and it may have negative effect on the heart, okay. There are 10 compensatory mechanisms, all of them put together I do not get a strong effect. So, but because I want to see the effect of norepinephrine per se, therefore I silence the system and I get.

So, the aim is only to, but it, okay, I think I will just move on. We have done this, I am doing it again. I will do it 10 times if it is necessary, it is so fundamental. Some of the preganglionic fibres of the sympathetic nervous system, what did I say? Some preganglionic fibres, okay. So, they terminate on the, they terminate, so where, what do I have here? I have here the spinal cord.

Are you okay so far? Spinal cord. In the spinal cord my cartoon shows a single neuron, okay, so far. I call this as a neuron 1 of the sympathetic ganglion, of the sympathetic nervous system. It gives rise to a fibre, that fibre comes out of the spinal cord, are you okay so far? And it goes and terminates on the second neuron because autonomous nervous system must have two neurons in a series. So, it must go through second neuron. In this particular case, the second neuron happens to be nothing but adrenal medulla, nothing but what? Adrenal medulla.

So, the cells of the adrenal medulla are getting a nerve supply from what? Some preganglionic fibres of the, you are right, you are absolutely correct, preganglionic fibres of the sympathetic nervous system. Are you okay so far? Now fill in the blank, fill in the blank. The neurotransmitter - fill in the blank. What is the nature of this neuron? Very good, say that loudly, excellent, say that again.

Acetylcholinergic neuron you can call, okay. And therefore, if this neuron is acetylcholinergic, then my cells of the medulla here on their plasma membrane, what kind of transmitter receptor are you going to find? Cholinergic receptor. But the moment you use the word cholinergic receptor, my counter question is going to be what type, what subtype? Nicotinic very good, say that again. Nicotinic so on the plasma membrane of the cells of your adrenal medulla, you are going to get what kind of receptor? Nicotinic, means what? Five subunits ionotropic, five subunits ionotropic. So, whenever acetylcholine will combine on it, it will open, it will allow the sodium ions to go through and then these neurons will be stimulated. What neurons? The neurons of the medulla will be stimulated.

Are you okay so far? These neurons of the medulla, they do not have post ganglionic fiber. They have, these are the neurons which are endocrine, okay. These are the neurons of what? They are endocrine neurons and they pour their secretion, they pour their secretion in what? Blood, where is it going? It is an endocrine gland, come on, it is an endocrine gland. So where will its secretion go? In the blood, in the blood. So we are talking of what adrenal? Talking of adrenal medulla.

Adrenal medulla, you see it is interesting because it synthesizes two hormones. It is an endocrine gland, it synthesizes two hormones. One is very familiar norepinephrine or noradrenaline, noradrenaline and the second molecule it also synthesizes is adrenaline. What is it? Adrenaline. So if I ask you a question, tell me what are the sources for noradrenaline in your body, dash and dash, fill in the blanks.

These are the two sources for norepinephrine in your body, dash and dash. What are you going to write there? Adrenal medulla and the other one? Post ganglionic. Post ganglionic, very good, very good. Post ganglionic fibers of the sympathetic nervous system.

Those two sources. But my next question is going to be, tell me what is the source for adrenaline? There is only one, there is only one. What is it? Adrenal medulla. Adrenal medulla. Good, good, good, good, good, good. You know something? You get lot of noradrenaline in your brain also.

In your brain, you get a lot of noradrenaline. There is a very elaborate system of neurons, which is continuously secreting noradrenaline and which is allowing you to focus your brain on a particular topic that you are interested in. If that system sleeps, you will also sleep. Noradrenaline is so special in your brain. That is a separate system, that is in the brain. So we have one independent system which uses noradrenaline as a molecule for communication in the brain, one.

Second is noradrenaline as a molecule in the postganglionic fibres of the sympathetic nervous system where noradrenaline is released on specific targets like heart and blood vessels, two. And number three, noradrenaline is released from the cells of the medulla, which is a hormone, which goes in the blood and acts everywhere. Wherever you will get adrenergic receptors, alpha, alpha 1, 2, 3 type of receptors, there you will get the action of noradrenaline or norepinephrine. You can read about this in this slide.

You can read about that, you can read about that. And okay now we have done this, once we will do it once again. You remember this? Why did this? We are very familiar figure, very familiar figure, we did it in context of what? Context of what? Homeostasis. Homeostasis, excellent. Did it in relation to what? Homeostasis.

Okay, let us focus more on this. So here you have the heart, here you have the aorta, from the aorta you get the branches of the carotids and you know as the carotids go, as the carotids go, you know somewhere in your neck, they swell a little and you call it as carotid sinus. What do you call it as? Carotid sinus. Carotid sinus and your aorta they are being innervated by the fibres, by the sensory fibres, we have done it and we have also done that. They are mechanoreceptors and they take information from aorta over the 10th cranial nerve which is also known as vagus.

Very good, very good. And the information from the carotid body is taken over the 9th cranial nerve which is known as glossopharyngeal and the information is taken to the medial oblongata and that is how the medial oblongata is continuously monitoring the stretch on these vessels and the stretch it is can be translated and provide information about the pressure which is being exerted by the blood at every systole and distole. Good, good. Now what I will do is, I will, I am going to put an electrode on the blood vessel that takes from where? Baroreceptor response membrane potential in millivolts. Baroreceptor, where are baroreceptors we saw in the previous slide, they are in two places either in the carotid sinus or in the aorta. I am going to take one of them and I am going to place my electrode and monitor the voltage differences that are there

Good. And then the second I am going to do is, I am going to monitor the arterial pressure. And then I find that as long as in this particular case, the arterial pressure is between 110/ 170 systolic/ diastolic. Look what am I recording? My electrode is on the, my electrode is on the baroreceptor is on the aorta and there, I am recording from there. I find that I get the action potentials from those baroreceptors which are sensory nerve terminals at a particular frequency which frequency is denoted there. Having explained to that, can somebody tell me what is the correlation, what is the change from the first column to the second column? It is there.

You tell me it is there, what is it? If for any reason the blood pressure goes that much, then what is happening to the frequency? Is increased and opposite? You can see, you can see the frequency has gone down. So, the blood pressure, this is how the blood pressure, the information about blood pressure is being communicated to the medial oblongata. Are you getting? Yes. If here the blood pressure oscillates between something like 50 to low like 40, we get the same as there being lower blood pressure.

It is more sensitive to the higher pressure. More sensitive. Your question is correct. It goes to, it is sensitive to the higher pressure, but you know something. You are normal.

You are in the first column. Then you develop blood pressure. So, the moment you develop, you may go to second column. So, you remain in the second column for a few hours and then you come back to the first column because the receptors are habituated. So, they are sensitive to the change. Okay, but after some time when change ceases then they go back to the original.

Okay, but do not bother about it. I mean since you raised the point, I explained this to you. I mean these are the details when you work out, when you go into as to what happens over a sustained period of time. Thank you. Thank you.