Human Physiology
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Week - 02
Lecture - 03

Hello, again welcome everyone to a brand new class of human physiology. Hopefully, you enjoyed the last class where we have discussed various components about blood and in this class we will discuss about blood coagulation or hemostasis. So, what are overall contents we will cover for this class, let us go into it. So, overall we will see like what is hemostasis, we will discuss like different stages of hemostasis. So, what are different stages? Mostly we have like 5 different stage starting with the first step is vascular spasm, the second step is platelet plug formation, the third step is clotting. which can also kind of run by two process intrinsic pathway and extrinsic pathway and there are like the fifth step fourth step which is like the clot retraction and repair.

So, this is the fourth step and then the last, but final step is like the fibrinolysis. So, we have like 5 stages of hemostasis process and one by one will thoroughly discuss about each of them. So, what is generally like hemostasis means? So, as you all know like our blood like continuously like flows from like one side to another side like delivering the oxygen, blood glucose, all different type of nutrients to all of our cells and tissues. So, the blood needs to be present in like a anti clotting condition because if there is a clot the blood flow will get hampered and we can experience like several other problem including like stroke and other issues.

So, to keep the blood in a non clotting condition what actually contributes that we first have to understand. So, as you can see here this is like a vascular like cell membrane where like the blood endothelial cells are present. These endothelial cells generally produce like few molecules, one of them is like nitric oxide, then another molecule is like the prostacyclin PGI 2. So, PGI 2 and what these molecules does these molecules inactivates the platelet, these are the platelet you can see. So, if these molecules like nitric oxides and PGI 2 they get secreted from the blood endothelial cells they inactivate the platelet and by in keeping them inactivated they prevent the blood clotting.

So, in a general condition when our in our body the blood is like flowing the platelets are in an inactivated situation preventing any type of blood clotting. There are other molecules also for example, in the endothelial cells you can see this is like heparin sulfate type of receptor. This heparin receptor what it does, it activates the antithrombine 3 type of molecule. So, one this, once this antithrombine free type of molecule gets activated, what it can do? It basically prevents the activation or the synthesis of like various clotting factors. These clotting factors are what? These are like various type of proteins.

And where from this proteins are get synthesized they generally are synthesized by our liver and this clotting factors generally participates or has a major role to play in the blood clotting like procedure. But activation of this antithrombine 3 generally like inactivates or destroys this type of blood clotting factor which are like 2, 9 and 10. And while this blood clotting factor gets inactive, the blood clotting procedure stops and the blood keeps in a fluidic condition. And then there are another third way the blood stays like anticoagulant condition in our body. For

example, like in this endothelial cell there is another protein molecule or receptor which is thrombomodulin.

And once the thrombin gets kind of coupled or conjugated with the thrombomodulin what it does like it activates the protein C and by activating the protein C it inactivates this few blood clotting factors which are like blood clotting factor 5 and blood clotting factor 8. So, this is also another way the important blood clotting factors get deactivated or in this inactivate condition they are unable to clot the blood. So, what are these three steps we discussed like the first one we discussed about like various secretion of molecules like nitric oxides and PGI 2, then it can be through the heparin mediated pathway by the activation of antithrombine 3 or it can be also the thrombomodulin pathway. So, by these three processes blood clotting generally is not possible in a normal condition and blood moves in a fluidic condition and delivers oxygen glucose and other nutrients to a body. But what happens if there is an injury? For example, in case of an injury, we need the blood to clot.

Otherwise, we have only a limited supply of blood in the body at a given time. And in case of like a significant blood loss, a person can experience dizziness, the person can experience weakness to the body. And even after some time, a significant blood loss can cause the mortality. So, we need our body system needs to create a significant pathway so that if the blood can get clotted in a rapid time. So, let us see what are the different steps of blood clotting.

So we have as we already said, we have five different steps. This all contributes for blood clotting and repair mechanism. So the first step is vascular spasm. The second step is formation of a platelet plug. Then the third step is formation of blood clot or like anticoagulation or coagulation.

And then the fourth step is clot retraction and repair. And then the fifth step is the fibrinolysis. So, let us see one by one how it works. So, the first step which is the vascular spasm. So, what happens basically when there is any injury there is as we said there would be like causes of like blood leakage or blood loss, but first try to see the structure of the blood vessels or the capillaries.

So, we have this blood endothelial cell lines for example, we have a significant injury that happens and that it causing the blood loss. Just below the endothelial cell, we also have like various sort of like collagen layer, smooth muscle layer, right and then we also have some nerves. So, what is happening whenever there is like a injury and cases of blood loss endothelin type of molecule that gets secreted or released by this endothelial cell. So, this is like a endothelin type of molecule it gets secreted by the endothelial cells near to the injured area. And what this endothelin type of molecule does, it participates in different type of mechanism.

For example, this endothelin molecule can activate the smooth muscle contraction. So, by activating the smooth muscle contraction, it will pull up this two side like injured area and try to kind of do a vasoconstriction. So, once this vasoconstriction is initiated, the blood loss will become restricted. And also this type of molecule like whenever there is a injury or direct injury to the smooth muscle a myogenic mechanism of contraction can also happen. And there is another type of mechanism which is called noicoceptor activation you can see this nerves.

So, whenever there is a injury various like molecules different type of histamines and other molecules get secreted these molecules can activate the noicoceptor. By activating the noicoceptor this again promotes like the muscle contraction. So, overall the goal of this

vascular spasm step is activating the smooth muscle cell contraction and by contraction they will basically pull this two side area and by pulling this two side injured area it will try to create a condition of constriction preventing significant blood loss. So, if you understand vascular spasm step, so we will go to the next step. What is the next step? Next step is a platelet plug formation.

So, first as you know like first it try to kind of reduce the area from where the blood loss kind of happen in the vascular spasm. Now, we still there might be little bit of gap right you can see like still there are like some gaps remain. So, we need to fill this gap right. So, unless we can fill this gap by some glue like or gummy like substance the blood will be continuously kind of leach out. So, let us see how it happens.

So, in the blood whenever there is like cases of injury, there is a one protein which is called von Willebrand factor. So, von Willebrand factor VWF, this generally is present in our blood and whenever there is like blood loss situation, this gets activated and you can see like this gets activated and gets synthesized. So, 2, 1, 11 factor molecule these 2 protein molecule kind of gets close to this injured area and with this 2 VWF molecule what happens the surrounding platelet molecule for example, initially the platelet molecule is kind of circulating right. So, and if there is no injury they are in an inactivate state, but if there is injury then what happens these platelet molecules kind of circulates and come close to this von Wildebrand factor. And as you can see like two von Willeben factor, there is another two platelet that can get simultaneously attached to it.

So, for initially in the first kind of step, two platelet molecule get attached with this von Willeben factor. And once this two platelet molecule attach with the von Willeben factor using like a using like a bond of glycoprotein 1B. Then what happens? This platelet gets activated. So, what I am saying that once the initial few or exactly two platelet molecule that gets kind of bind with this 1, 11 factor, these two platelet molecule gets activated and then they start to secrete different type of molecules. What different type of molecules they secrete? They secrete like ADP, they secrete like thromboxane, they secrete like serotonin.

And what it does? All these ADP, thromboxane, serotonin, they kind of attract like more and more platelet to be aggregated on this surface of the initial two junction of this VWF and the two platelet. So, now all these molecule will activate the other circulating platelet and they will kind of come close to this area and you can see like this rapid plaque formation like one by one layer multiple layer of like rapid plaque formation of the platelet happens. So, by this rapid plaque formation now it prevents like the blood to leach outside of the injured area. So, this is about the second step which is the platelet clot formation and then we will go to the most important state which is the blood coagulation pathway. So, let us see how the blood clotting or the blood coagulation step happens.

So, one thing you have to remember before we can discuss that in the blood clotting pathway there is two different method, one is like the intrinsic pathway and another is the extrinsic pathway. So, in very general layman term what is the difference between the intrinsic and extrinsic pathway. So, as we are saying right like what is the difference between intrinsic and extrinsic pathway. So, in cases of intrinsic pathway if I remove your blood and keep in a glass tube. Due to the glass tube surface charge and surface pattern, the blood can clot after sometime.

But in cases of extrinsic pathway, there is direct injury is required and whenever there is a direct injury to our body, the tissues near to the injured area secrete like a tissue release factor

or tissue release factor 3. And once this tissue release factor secretes, it activates the clotting pathway. So, this is basically a very simple difference between the intrinsic and extrinsic pathway and let us see one by one how it works. So, first we will discuss about the intrinsic pathway. So, as you remember in the last step what we discussed that the first was initially vascular spasm and the second step was the platelet plug formation.

So, basically the platelet all together form like a plug preventing like any secretion or any leaching of the blood. Now, this platelets has like phosphatidylserine type of like molecules on the surface and these are negatively charged. You can see this phosphatidylserine which are negatively charged. So, because of these molecules the platelet plug the surface of the platelet plug becomes negative in charge. Now, when they become negative in charge, you remember what I said we have like this liver type of we have liver organ right and this liver secretes lot of like protein which are called clotting factor.

So, liver secretes lot of protein which are called clotting factor. So, generally what happens this clotting factor stays in an inactivated situation whenever there is no injury, but whenever there is injury once this platelet plug the surface becomes negative in charge this clotting factor specifically the clotting factor 12 whenever it comes close to the negative charge it becomes activated. So, what happens like some clotting factor which is called like clotting factor 12, when during the circulating condition it comes close to the platelet plug due to the surface negative charge, it becomes activated and it becomes to the clotting factor 12 too. So, what it becomes from clotting factor 12 too, it becomes activated clotting factor 12a. So, from activated clotting factor 12 way, then what will happen? It influences the activation of pathway 11.

So, clotting factor 12 happens right and this is something mistake please disregard about this and then once the clotting factor 12 way becomes activated it kind of stimulates the clotting factor 11. So, here clotting factor 12 way It promotes the activation of clotting factor 11 to 11a. So, this is a chain reaction, I know there will be lot of step, but try to listen it slowly and kind of recapitulate one more time once the classes is done. And if you do not understand anything, we are happy to answer any your question in the live session. So, when the clotting factor 11 gets activated, what it does, it comes close to like the clotting factor 9 and then the clotting factor 9 gets converted to clotting factor 9a.

So, each a step everywhere the factor is getting activated and this cascade kind of continues right, in between clotting factor 5 participates and clotting factor 9a together along with this PF3 factor and the calcium which both of are like a cofactor. So, along with the presence of 9a, clotting factor 8, PF3 and the calcium +2 the clotting factor 10 gets converted to clotting factor 10a and this is very important to remember that 10 gets converted to 10a. Why it is important to remember? Because both the intrinsic pathway and the extrinsic pathway gets merged here. So, what happens in this 10 to 10a both intrinsic pathway and extrinsic pathway gets merged in this place. So, that is why it is important to remember.

So, when this clotting factor 10 gets activated. Again, further step happens, for example, like clotting factor 5, PF3 factor and calcium 2+, they again gets come close to each other and kind of activates the prothrombin factor. So, eventually, prothrombin factor gets activated. This stimulates the conversion of factor 2 to factor 2A. So, what is it? Like prothrombin, prothrombin, to thrombin.

So, this series of cascade of events happens, after happening eventually prothrombin which is also called that factor IIa, II, it gets converted to thrombin which is factor IIa and finally, when

this thrombin is formed or the factor IIa is formed, it activates the formation of fibrin from the fibrinogen. Fibrin is also called factor 1. So, what are basically fibrinogen? These are like soluble molecules of monomer. These are basically monomers and these are soluble in water. But when they get activated into 1A or fibrin, you see what is happening? The monomer is getting joined together and it is becoming like a polymeric chain.

So, from fibrinogen which was initially a monomer, when it gets activated, several molecules of this monomer get joined with together and form like a polymeric chain which is called fibrin. Finally, what happens is like another factor which is like factor 13. So, factor 13 gets activated to factor 13a. Okay, so during the same time, during the same time, whenever there is this clotting process going on, factor XIII gets activated to factor XIIIa. And what this factor XIIIa does? This factor XIIIa, this kind of prepare the meshes of fibrin.

That means one fibrin chain now, you see here first one fibrin chain form, Now factor XIIIa prepares or kind of creates multiple layers of fibrin chain. So, they basically joins multiple rounds of fibrin and they prepare multiple like a like multiple kind of a cross linking network of the fibrin mesh. So, eventually what we get from this all big like extensive pathway, I understand is that too much of information for you, but try to kind of read again. So, eventually we get to this very nice like fibrin mesh and what was the goal, eventual goal to prepare the fibrin mesh? The goal was that initially this platelet plaque form right, but this plaque can actually come off from this injured area in a small fraction and what will happen if that happens? So, small type of platelet plug can come out from this area and can keep circulating condition in our blood and it may kind of blocks our natural blood flow and that can be very detrimental. So, because we do not want this small fractions of platelet plug to come out from this area Our body naturally produce a mesh or kind of a net, holding net.

So, this fibrin mesh what it does, it basically kind of sits on top of this platelet plug to hold off any removal of like any small clot. So, hopefully you were able to understand the intrinsic pathway. Now, we will briefly discuss about the extrinsic pathway. So, in case of extrinsic pathway as you can see in the diagram there might be some sort of like injury and if any injury happens you can see like this factor 3 or which is like a tissue factor that can be released. And now this factor 3 what it can do basically it can activate the factor 7 from factor 7 to 7a.

So, what we just said like after any type of injury in case of external pathway, it can first release certain tissue factor or factor 3 and this factor 3 can activate from factor 7 to factor 7a. And this factor 7a what it can do? It can work in two different way. First of all, it can activate factor 9 to factor 9a or it can directly like activate the factor 10 to 10a. So, two thing it can do factor VIIa either it can activate from IX to IXa or it can directly activate from factor X to Xa. And now as you know like from factor X to Xa all the common pathway eventually start.

So, in presence of like prothrombin factor III and calcium and also in presence of factor V what it does is like the prothrombin factor can activate factor II to factor IIa. And eventually the factor 2a can be used for activation of fibrinogen to fibrin. So, this is in general like the extrinsic pathway only the left part this part is different, but when the common part starts it is already discussed in the extrinsic pathway. Then these are the same thing, I am not repeating one more time, but if you want to remember well, you can write down like this pathway 10 here, which is the most important plotting factor 10a from the 10 and then you can start from like 12, 11, 9, I am skipping 10, please remember, so 12, 11, 9 and 8 followed by 10. right and in case of extrinsic pathway tissue factor 3 that gets kind of it activates the factor 7 right and then again it can activate the 8, 7 from like factor 10 to 10, okay.

So, this is like the whole pathway of intrinsic and extrinsic pathway. Now, the fourth one is the clot retraction and repair, okay. So, initially as you see like clot formation happen, but this type of clot condition cannot stay in our body for longer time, right because as you know like sometime the clot can break and that can cause like blocking of like blood flow. So, we need to basically repair those clot. So, what happens basically how the clot basically repairs.

So, you remember what we said like there is this endothelial cell we have here and now we have lot of like platelet plug right, we have lot of platelet plug and there is this fibrin mesh. Now, we need to repair this. How it get repairs? So, just remember we will not discuss too much in details, but this endothelial cells secret like a growth factor called VEGF. What is this growth factor? This is vascular endothelial growth factor. So, vascular endothelial growth factor, this gets secreted by the near injured endothelial cell.

Also, this platelet plug or the platelets, they also can secrete another growth factor which is called platelet derived growth factor or PDGF. So, these are various growth factor and by the name you can understand that this growth factor can stimulate the proliferation of all these adjacent cell. So, VEGF can stimulate the proliferation of endothelial cell, PDGF or the platelet derived growth factor can stimulate the proliferation of both smooth muscle cells, collagen layer and endothelial cells okay and another way this plug also kind of pulls this adjacent area. So, they will initially try to like contract the area and after that secretion of growth factor will basically stimulate the cell proliferation, new tissue generation and eventually after all this step all these clots will be completely repaired right all this injured area when initially this injured area was it will be now completely healed and repaired even like the collagen layer if there is any damage it will also get repaired if there is any smooth muscle cells adjacent layer they will also get repaired.

Now the last step which is the fibrinolysis. So in the last in the last two last step in the clot retraction or repair the injury gets repaired right, but there might be still some clot like the platelet plug and the fibrin mesh they may still exist but we should not keep them near to this artery or blood vessel area because they can prevent like natural flow of blood, right. So, we have to basically destroy this. So, how to destroy? Our tissue endothelial cell has a receptor or like a molecule which is TPA or tissue plasminogen activator. What is it? It is tissue plasminogen activator. So, this molecule we have and whenever there is a blood clotting situation this tPA concentration becomes little bit higher and this tPA molecule what it does, it basically converts it basically converts plasminogen to plasmin, okay.

So, what it does, the tPA, it converts plasminogen to plasmin and this plasmin molecule, when it converts or like becomes synthesized or activated, what it does, it chops up all this clot. So, basically what it does, right, it can chop off this clotting mesh, fibrin mesh and basically lyse these clots. So, this presence of the tissue plasminogen activator in turn activates the formation of plasmin and this molecule eventually chops off or lyse all the remaining clots and the complete processes of blood coagulation followed by the healing and repair mechanism is complete now. So, I hope you learned about all the steps of the clotting. So, think about this we discussed two different pathway right intrinsic pathway and extrinsic pathway and you remember very well right like how both pathways are of course complicated first of all but also intrinsic pathway has lot more like different plotting factors associated to it compared to the extrinsic pathway which was involved with the less number of clotting factor.

So, can you predict like which pathway can may take like more time to clot the blood. This is your kind of the takeaway task. So, please think about this and I hope you enjoyed this exciting class of hemostasis. You learned about how the blood clots, how different steps participates in the blood clotting and eventually how it repairs.

So, again thank you for attending our class. You can also refer this video, there is very interesting video. You can also refer different textbooks like Guyton, Tortora textbook. So, if you have still further question, please contact us. Thank you again. We are hoping to bring you another exciting class of human physiology and see you soon. Thank you.