Human Physiology
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Lecture – 09
How does the heart muscle work? Part: 2

Muscle - Now here we try to understand the entire sequence of events. Let us follow this, a very interesting diagram, and if you follow this, we have understood a lot of the mechanisms. I am sure you understand we are looking at a single cardiomyocyte, single cell, done. Then number 2 - you can see the T-tubule there, number 2, okay. Number 3 is you can see that on the plasma membrane there you can see that red part, red part here. Here the message is that an action potential has arrived or an electrical signal has arrived.

Now who has initiated the signal? We will see later. It has arrived, okay. Now as a result of that, if we go here in the plasma membrane here you have what - DHPR. What do you have there? DHPR.

This is DHPR is a voltage-gated ion channel and as a result of action potential arriving here, the calcium ion channels have opened and it has all the calcium ions going through. Are you okay so far? Now as a result of the opening of calcium ion channels, now calcium ions are inside, okay. They interact with yet another protein system with which we are very familiar and that protein system is sitting on the plasma membrane and that protein system is called as RYR2. We talked about then was RyR1. So what is RyR1? Say that again.

Ryanodine receptor 1. Okay. It is the peculiarity of the skeletal muscle. Absorb the message. Hello? Peculiarity of what? So if I ask you give me RYR1 you will go to what tissue? Skeletal muscle. Okay and if I say RyR2, then you will go to what muscle? Cardiac muscle.

Cardiac muscle. RyR3 which you get in several types of tissues - include neurons, but we will not bother about at this stage. Now this is located where? This endoplasmic reticulum, sarcoplasmic reticulum in its membrane you have this protein system which we call as RyR2 or ryanodine receptor 2, okay. Now this ryanodine receptor 2 is interesting because, I will take you to the skeletal muscle and in the skeletal muscle the issue was that there was DHPR in the plasma membrane and there was RyR1 in the sarcoplasmic reticulum and they were mechanically linked to one another. And if this undergoes change because of voltage this also undergoes a change and it allows the flow

of calcium ions from within the sarcoplasmic reticulum into the cytosol, okay.

That was a mechanical phenomenon. Here it is not a mechanical phenomenon. Here the phenomenon is that when the calcium ions enter into the cytosol, calcium ions stimulate the RyR2, ryanodine receptor 2 and as a result of that, the ryanodine receptor 2 open and then as a result of that a large number of calcium ions which are stored in the sarcoplasmic reticulum are now released into the cytosol. Are you getting the story? Therefore, this phenomenon, what phenomenon, what phenomenon - that RYR2, ryanodine receptor 2 being stimulated by calcium ions and what is the response? Release of more calcium ions. Calcium induced calcium release.

What did I say? Say that again. Calcium induced calcium release. Say that again. Calcium induced calcium release.

CICR. What is it? CICR. CICR, okay. So, first calcium is coming from where? Outside. So, calcium is coming from where? Sarcoplasmic reticulum and this huge amount of calcium now will go where? It is now available to, it is now available to the troponin.

Hello. It will go to, there is troponin there. On the troponin there are three subunits. One of them has a binding site for calcium. It will bind to the calcium. It will take, it will pull the tropomyosin away on the G protein.

There is a site. actin-myosin interaction will happen and sliding will happen and the muscle will contract. Good so far? Now, but you see, the heartbeat has to happen within a period of 0.8 second. Well, heartbeat 72 times in a minute.

So each heartbeat has about how much time? 0.8 seconds. How much it is less than a second? 0.8 seconds. If your pulse rate is 60, then your, each pulse is taking 1 second.

Am I done there? Right. So here we have the, so this calcium is being pumped back, okay. How it is being pumped back? Because again in the sarcoplasmic, whether you are here or here in the plasma membrane, we have, we have what? Calcium pump? Calcium pump. What is the calcium pump? It is an ATP driven system, okay, which will take the calcium ions taken into the sarcoplasmic reticulum. You know something?

I have a choice, I will tell you. Ion as an ion. So I have, I have a lot of ions here. How much? 10 raised to the power of minus 5, okay. And I have much less here, 10 raised to the power of minus 7.

100-fold difference. Are you with me? 100-fold, 100-fold. If I keep everything in the ionic form, okay, there will be a certain, there will be a certain load on the plasma membrane, okay. It is ion, okay. I mean after all, after all, everything has a limit. How much can you store? Okay.

So the nature has come up with a beautiful solution. Can you think of that? There is a protein, calsequestrin, okay, which loosely binds the calcium ion. So once you bind the calcium ion, it is not an ion anymore, okay. But the bond is so loose, so weak, the bond is so weak, okay, that any signal comes, calcium ion is immediately released from the protein molecule and it is made available, okay. So when it is stored, so the point that I am trying to make is when calcium ions are stored in the endoplasmic reticulum, they are not stored as, of course some of them are there, but not, the whole of it is not stored as in the form of calcium ions, but it is stored in what form? It is bound to a large protein molecule which is called as calsequestrin or different types of binding molecules are there and the calcium remains bound to that molecule.

Are you okay so far? No. So every time there is a gush of calcium, every beat is a gush of calcium because suddenly you have to make huge amount of calcium available for every cross bridge to bind and slide, okay and make sure that the filament slide, you have to have a huge amount of calcium, okay. Now to make my point, I got a very interesting video, this is in vivo preparation. We have a cell, okay, it is in the medium, okay and in the cell you have introduced a calcium dye. What have you introduced? Calcium dye and just appreciate the beauty of the system. You got the message there? Suddenly the calcium is being released, you are able to see the calcium because you have a calcium, there is a dye, okay, that dye lights up whenever the calcium level goes up, okay.

So calcium level goes up, goes down, goes up, goes down and this phenomena, what happened to, oh that is finished, okay. This phenomenon is called as what? Calcium spark. Yeah, somebody had a question? Yeah, please go ahead. So when the ryanodine receptors are stimulated and calcium is released from the sarcoplasmic reticulum, the calcium which is released also can stimulate the ryanodine receptor itself because it is activated by the calcium which is coming from the outside.

Sure. So this system will always be in the activated state. Even if the pumps are working because calcium will again activate and there will be a rush of calcium which will be released from your sarcoplasmic reticulum. You are forgetting a very interesting point. These channels, all the channels, good you mentioned that point, all the channels when stimulated to open, they will open. But having opened within a frame of time, they will close.

They will close. This is the system of the protein. So it is not a question of channel opening and opening. No. That it should close is a part of the program. That protein system when it undergoes through a cycle, so there is a huge protein molecule, there is a charge here, there is a charge here. I do not know how, but as a result of that sudden change the proteins has to open and close.

But this stage is very transient. It will close. But calcium will again activate the state. No. The answer to that question is during this period when the cell is depolarized, the cell cannot respond to another stimulus and this period is called as refractory period.

It cannot. That protein system is, the protein system has to go through the entire cycle, then only it can be stimulated again. You got the answer now? You can read about this slide. We talked more about the L-type of calcium channel. This is the protein system that is the, what is that? What is that? Crystallography? Okay, alright.

Now comes a very interesting part. Listen to this, listen to this. For the treatment of several patients who are suffering from a disease like angina pectoris which means pain in the heart or in the shoulder or in the related area because of the problem in the heart or because of high pressure, okay, high blood pressure, hypertension, okay. One of the established strategies for treatment is called as, I am sure you will immediately appreciate, a class of drugs which we call as calcium antagonist. Please appreciate this point. What do I call it as? Calcium antagonists.

What would they do? The calcium antagonists will act, okay, and they will not allow, you see, they will act on the DHPR, okay, and they will reduce the efficiency of the DHPR so that you do not allow so many and thereby you are reducing the force with which the heart is going to contract. As if you are limiting the availability of the calcium to the actin-myosin filaments. Are you getting the point? What do you call that family of drugs is? Say that again.

Calcium Antagonist. Calcium Antagonist. Remember, remember, there are three very important class of drugs which are used for hypertension in the clinical practice. I am going to introduce all the three to you one by one and right now I am introducing you to a very interesting class of drugs which you call as what?

Calcium antagonist. Calcium antagonist. Please read about this. And one such drug is called as nefidipine. What is nefidipine? It is a drug. It is a drug, okay.

It falls in which category? Calcium antagonist.

Say that again, loudly. Calcium antagonist. And it acts on, so here we have, so this is a DHPR, this is a calcium ion channel, this is a nefidipine, these are all the different types of, verapamil, these are all different forms of calcium antagonists that are available in the market. Look at this. This is an animation but it shows how the cell undergoes the mechanical change continuously.

Alright, let us move on now. Yeah. Sure. Sure, sure, sure, sure. One thing for sure is that they reduce the strength with which the heart contracts and it has been found that the entire the entire plateau, at whatever height it is, okay, it is slightly, it is slightly, it is lowered by about 5 to 10 percent. Time duration is same. Time duration is same.