Biomechanics
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Lecture - 18
Excitation Contraction Coupling

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Welcome to this video on biomechanics. We have been looking at skeletal muscles specifically we are interested in understanding what is a sarcomere and how a sarcomere produces force. So, in this video we will discuss sarcomeres and how sarcomeres convert excitation to contraction or how a command coming from the central nervous system is converted into force.

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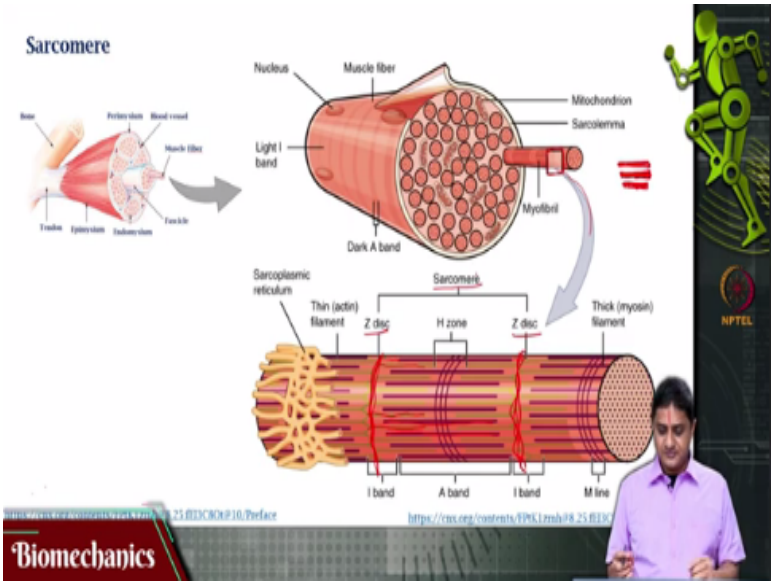

So, if we continue our discussion on muscles and the hierarchical arrangement of muscles. So, if you take a muscle fibre and if you subject it to light microscope and you view you will find there are these thick bands. I am discussing the bands that you see for a striated muscle; skeletal muscle is a striated muscle, it is clarification. You will see these bands so you will have alternating thick and thin bands like stripes in a shirt like you have a striped shirt.

So, alternating stripes that you will see these stripes that are seen since they are present in the muscle that muscle itself is called as striated muscle. Striated muscle means those muscles that have these stripes. But what is the functional significance of these stripes of these lines of this striations? So, you will have these thick lines that are there, here and then on top in this figure this is seen in green here that there are some other relatively thinner filaments that are seen.

And it appears as though the thick threads or filaments are hanging loose in air. But this is not the case you need to just zoom in a little bit to see more details. So, if you take a myofibril a muscle fibre and a myofibril so and you zoom in and you see these lines. And what do these lines represent? Remember that at the highest level you have the muzzle itself and this muscle is composed of bundles of fascicles which are further having smaller bundles.

And then you have one fascicle which is composed of several myofibrils and then you have within this myofibril you have these striations, these lines, these zones. So, you are having this

you are having this unique arrangement in which there are these thick lines followed by thin lines. And the point from which these thin lines originate from which the thick lines are suspended using a very thin not visible in this picture is a protein called titin through that protein.

From these two ends the thick filament are the striated filament the one that appears as striations that filament and the thinner filament are suspended. The point from which this suspending of these filaments happen is called as a Z disc and the zone between two Z disc are all the components between two consecutive Z discs is called as a sarcomere. Sarcomere is this smallest functional unit of a muscle. So, functionally this is how small it can get.

So, if you would like to explain the function of a muscle you start with the function of a sarcomere. So, the zone are that region or that set of components between two Z disc constitute a sarcomere this is the smallest functional unit in a muscle.

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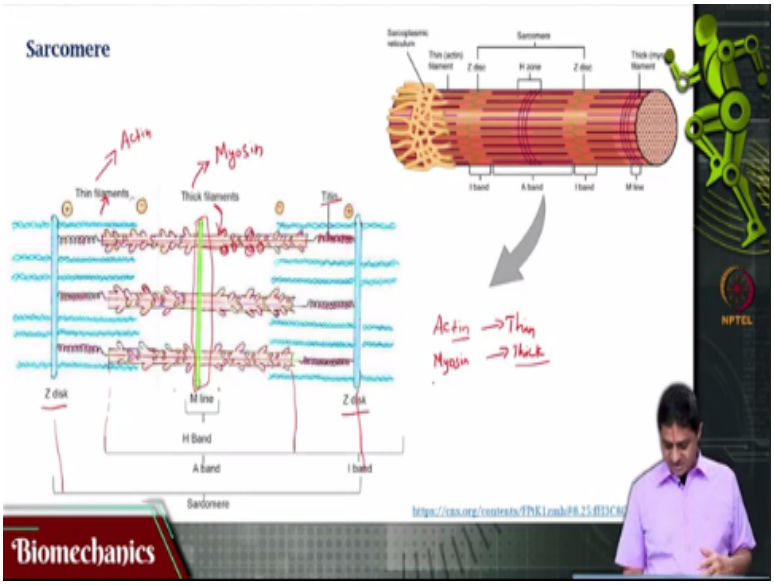

Let us zoom in a little bit, I am zooming in further. So, you are having these thick filaments and you are having these thin filaments and I am zooming in. If I zoom in what I find is that there are these tin filaments shown here as blue and the thicker filaments. These are the thicker filaments thick filaments are here shown in light orange, these are the thin filaments shown in blue. Now you can see that there is a spring like material the protein called titin which is holding the thick filament in space between two Z discs.

In the middle of this you have an M band and the region where the thick filament starts and ends is called as a H band and the set of all components between two Z discs is called a sarcomere which is the smallest functional unit in a muscle. Now what do this thick contain filament signify? How do this produce force? This is of interest for us. It turns out that the thick filament has these heads like small buds in a stem.

These heads are capable of attaching to specific points on the thin filament. Specific points on the thin filament are capable of attaching to these heads and under specific conditions this attachment between the thick filament and thin filament will be so strong. And the thick filament will undergo a conformational change pulling the thin filament thus making a really minuscule a very small amount of contraction.

We will discuss the physiological details or we will discuss the functional details of how this happens in a future video. But here we just introduce these two motions. This thick filament is called technical name myosin, the thin filament is called actin. Frequently students will find it difficult to remember this. In the class in future classes I will frequently switch between thick film and thin filament and myosin and actin I will keep on interchanging this.

You need to remember which is myosin and which is actin, simple way to remember. Actin is thin, the other one is myosin, actin is like thin the other one is thick this is how you need to remember which is which. Now what are the conditions that lead to the situation in which this force development happens. First of all, before this we need to understand how and where the command comes from and how this command is processed in the muscle cell.

So, in the central nervous system a decision is made likely the frontal lobe of the brain not necessarily always the frontal lobe of the brain. So, there is this question not all moments are voluntary, may be some of the movements are being generated only at the spinal cord maybe it is a reflexive movement. Without going into the details of what this is somewhere in the central nervous system a decision to make a movement has been made.

We will just say this for the purpose of this discussion. And this is communicated to a muscle through a neuromuscular junction. For the purpose of this course, we will not get into the details of how the neuron and neuromuscular junction functions because we restrict our attention to the biomechanics part. So, if you are interested in understanding the neuroscience of how this happens, I request you to check my other courses.

Or the other videos in which I have discussed neuromuscular junction, how the decision is converted into a command and how that is being communicated that I request you to please check in YouTube or just Google you will be able to find that. So, we restrict our attention to how the command that is received from the neuron is processed in the muscle cell. We are interested in how the muscle cell is converting this electrical signal that is received into a mechanical output which is this phenomenon.

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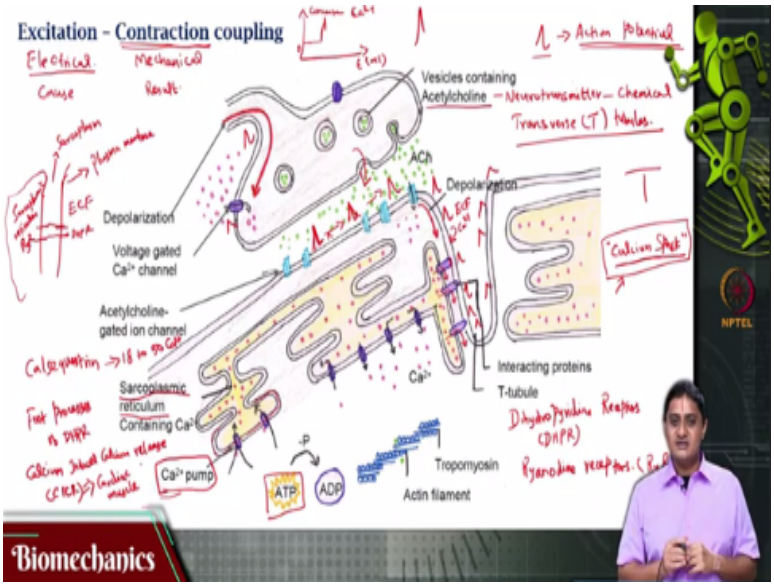

In which an electrical signal is converted into a mechanical output is called excitation contraction coupling. Excitation means something that is electrical in origin, contraction means is the result. This is the cause; this is the result. So, this excitation is in electrical form and the output is contraction. We are interested in understanding contraction because contraction is a mechanical aspect. We are interested in biomechanics of how this happens.

But first there must still be some processing of this electrical signal how is this happening, that is the question. We focus our attention to that topic in this slide. So, what happens briefly is that a neuron receives and sends a command to the muscle to start contracting. This is received through what are called as neurotransmitter. In this case this neurotransmitter is called acetylcholine, this is a bit of a detail but better to start here.

This neurotransmitter is received by the receptors or a special kind of channel that is present in the muscle cell plasma membrane. This channel is sensitive to acetylcholine. So, whenever acetylcholine is present in its vicinity or when it is present are attached to a specific region in that channel that channel will open and let in a lot of sodium. This sodium that is coming in will be so high that it will change the membrane potential in that region and cause a chain of events or the so-called domino effect.

It will cause a chain of events that will lead to an electrical pulse is getting generated here. This pulse is called an action potential. So, this domino effect, a lot of sodium enters inside because the command has been received through chemical means remember acetylcholine is a neurotransmitter which is a chemical. And this leads to a chain of events or a domino effect whereby electrical signal or a particular pulse with a specific characteristic is generated that is called action potential.

This action potential has a tendency to travel along the plasma membrane of the muscle cell because neurons and muscle cells are excitable cells and because muscle is also an excitable cell it has this potential and the tendency to conduct electricity conduct this action potential. So, if a pulse is generated at one part of the muscle cell it gets transmitted throughout the rest of the plasma membrane. So, this pulse will go in this direction.

So, it will be felt here and then it will be felt here actually it will be regenerated in each point. But that is a matter of detail I request you to check in other videos. So, this pulse is coming through this and it turns out that the nature of the muscle cell is such that every now and then there are these transverse tubules that you see in the muscle cell. This transverse tubules are such that it resembles the English capital alphabet T.

It goes like this and then takes a dip and then goes like goes back like this. That is the nature of this T tubule or the transverse tube going forward I will only use this call this as T tubule. So, this T tubules are present which also conducts this pulse and the nature of this T tubule is such that very close to it. There are this so-called sarcoplasmic reticulum, this is the equivalent of the endoplasmic reticulum but found in the muscle cell.

Endoplasmic reticulum in the general animal cell when specialized to muscle cell is called as a sarcoplasmic reticulum. It turns out that this sarcoplasmic reticulum has some channels that are attached on two sides. One on the sarcoplasmic reticulum itself and the other because T tubule is very close the other end of this T tubule the other end of this channel is attached to the T tubule. And the nature of this channel is such that whenever it detects an action potential whenever it detects a pulse an electrical pulse travelling at the T tubule it will open.

And when it opens it also opens its partner under sarcoplasmic reticulum side. So, it is like two doors when one door open the other door also opens. The first door here is on the T tubule that first door is called as the dihydropyridine receptors are in short DHPR receptors. These DHPR receptors are such that whenever it detects the presence of an pulse or an electrical activation or an action potential it will open.

And when it opens it also opens the other door that it is connected to that other door is present not on the T tubule but on the sarcoplasmic reticulum that other door or that other channel is called ryanodine receptors are R y R. So, let us review this one more time. So, whenever the command is received from the neuron an action potential is generated in the muscle cell and this action potential has the tendency to travel along the length of the plasma membrane of the muscle cell.

And as it is travelling it will also go through the transverse tubule or the T tubule and in the T tubule you have two receptors. Actually, in the T tubule you have one receptor that is sensitive to this action potential. Whenever there is this action potential it will open but when it opens it also opens a door or a channel that is attached to the sarcoplasmic reticulum. Sarcoplasmic reticulum

is not on the plasma membrane, sarcoplasmic reticulum is in the cytoplasm of this muscle cell or rather the sarcoplasm of the muscle cell.

What is the difference between cytoplasm and sarcoplasm? Cytoplasm in the general animal cell when we apply to the muscle cell is called sarcoplasm. So, the sarcoplasmic reticulum is in the sarcoplasm of the muscle cell, it is not on the T tubule. So, it is like this there are two consecutive doors. The first door opens whenever there is an electrical activity but this door has the tendency to open another door on the other side of the corridor.

There is a corridor there is a small gap in between so you see this is the corridor that I am speaking about. So, there is one door which will open whenever there is an action potential but this door has this tendency to open the other door or door on the other side of the corridor which is on the sarcoplasmic reticulum. What is so special about this sarcoplasmic reticulum? It turns out that the sarcoplasmic reticulum is capable of storing a large amount of calcium.

And it turns out that calcium is very crucial for conversion of force for production of force. Why is this? We will see in a future video but for now let us just assume that we need a lot of calcium to produce force in a muscle and all this calcium is collected and stored inside sarcoplasmic reticulum to be released only when the command is received from the neuron. Command is received from the neuron.

Action potential is generated in the muscle fibre and it is traveling to through the T tubule and it is detected by the DHPR receptors. And when that DHPR receptor opens it also opens the ryanodine receptor on the sarcoplasmic reticulum this is where we are. And when this receptor opens when the door on the other side of the corridor when that opens so there is this is the corridor that I am speaking about there is a door here there is a door here and there is one more door here.

This is extracellular fluid, this is sarcoplasm, this is the sarcoplasmic reticulum. Whenever the action potential reaches along the plasma membrane and this is the plasma membrane or the sarcolemma, plasma membrane of the cell. So, whenever the action potential reaches it opens

this DHPR receptor. This door is called the DHPR this door is called as the ryanodine receptor. Whenever the DHPR is opened it has the tendency to also open because it is not like this.

There is a connection between the two through the sarcoplasm such that whenever DHPR receptor opens it also opens a ryanoid receptor that opens the gate through which calcium can leave. Because of the nature of the fluids within the cytoplasm it turns out that or in any fluid if there is a semi-permeable membrane there will always be exodus of particles from a region of high concentration to a region of low concentration something that we know.

And because a lot of calcium is stored inside the sarcoplasmic reticulum and the rest of the cytoplasm is maintained practically free of any calcium there will be a huge concentration gradient between the sarcoplasm and the sarcoplasmic reticulum. Remember both of these are within the muscle cell under discussion both the sarcoplasm and the sarcoplasmic reticulum are within the muscles cell the same cell.

But when the; sarcoplasmic reticulum opens because the concentration gradient is so huge when it opens a lot of calcium leaves from the sarcoplasmic reticulum into the sarcoplasm. This situation in which there is a sudden build-up of a large amount of calcium within the rest of the sarcoplasm not counting the sarcoplasmic reticulum is called calcium spark. This situation is called calcium spark, the build-up of suppose I were to plot the amount of calcium as a function of time.

Let us say this is time in milliseconds or microseconds as the case may be and this is the let us say concentration in the y axis, I have concentration of C a 2 plus, you will have a baseline concentration which is very close to zero actually this is very let us say that is zero slightly above zero or maybe you have this and then there is a sudden increase of calcium that goes happens. There is a sudden spike that happens, this spike is called calcium spark.

It role is so functionally crucial for the production of muscle force. We will see why in a future video. For now, it is sufficient for us to know that this build-up of calcium or this maintaining of calcium concentration gradient is crucial for the production of this calcium spark and other after

effects of this calcium spark. But why do this, how do you do this? Because now that I have said that there is this calcium spark that means calcium is leaving and spreading in the rest of the cytoplasm.

Once that is spread how will it come back to the sarcoplasmic reticulum? Because once it is not like one muscle is a use on throw muscle single-use muscle. It is not like that once it contracts again it will have to contract within a few milliseconds again. So, that means that there is a need to maintain the calcium within sarcoplasmic reticulum bring the calcium back from the rest of the cytoplasm are from the sarcoplasm back into the sarcoplasmic reticulum.

How is this achieved? Through a mechanism called calcium pump. This is a matter of detail, without going into much detail I will try to very briefly explain what this is. So, whenever you need water that you need to pump from the sump or from an underground well. For example, maybe a bore well or a real well or whatever or from a sump you want to pump it to a overhead tank. Why do you need that? So, that you will have what is called as running water.

You open the tap water will come in the tap, how does it come? Because there is water in the overhead tank. And because we live in planet earth and there is gravity when you open water rushes in from the overhead tank to your tap water is always running. One of the reasons why we waste water. Suppose you have to carry this water from ground floor to the place where you live you, we would not waste water anyhow that is a distraction, coming back.

So, I opened the tap water comes. For me to do this first of all I will have to pump the water from the sump to the overhead tank. How do I do that? I use a pump; water pump I spend electricity it is an electric motor that pumps water from the sump to the overhead tank. Because this pumping has to happen against the gradient against gravity, I will have to expend energy. I pay for this electricity electrical energy is expended to pump this water from a region of essentially from a low height to a higher height.

Let us just say that from a lower from a lower level to a higher level against the gradient. So, whenever you want to push something against the gradient you have to spend money or you have

to spend energy that is what we do. So, we are expending electrical energy we pay for this in rupees, dollars whatever is we pay for this we expend energy we send the water from the pump to the power head tank.

Similarly, suppose I would like to add calcium to the sarcoplasmic reticulum which is already having a large amount of calcium this is against the gradient. Suppose there was an opening suppose there was a channel that allows passage of calcium naturally calcium will go from the region of higher concentration which is the sarcoplasmic reticulum to the region of lower concentration which is the rest of the cytoplasm or the sarcoplasm.

So, if there is this channel that generally allows calcium to leave calcium will be leaving from the sarcoplasmic reticulum to the sarcoplasm because in general sarcoplasmic reticulum has a lot of calcium. This is the same situation that happens when you open the tap, why does water come down? Because there is a gradient difference from a higher potential energy to a region of lower potential energy. I am just opening it up water comes.

When the water does not come that means that there is no more water or you are at the same potential energy perhaps that. So, for this so for you to push the water up you need to expand energy. Suppose I want to push calcium from the sarcoplasm to the sarcoplasmic reticulum that is from a region of low concentration to a region of higher concentration that is against the gradient like you are pushing against gravity against the gradient you expend energy through in the form of ATP.

You spend energy and pump this calcium. Find wherever the calcium ions are and then push them inside the sarcoplasmic reticulum. There must be some very good evolutionary reason for this to happen. There must be some very good evolutionary reason there better be a good reason for us to do this. Why would you do this? Because you have to expend energy. Normally this is not needed why do you even need this now such is the importance of calcium in this function.

So, you need to spend money or in this case energy to push this calcium inside the sarcoplasmic reticulum. Maintenance of this huge concentration gradient between the sarcoplasmic reticulum

and sarcoplasm is extraordinarily crucial for the function of the muscle. Because of this reason the system goes to extreme lengths in terms of spending the energy to maintain this concentration gradient between the sarcoplasmic reticulum and the sarcoplasm.

Such that any small opening in the channels in the sarcoplasmic reticulum will lead to a huge build-up of calcium because of the great difference in the concentration gradient leading to this calcium spark situation. You want this calcium spark situation for muscle force production. But how is the sarcoplasmic reticulum able to store so much calcium? Because this is a bit of deep physiology. So, we will spend some time on this.

Because the sarcoplasmic reticulum has some special proteins such as calsequestrin. Calsequestrin is this special protein that has the ability to hold anywhere from 18 to 50 calcium ions. It can hold and absorb up to 50 calcium ions a single calsequestrin molecule has the ability to hold on to 50 calcium ions. With the use of such special enzymes this sarcoplasmic reticulum is able to hold on to a huge amount of calcium.

So, through this pump and through the functions of these proteins like calsequestrin it is holding on to a large amount of calcium. So, this is how calcium is maintained within the sarcoplasmic reticulum and whenever the command comes from the neuron the action potential is generated in the muscle cell plasma membrane. And this travels along the plasma membrane and it reaches the T tubules.

And it opens the DHPR receptors which further leads to the opening of the ryanodine receptors on the other side through what are called as foot processes of the DHPR. Through those the ryanodine receptors open that is the opening that calcium was waiting for. A lot of calcium is present inside and all that calcium are a large amount of that calcium will suddenly rush out a huge out flux of calcium not outside the cell within the cell. All this happens within the muscle cell.

From within the sarcoplasmic reticulum to the sarcoplasm that is a huge gush of calcium. This leads to a situation in which calcium is suddenly becoming abundant in the sarcoplasm and this

calcium and detection of this calcium happens in the muscle fibre at the thick thin filament interaction level leading to a situation in which contraction happens. So, this is how the excitation that happens in the muscle cell are rather in the neuron.

There is this excitation which leads to this chemical being released which then regenerates an excitation in the muscle cell is converted into contraction. Exactly how this contraction is developed is something that we will see in the future video. So, a large amount of calcium is stored within the sarcoplasmic reticulum and this is open through the action of this action potential through the interaction of the DHPR receptor.

And the ryanodine receptor leading to a situation in which a huge amount of calcium leaves that is called calcium spark. As an aside something that we also want to look at is the special case wherein sometimes what happens is there are some channels in some muscles there are some channels that are sensitive to action potential that are present in the T tubule that has a tendency to let in calcium from the extracellular fluids.

These are the special l-type calcium channels that open whenever the action potential reaches. These are depolarization sensitive are the action potential sensitive channels that open and let in some calcium inside. And there are some more channels on the sarcoplasmic reticulum that are sensitive to the presence of calcium which will open. So, there are two channels one here and one on the sarcoplasmic reticulum through which calcium enters.

And calcium sensitive channels are also present on the sarcoplasmic reticulum that detects the presence of calcium outside the sarcoplasmic reticulum are in the sarcoplasm. So, whenever calcium comes from outside the cell to inside the cell through the cell calcium channels it detects and the sarcoplasmic reticulum opens leading to a situation called and when that sarcoplasmic reticulum channel opens it releases a lot of calcium. The reason why it releases a lot of calcium?

It is because it detected the presence of calcium just outside the sarcoplasmic reticulum. So, it releases this calcium from the inside. So, this situation is called calcium induced calcium release or rather CICR. In the good old days, it was thought this is how calcium is released from the

sarcoplasmic reticulum. From the outside of the cell calcium is entering and that opens the calcium channels from the sarcoplasmic reticulum.

But now it is understood that this happens only in a specific kind of muscle cells but not in all the muscles. In particular the first method that I described which is the DHPR receptor, ryanodine receptor interaction is how the skeletal muscles lead to calcium spark. But then where does this happen the calcium into calcium release? The calcium induced calcium release is known to happen predominantly as a predominant factor in the cardiac muscle.

Slightly different from the focus of this course they are interested in their skeletal muscles. CICR is something that is more pronounced in the cardiac muscle that does not mean that it does not happen in the skeletal muscle. In the skeletal muscle the most important mechanism by which this calcium is released is through the interaction of the DHPR receptors and the ryanodine receptors.

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So, with this we come to the end of this video. In this video we discussed what is a sarcomere and how excitation coming in from a neuron is converted into the build-up of calcium which will then further lead to a contraction in the muscle. Thank you very much for your attention.