Human Physiology
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Lecture – 43
Physiology of smooth muscles and digestive system - Part 3

So, what was the major difference that we found when it comes to exciting a smooth muscle versus a skeletal muscle? The skeletal muscle is simple and straight what is the agent that we need to use? Skeletal muscle can be excited with what you are still I will I need to pick you up with acetylcholine. Acetylcholine coming over what fiber coming over the motor fiber from spinal cord whatever. Are you are you with me so far? In the case of smooth muscles, however, it is very complicated. There are n number of agents right from stretch to chemicals and the thing is there is enormous variety in which a smooth muscle can be excited, whereas a skeletal muscle can be excited but cannot be inhibited. The only way to inhibit it is to let the acetylcholine be chewed away by the acetylcholine esterase. When there is no acetylcholine the muscle will relax. But here in the case of smooth muscle, you can have an agent that will excite, you can have a muscle that will inhibit - you will have a muscle that can relax. Both systems are extremely elaborate. What is further exciting is you cannot have the excitation of a skeletal muscle without action potential hello. Action potential has to be there - has to be typical spike, has to be there. In the case of smooth muscle - do not worry about it - may be may not be - depends on individual source by which muscle cell is reactivated. So listen to this. Can a muscle cell be activated without action potential? Yes it can be it can be. There can be - so there comes an agent from outside it excites a particular receptor in the plasma membrane - it takes a signal inside and finally the signal goes to - there is increase in calcium ion channels and the actin-myosin filaments slide on one another - and the muscle contracts. At no stage - did you encounter any action potential. Wonderful phenomenon. It can do without action potential - but that does not mean that - no it can do. It can. There can be action potential - there may not be action potential. So we have seen this. So the calcium is the key element for the excitation - the calcium ions will go in and then we have seen that calcium will combine with this very interesting molecule called as what? Calmodulin. Okay, calmodulin. There can you see four tiny red dots there. Each dot represents a calcium ion and when the calcium ion combines with this calmodulin molecule undergoes a configurational change, okay. As a result of that - it activates the kinase enzyme what you call as the MLCK kinase and then it brings about the phosphorylation of this essential light chain and that finally leads to the what? On the myosin molecule there is ATPase that it is inactive. That is activated and once that is activated it will start cycling and you will have the contraction. This is just to give some more details of the same. We have different look at a smooth muscle here okay. So far there is a plasma membrane okay. So far there are different ways by which there could be signaling molecule could come through a capillary or it could come as a neurotransmitter released by a terminal okay. Either a hormone or a neurotransmitter or it simply simply stretching. So many things can give rise to - either it can combine with this G protein coupled system - this is a G protein it activates what - this is

phospholipase C - it converts PIP2 into inositol phosphate 3 - the inositol phosphate 3 goes and binds to this particular calcium channel which is sitting on the sarcoplasmic reticulum. And the sarcoplasmic reticulum releases calcium so you have plenty of calcium. It depends on what type of cell you are. Maybe you have lot of calcium - rest of the story is same calcium combines with what? Calmodulin and then and the rest is the conversion of inactive form active form - this of course you can identify this - is the cross bridge hello. Cross bridge - there is inactive ATP - it will become active ATP – once it becomes active then it will bind myosin head - will bind with the active element and the sliding phenomena will happen. This is sequence of events. What we have seen will help you to remember the steps. Now whereas we saw the starting point there is a signaling agent which is coming from outside okay - and that excites and you take a signal inside - cascade of events when you get contraction of the muscle. Good two points. Most of this action is happening at the level of caveoli - get my point? what is the caveoli? If this is a spindle shaped cell, hello - fatty in the middle okay tapering at the end. What do I have in front of you is a muscle cell okay. The length is about 250 to 300 microns - the thickness may be about 2, 3, 5, 6, 7, 8, 9, 10 or 15 microns - depending on what tissue you are talking about. If you walk along the surface - you go and - suddenly there is a pit - again a pit - what is the technical name for the pit? Caveoli. In this caveoli you will find all those receptors are sitting - where are they? They are in the caveoli okay. And the second anatomical beauty of the caveoli is that from the caveoli there is plasma membrane which is like a pit. If you cross the plasma membrane and go inside the cell you will inevitably find sarcoplasmic reticulum. There is plasma membrane occasionally there is a pit caveoli and immediately inside you will get what sarcoplasmic reticulum. So we are already in a caveoli and then you will have the sequence of events and here we have a diagram that tells us as to how the contraction will happen. Does it mean that always contraction - The author just gives us another example where can we see the two circles - the two circles take a section right in the neck okay and in the front you will have trachea and behind that you will have esophagus are you okay? In the pharynx - the nasal passage will go from your nose - it will go okay and then you will have the nasal passage going to the trachea which comes in front and the two passages cross. I do not have to tell you that anatomy and then we have the esophagus and the trachea. The author is drawing our attention to this muscle called as what? Can you read it as trachealis muscle? It is a smooth muscle okay which is lining a part of the trachea. Are you okay so far? Okay now you have an allergic reaction or something that you have inhaled that does not agree with you. And the muscle has gone into spasm okay and then you want to relax it. How would your biological system react to that. Well the sympathetic nervous system may be stimulated - the adrenal medulla may release epinephrine sorry - it will release what? Epinephrine okay from the adrenal medulla. It will get into the blood - it will go everywhere along with that it will go on the smooth muscles and on the smooth muscle plasma membrane you have a receptor. What receptor is there? Beta 2 adrenergic receptor. It is a G-protein coupled and as you can see the protein goes up and down 7 times. We are okay so far - so somewhere here there is affinity for epinephrine okay. It will give rise to adenine cyclase - cyclic AMP and then finally it will have downstream effect - series of steps and then you will have the relaxation of the smooth muscle. So what do you have - relaxation the muscle. We have already seen okay. What was the first line of treatment? Acute treatment for the patient of asthma injection? Injection of

what? Injection of epinephrine injection of what? In extreme cases but that is used. So how does it act? So you have a patient in front of you he has severe asthmatic attack and the doctor gives him a shot of what? Epinephrine and then you can look at this diagram and predict what is happening. It enters into the blood - goes where? Everywhere and then it will specifically bind where? Smooth muscle what receptor it is there beta 2 receptor - I mean I cannot make it simpler. I am talking to - you think it is too simple and so it can be ignored okay. No it is not important. Then you have entire cascade of events and what is the net result do we have? Relaxing of smooth muscle. So we have a firm idea okay that the smooth muscles can be excited - they can be inhibited - depending on and actually we have been repeatedly addressing this point okay. Now this is a very interesting anatomical peculiarity of smooth muscles You will enjoy this. Just be with me. If I look at this I know - I do not have to tell you what is this. Skeletal muscle - Z membranes. Hello anchored on them are the actin filaments and then myosin filaments we have done it 100 times. Good so far. And somewhere here is the M line. But I want you to focus just here. And supposing you are on the myosin filament where are you? You are sitting on a myosin filament okay and you are facing the Z membrane okay. With me so far? And then you have two oars in your hand - so that you are pulling the myosin filament towards this Z membrane okay or now both hands okay. You are pulling in the same direction I am underlining the word, what word - I am underscoring same word okay. So there is a cross bridge on this actin and there is a cross bridge on this actin - there may be one more actin. Let us not bother about it but you are all working in the same direction. Are you with me? Are you okay so far? Now let us change the focus to the smooth muscle and I will draw your attention to - let us say this at the top okay. Can you see a dense body there at this end okay can you see the dense body there? Can you see the dense body there? Yes or no? Anchored on the dense body is the red actin filament, okay. Then this is that green thing codifies myosin and then another myosin and the last one is anchored on the dense body okay so far? So how many myosin filaments can you count there? Three. How many actin filaments can you count there? Four - okay so far. Now listen look at this myosin filament whereas - it pulls this actin filament in this direction, it pulls the other myosin in the opposite direction, hello are you with me? And then look at this one look at the middle guy. Look at this middle myosin in which direction it is pulling this actin? It is pulling that actin same or different? Opposite direction and thatis yes or no? Yes. Then that is very well shown here. The author simplifies that - supposing this is one dense body this is another dense body anchored on them - actin - when this myosin filament has a crossbridge and pulls this actin filament. Look at the arrow - this direction and this actin filament in the opposite direction. A phenomenon that can never be seen in the case of skeletal muscles an amazing phenomenon - okay in opposite direction. As a result of that - whereas a skeletal muscle can contract from whatever - it is to 70 percent, are you with me? Whatever is the distance between Z membrane and when it contracts it can bring down to 90, 80, 70 percent. Because of this interesting arrangement from 100 it can go to 30, 100 to 30 are you with me? Yes or no? It can pull so much because of this very interesting arrangement of the actin-myosin arrangement and the cross bridge. Are we all on the same page everybody okay just appreciate the beauty of the smooth muscle here.

So just see because there is actin there is a myosin filament it will pull acting in this

direction and the whole cell can become very small - the two tips will be 30 percent as compared to the original. Then there is yet another trick of the sleeve of actin myosin filament. I talked to one of you I do not remember who. When we studied the cycling of the actin myosin filament with reference to the skeletal muscle there was a transient step which we call as rigor.

Rigor okay and when you die there is rigor mortis and that happens because actin-myosin filaments they remain attached to one another and the body becomes stiff okay. That is the rigor mortis just forget about it. Just rigor and this is transient it just comes and within a few milliseconds - it goes it is a transient step okay. Now this actin-myosin filament remaining attached to one another for quite some time is a regular phenomenon in the case of smooth muscles. We do not ever use the word rigor - we use the word latch formation - what word we use - latch formation. What is the advantage? The advantage is supposing - I want to lift half a kg of weight okay. As long as I am holding it like this - all the muscles of my hand actin-myosin filaments have to cycle and cycle and cycle and cycle as long as I am holding it, okay. Cycling has to happen and for every cycle I need to use one ATP okay. So skeletal muscles are expensive okay. Now in the case of smooth muscles - this amazing physiology has evolved - where everything is slow but when you want a particular muscle to remain contracted okay for 5 minutes, 10 minutes, 15 minutes - the food has entered into the stomach - the stomach is vigorously mixing the food with the enzymes and the acid. You do not want the food to reflux back into the esophagus. You do not want that to happen because the esophagus is not equipped to deal with the acidity and the acidity may be pH 2 to 2.5. It is very acidic. Stomach can deal with it but the esophagus cannot. To ensure that you need to have a valve where? At the junction between the esophagus and the stomach and the valve needs to remain closed for 15 minutes, 20 minutes, 30 minutes okay. In such a scenario, the smooth muscles show the phenomenon of latch formation. Means what - you let the actin-myosin filaments to remain joined - let the muscle remain contracted okay for as long as it is being ordered by some signal that you remain contracted. Why you remain contracted is because you do not want the food to go reflux from the stomach into the esophagus and that is going to take half an hour okay. So remain contracted and during that period I am not going to use any ATP. How can I do that. I can if I can somehow manage that the smooth muscles of the valve - that guard the opening from the esophagus into the stomach - if I can make the muscle remain contracted for half an hour without using energy – perfect. That is exactly what the smooth muscles do. And let us see another beauty, the real beauty is we do not know how it really happens okay. We do not know, okay. We do not know and we hypothesize - we suggest -there are couple of theories floating around that try to explain as to why this is happening and I will introduce you to one of them.

Let us look at that, okay. Now I will introduce you to two very basic words - I want you to understand and remember those two words. Let us look at the smooth muscle of the stomach, okay. What about it - well you have taken food it has gone from the esophagus into the stomach and as a result of the arrival of the food the stomach has released its acids and its enzymes. How that happens I will tell you may be in the next lecture or whatever. And then the walls of the stomach undertakes vigorous contraction relaxation activity - actually it starts

as - this stomach is a bag - I do not have to tell you. We have seen and studied and drawn the stomach okay. From the rostral end immediately after the vigorous contraction a wave starts a sort of peristalsis - it goes all the way to the duodenal end which is called as pyloric end and another wave comes and another wave comes but the pyloric sphincter that guards the opening from the stomach into the duodenum is also closed why? Because the food is not ready to be discharged into the duodenum. It has not been digested - all the enzymes of the stomach which need to act on have not yet acted on. So you need that 15, 20, 30 minutes of time during which the stomach is on its own and there is a wave of peristalsis another wave of peristalsis another wave of peristalsis every time a smooth muscle goes through a wave of contraction and relaxation - which may take 30 seconds or which may take 1 minute which may take 90 seconds. I will call that as the phasic contraction. What do I call it as? Say that again phasic contraction. What do I call it as? Phasic contraction - it comes and goes okay. Why is it coming why is that happening? That is happening because the smooth muscles of the longitudinal and circular muscles okay contract alternately okay. They contract stay contracted contract 30 seconds 40 seconds 60 seconds and then relax. But the next one will contract and the next one - this is how the wave will go from the anterior end to the caudal end, are you okay so far? I am just describing how that peristalsis - we have done peristalsis - is happening at the level of stomach. We are focused on why is that muscle contracting why is that particular circular muscle is contracting. Because it is being told by whom by the myentric plexus - by whom and how does that happen? That also I will tell you - by the myentric plexus - is doing so what is myentric plexus doing? A stimulation to whom? The smooth muscle - what smooth muscles? Circular smooth muscle which it is there in the neighborhood. I am going to show the myentric cell which is going to stimulate the smooth muscle okay. You contract and it remains contracted for 30 seconds and then you relax and then the other guy will contract and the other guy. In this way the wave of contraction will go from one end to another end of the stomach and the second wave and the third wave and the fourth wave are you okay so far? Everybody great. If you look at a single muscle - there you will find it contracts and relaxes. I will call that phenomenon again. I have explained so what? We are stimulating it because there is a neuron of the myentric which is releasing an excitatory neurotransmitter on the smooth muscle and the smooth muscle is contracting in a phasic manner. So it is stimulating - that stimulation stays for 30 seconds for 30 seconds the muscle is contracted and then the stimulation goes away okay then the next one and the next one in this way the wave goes from one end to another end. Whereas that is the story at the level of a smooth muscle which is lining the stomach proper I am talking about the esophageal sphincter and the pyloric sphincter. The names are self-evident esophageal is esophageal and pyloric is pyloric. Once you have taken whatever food you have taken and then the esophageal sphincter okay - now knows that it is time for me to contract and stay contracted, why? Because the sphincter has been told by whom by again the myentric plexus. That myentric plexus is now telling the smooth muscle to contract and stay contracted for 30 minutes. You will call the phenomenon as what? Call it as what tonic contraction. So have you fully absorbed the meaning of the two words which I gave you? What are the two words I gave you? Phasic contraction and tonic contraction okay. Both of them will need a stimulation, they have to be and then let us see what happens. We are looking at a smooth muscle that smooth muscle is somewhere in the wall of the stomach okay. That has been

stimulated by an excitatory neurotransmitter from a neuron of the myentric plexus for a very brief period. As a result of that, within that cell something has happened with reference to this peak what is that peak read for me? The first one calcium has gone we have seen that 100 times calcium has gone up. Makes sense. Up and down spike in calcium. This is followed by the second one the blue one which is called as what? Read for me velocity and cross bridge phosphorylation okay. It goes up and that also goes down and this is followed by the red curve. What is the red curve? The force of contraction where actually - that we have seen in details. All the three steps are there okay. Whereas this is happening every 30 seconds, so one wave has gone after two minutes, another wave another wave, another - phase - done so far. Now author tells us about this sphincter muscle and this sphincter muscle - and in the case of these two sphincter muscles - the stimulus comes and stays, stays, stays, for quite some time okay. Now as a result of the arrival of the stimulus - means what - a particular neuron of the myentric plexus - which has released an excitatory neurotransmitter on the smooth muscle of the sphincter - and in that smooth muscle again calcium has gone up. No problem the velocity and cross bridge phosphorylation has gone up. But after that something interesting happens - you know that kinase activity was there without kinase nothing will happen. What was that – MLK. What kinase was there? You know I have forgotten. Very good very good - that kinase okay. That kinase is there which takes the muscle towards contraction and there is another phosphatase which will end or which will terminate the contraction. The hypothesis tells us that there is a delicate balance between the two and both of them go down both means what? On one hand and activity of both are in a balance wave - goes down how it happens? We do not know - magic like it happens okay. Therefore I want you to read the bottom three lines. How does this happen - one hypothesis is that the balance between the activity levels of myosin light chain kinase and myosin phosphatase determines the rate at which cross bridges cycle. The activity of both is depressed okay. I am sure you are confused as I am – okay. But that only tells us what? What is unsolved problem okay, how it actually happens okay? Good good. But because of this phenomenon - just see how far how far these two smooth muscles remain contracted - is there cycling happening - there is no cycling happening. No. As a result of this, there is no cycling happening. Only the actin-myosin filaments - they just remain in a what state - I gave you the word latch state say that again in the latch state they remain contracted in latch state without using the ATP. An amazing phenomenon. How the nature has found a solution that when you want to keep a muscle contracted for a very long time and you do not want to spend energy on that then engage a latch phenomenon. Shall I tell you something? All the answers could be true absolutely true, okay. He is asking a very interesting question. First of all, I do not know the answer. But I am trying to make a guess. Let me take the sphincter muscle from the wall of the wall of the stomach okay. Take two pieces and extract myosin and let me get a look. Is this myosin identical with that myosin. The answer to the question I do not know it may be identical it may not be identical. Number one even if it is identical it is quite possible that there is there is a different neurotransmitter that is regulating this and the circuit that could be different. So the answer could be anywhere there. Got it okay are we okay so far or this is mumbo-jumbo we are good yeah. Stimulus has to be there. You are right.