**Biological Inorganic Chemistry**
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**Lecture 29**
**Module 06: Phosphate Metabolism and Cellular Signaling**
**Ca+2 transporting, binding and sensor proteins**

Good morning, everybody. So, today we will start again in that last part basically. So today we will just try to complete the lecture number 29 where again we will just bring the fourth metal ion starting from your sodium, potassium, magnesium and then calcium. So in terms of your phosphate metabolism and cellular signaling module, we will talk the corresponding calcium two plus is transporting binding and the sensing why this particular metal ion which is very important.

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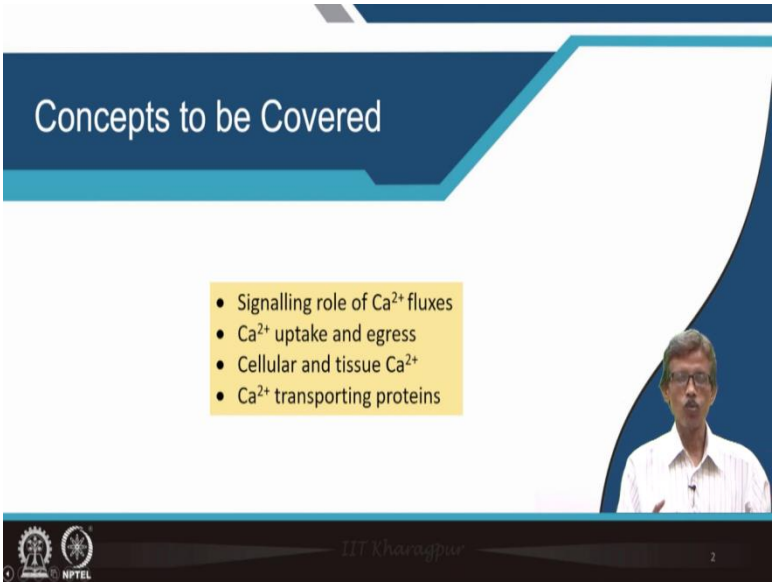


Because we take calcium from our food material and we can absorb it and we know also about little bit the homeostasis how that calcium impartment you can have in your body. So, how the calcium as well as the calcium interaction the coordination or binding can give a thing which can be considered as the calcium two plus fluxes, and whether that can influence your signaling, then we will talk about the calcium to uptake and egress, then cellular and tissue of the calcium the cellular tissue presence of these calcium and the calcium transporting proteins and also the sensing there.

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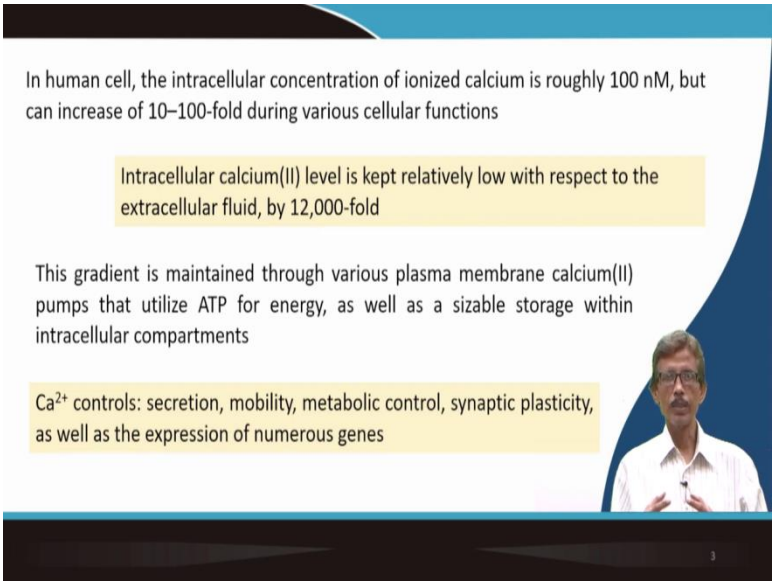


So, what we find that in the late all living human cell or the mammalian cell, the intracellular within the cell, what is the concentration of ionized calcium that means, we are always talking about calcium 2 plus not in terms of the corresponding one in the solid form in the mineralized form, because side by side if I tell you about the corresponding mineralization process or the biomineralization process of calcium 2 plus what you can understand is that we can talk about in terms of your bone formation, your tissue formation, who had the calcium is or the cartilage formation or teeth formation.

But when you have the presence of that calcium within our cell environment or within the corresponding liquefied environment, so, we find that about 100 nanometers of these ionized calcium, if you consider that there is an equilibrium between the mineralization process and the dissolution process from the bone material say, we all know that you can have iron and when you have the supersaturated solution, you can go for the crystallization.

So, this particular bone mineralization or the teeth mineralization process is also associated with the corresponding availability of a supersaturated solution. So, if you have a highly concentrated supersaturated solution, then further evaporation in that particular point can go for the crystals. So, this particular variation in all this concentration which is your supersaturated constant is an n which is not that we can find and there can be an increase in 10 to 100 fold the various cellular functions.

Already we have seen from our sodium ion days or the potassium ion days, we have seen that you can have two different concentrations within the cell and outside the cell. So, that means

there is a cell gradient. But in case of calcium, we will find some interesting thing that suddenly the concentration can be high there and due to that high concentration or the higher concentration gradient, it can go for some beautiful cellular functions particularly the signaling.

It can send signals to the cells or to the muscles or to the tissues and the body in a whole to go for some work or some functions. So, this within cell concentration of calcium to iron which you can detect also by different techniques, different analytical techniques or the physical methods are also very much available to find out the actual concentration what you can have within the cell, outside the cell, within that tissue and within the your muscle also, and sometime during the bone formation period also how the calcium concentration can work.

So, with respect to the extracellular fluid, the intracellular concentration is sometimes it is 12,000 fold higher than that of that thing. So, that is why a very high concentration of calcium ion within the cell is required for all these processes. So, quantitatively if we consider that that particular higher level of concentrations because it is very difficult to maintain that particular concentration.

So, some processes some biochemical or biophysical processes are there, which can be available for giving you that kind of high concentration or sometimes the highest level of concentration. So, when you maintain a concentration gradient, and you have the plasma membrane and the calcium ion pumps that is why we can bring that that we have seen that you can have the channels from moving from a higher concentration to the lower concentration, which is true not only for your sodium ions or the potassium ion, it is also true for the magnesium ions and now, we see is also applicable to your calcium ions.

So, while you move from one particular membrane side to the other side, if you go for a pumping mechanism, that means, you can pose the concentration from a lower end to the higher end that means, a low energy situation to a higher energy situation by utilizing the energy currency the phosphate energy currency in terms of your hydrolysis of the ATP molecule to ADP molecules will find that we can have the different level of concentrations and particularly within the intracellular compartments within the cell basically, you can have a higher concentrations of the calcium ion.

And now, we see that what are the things the biological things are by the activity can be controlled by the variation in the calcium two plus concentrations. So, definitely we can have

a diseased condition or an unusual concentration when you have less amount of calcium than that prescribed amount of calcium to be present within the cell.

So, basically that particular amount of calcium which is available within the cell is responsible for the secretion of different fluids, different solutions, the mobility of our knobs and mobility of our different muscles and tissues also, then, metabolic control the corresponding metabolism is our whole body, then synaptic plasticity that this knob synapses are there, and that synaptic plasticity is also required for your movement of the calcium and the accumulation of the calcium and finally, while you express some different types of genes, we have to go for the dependence on this particular metal ion.

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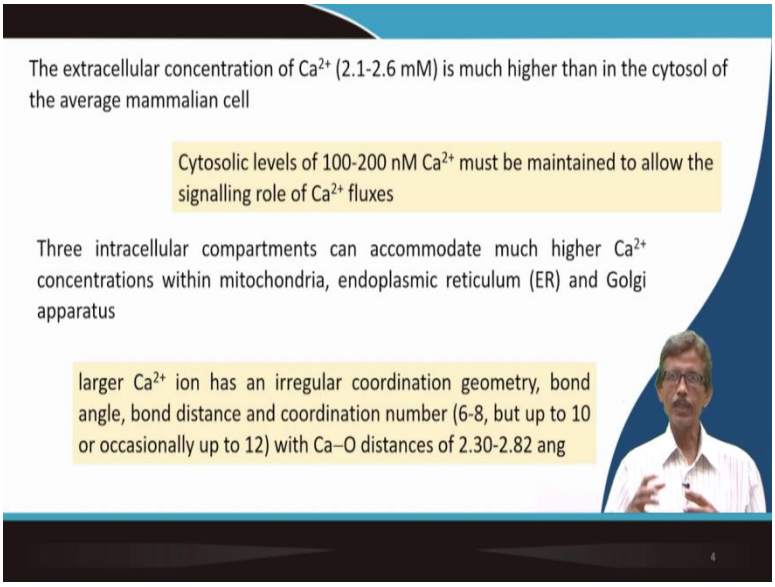


So, these metal ion they are for a very useful one and a very beautiful one in handling all these biochemical processes. Compared to that concentration, what we are talking about the within the cell concentration, your outside cell concentration is very less is only 2.1 to 2.6 millimolar and much higher than that in the cytosol of average mammalian cell, but it is higher than the cytosol average cytosol basically, of the average mammalian cell.

So, you always have the corresponding concentrations, because you have the cytosolic level of calcium concentration within a nanomolar range. So, is the millimolar range and the nanomolar range concentrations always we should have is have consideration, then you can have this to maintain that particular concentration and the signaling role of the calcium fluxes.

So, due to that concentration variation or the maintenance of that particular concentration gradient, you will find that the calcium can go for the coordination and that coordination can give you some signal and is not that calcium is doing something where it is acting like other metal ions like your iron, like your copper or like your nickel, it may not be your active side center, but when it is binding, the character of the protein is basically getting changed so, you can have some calcium bound condition and it is calcium precondition of those proteins and though are functionally different.

So, if we consider that we have within the cell you know from the corresponding structure or the corresponding drawing or the diagram of the whole cell, we know there are mitochondria, they are endoplasmic reticulum and Golgi apparatus. So, these are basically the three chambers within the cell. So, they can be considered as the intracellular compartments also because, these compartments are basically different pockets and these pockets can control them can take up many number of these ions.

So, if you go for enrichment of calcium concentration, we can go for a higher concentration of calcium within these pockets. Then we will see some interesting thing that okay the calcium is there the tonal groups will be available. So, these donor groups will come and try to grab the calcium ion as if you are supplied with a corresponding huge ligand envelope.

So, the ligand envelop is giving you the corresponding donor grooves and their donor grooves is basically trap the trap or the hole the corresponding calcium ion whichever is available from your site of salts. So, the larger compared to all other three the corresponding metal ions what we are considering right now, starting from your sodium potassium magnesium, calcium is a bigger one.

So, once it is a bigger one, you know that the size of the coordination environment will also be big. And once it is big it can accommodate more number of donor groups. So, it is not that when we find that iron you have is very difficult to get or change or increase the coordination number of iron from 6 to 7 or 7 to 8. But when you have bigger calcium and it is some time is distorted, that is why you had the irregular coordination geometry is not a regular one regular means, where you can have the corresponding typical geometry if you are having a four coordinate geometry you can consider it can be a tetrahedral geometry or a square planar geometry.

Similarly, you can have the regular coordination environment for five coordinate geometry, but if you go for at least six it may not be a true octahedral geometry because your calcium side is more or bigger. So, it can move from six to eight sometimes it can go up to 10. And occasionally in few cases only, it can go up to 12 which we basically find for the lanthanides the foredeck metal ions like dysprosium, holmium, Terbium and all these, so, these are bigger sizes.

So, this coordination number 12 is also very interesting. So, depending upon its interaction or the binding, it can So, different types of activities starting from its enzymatic activity to that of your signal processing or sending up the signals and you will see, since it is bigger the coordination environment is also being your calcium oxygen distances are beyond two angstrom average in an on an average only find that are an oxygen distance very kind oxygen distance will find that it will be close to two either it is 1.9 or 2.05 or 2.1.

But, you see here the bond distance is going up to 2.3 angstrom he is the angstrom you can write in symbol or you can add also the angstrom and then it is going to the maximum range is 2.82 which is in the range of hydrogen bonding interactions for the distances of the two bigger atoms.

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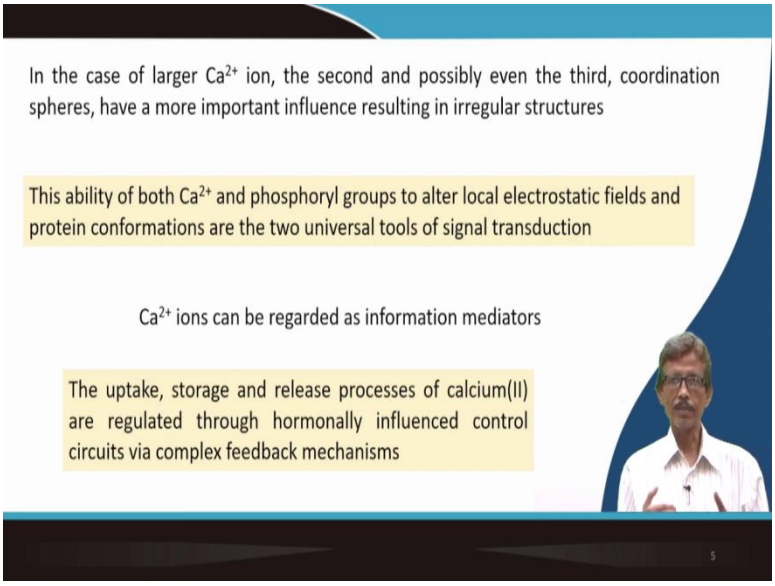


So, we are assuming that we know the ionic side we know the hydrogen sphere and also hydrated calcium ion or the Bayer calcium ion when it is there and you can have the second coordinate and sphere interactions or the third coordinate since we our interactions are there. So, what do you find that we know all that when you have a particular ligand say biacetyl

(())(12:59) then we call all dimethyl glyauxin, so DMG we know for the nickel binding the DMG is there, but you know that DMG what you can have the corresponding oxygen is there at the end before that you have the nitrogen.

So, auxin function, N OH function. So, if you have a typical N OH function and that N OH function if it binds to the metal ion through the nitrogen and you can have the OH the dangling or the pendant OH group which is true for your DMT molecule legal DMT complex as we all know. So, dimethylglyoxime or biacytel monoauxins, one monoauxin or two monoauxin which is diauxin.

So, when it is coordinating through nitrogen you are always free and if that OH it is not even free, but it is attached to hydrogen. So, after coordination to the nickel that is why we all know is a macro cyclic pseudo macro cyclic diagram or scrap or nickel DMG 2 that DMG H basically one hydrogen is protonated and another one oxygen is protonated and another oxygen is deprotonated.

So, then you can have the pseudo macro cyclic ring structure through hydrogen bonding interaction. So, that is nothing but your typical example of second sphere of coordination environment interactions. Sometime it can also bring some other ends of the protein chain through hydrogen bonding interactions. Sometime it is not available so, nuclear bases are there in water it will come and bind to your calcium center and that water we all know the oxygen is coordinating to your calcium center, but you have the OH bonds to H bonds and that OH function can be a very good hydrogen bond donor.

So, that can interact with the nitrogen, some available nitrogen side of the nuclear base or any other base material. So, you can have another hydrogen bonding interactions and hydrogen bonding network basically. So, that can also be considered in another level which can be considered as the third level or third chords in sphere.

So, you can stabilize that regular structure in that fashion not only the primary coordination, but you can have the secondary coordination as well as the third coordination environment. So not only calcium as we have seen in case of your magnesium that you can have also the phosphoryl group. So, if you bring those phosphoryl groups in terms of your ATP or ADP molecules, what do you find that the phosphate and ions the possible function and it is O minus groups can come and interact with your calcium center and interaction with those

calcium centers basically can alter the local electrostatic fields and the protein conformation and these two are basically therefore, some tools for signal transduction.

So, if we go for any kind of signal transduction, we can find that will have these interactions due to the presence of not only calcium two plus, but also for the phosphoryl function then we find that calcium ion can be regarded as an information mediator. So, if it is giving some signals, calcium is coming and binding to that particular center or that particular protein system then it can go for the corresponding mediation for the signal processing.

So, right now, what do you see here is that the uptake, the storage and the release the three things are there which are always true not only for calcium we will also see in the future that for iron also how we take up that thing that means uptake process from the food material, how you store it and how you release it for different purposes.

So, they are sometimes can be controlled if you bring other interesting molecule like hormones. So, hormones that they are and hormone influence control circuits are there. So, it is like electrical circuits or electronic circuits we call these the biological circuits basically, can have some mechanism where you can have the complex feedback mechanism so, if it is interacts in is there, like your reaction accent and the reaction, you are going to have the feedback mechanism that means signals can be transferred from one part to the other part of your body.

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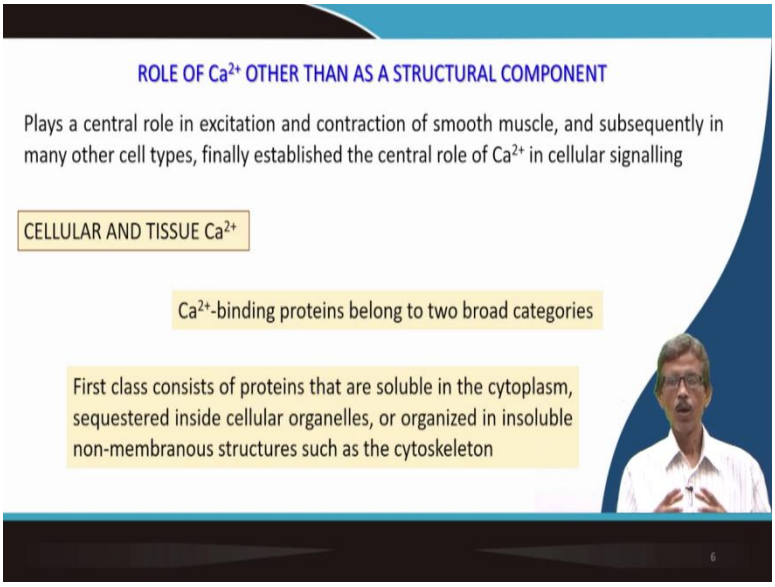


So, apart from that the calcium we know we are not talking here in terms of we do not have enough time to discuss about all about calcium because the calcium itself that we suggest

afterwards at the end also the calcium in biology, if you go for citing the Wikipedia page, so, everything for calcium, so, biological world for calcium, we are not going for studying the corresponding biomineralization process or the (())(18:11) formation like your bone formation or teeth formation.

So, we are taking apart that structural component we are just only going for the solution chemistry solution chemistry of all these calcium because we are talking some little bit complicated thing because these all these minerals and mineralization process are well known like the geology thing is several 100 years old thing like the mineralization and process also we are trying to know how the mineralization is going on.

But apart from that, if you have the typical signaling process the calcium is present, but you have your body is deficit in calcium the know right amount of signaling is there they are not there. So, signaling for every useful reactions basically, even for your mineralization process. So, they are playing some important role for what for your muscle movement for the different walks in your cell ties.

And that is why the calcium is very much important in giving you all the different types of signaling processes which can be available in cells. So if we now move that calcium not from bone and not from teeth, it moved calcium to the cellular and the tissues. So the cellular calcium in the tissue calcium, these are all solubilized calcium is not the mineralized calcium. So calcium binding proteins basically we can have now two broad categories where the calcium can go and bind not that that calcium, giving you a calcium carbonate, calcium phosphate or calcium sulfate and then realized with that of your other biological cartilage and all these things.

So the class or the first class or the class number one or two proteins that are soluble in cytoplasm and sequestered that means they are separated inside cellular organelles and organized in insoluble non membranous structures such as cytoskeleton. So, you just think all these in terms of your keywords, you should know that the calcium is related to your cytoskeleton, it is not the skeleton what we can have with regard to that of your bone and muscles, but, the cytoplasm related thing that you can have certain thing where you can have the involvement of the cytoplasm as well as the involvement of the calcium for the structure of these cytoskeleton.

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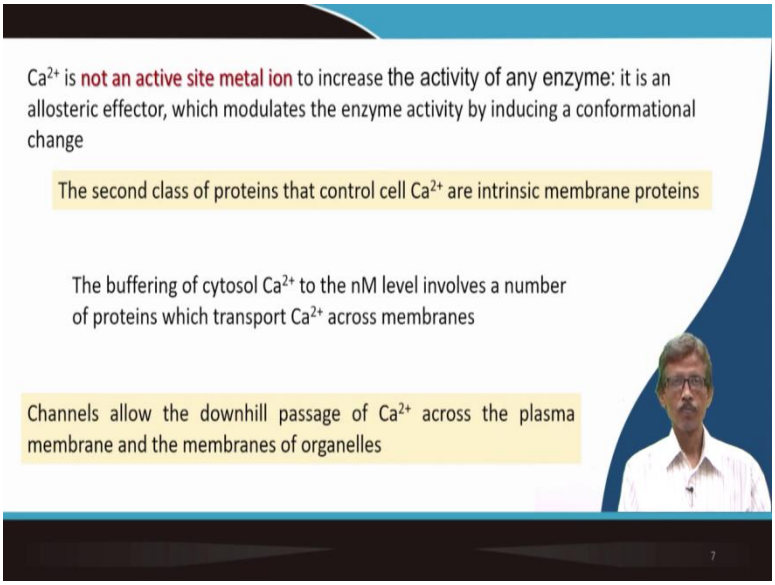


That means, the cytoplasm related some skeletal structure but, as I told you that is not an active metal ion that means, the metal ion is not sitting at the active site and showing some enzymatic functions It is only activating. So, which basically then increase the activity of any other particular type of enzyme. That is why we can consider these as an allosteric effector.

What is that allosteric effector? Allosteric effector is that some group is that it may or may not be a metal ion also; it can have the phosphoglycerate type of thing when you have the myoglobin, we will study all these things again, what is the allosteric effector and what is that corresponding function. So, when it is there, so, all other protein molecules can assemble through hydrogen bonding interactions and many other non-covalent interactions to give you a particular type of structure.

So, similarly calcium, it is showing coordination is not that it is not showing any coordination or only hydrogen bonding interactions, but, the primary duty of doing that calcium is your coordination then it can go for the secondary interactions through hydrogen bonds or the other tertiary interactions. So, this basically will modulate the enzyme activity and the conformational change.

So, calcium binding you have the conformational change and it will definitely go for your change in the corresponding activity of these enzymes. Then, the second class of proteins will control the cell our intrinsic membrane protein. So, one is of one type and another is a membrane bound type and then we can have the different level of concentrations of calcium

in the cytosol is a nanomolar, not millimolar. So, nanomolar level again we are considering because the concentration is very less.

So, some proteins will be available, which are sitting above the membrane and which will be responsible for the transport of calcium ions, what we have seen in case of your sodium and potassium. So, you have the pumps for calcium again and you have the channels for calcium again and we all know that you can have some downhill movement by the channels and uphill moment by the pumps.

So, the different organelles can have all these membranes and all these membrane can allow the passage of like your sodium and potassium ion passage of the calcium ions throughout these membranes are the membrane barrier.

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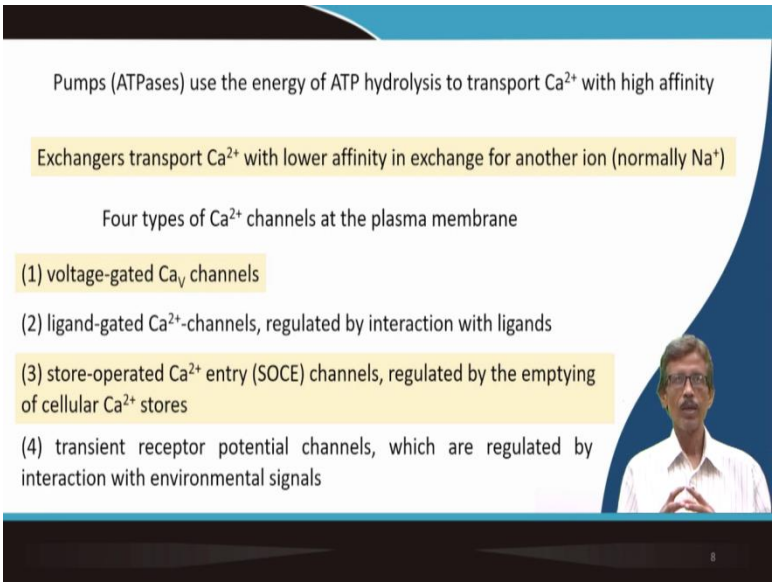


So, after channels you have the pumps, we have already learnt it we know now very well about the corresponding sodium and the potassium on where you have channel and why do you have the pumps and to run the pumps, the way we usually run the electrical pump you have to use the electrical energy. Similarly, to run the biological pumps or the calcium pumps, we require the use of ATPases, adenosine triphosphate hydrolyzed zinc agents there.

So, ATPases basically can hydrolyze and supply the corresponding phosphate groups as inorganic phosphate, but at the same time, it will give you the corresponding free energy and energy to run the system. So, for that you can have the calcium transport and can have the affinity then, we can have also something which can exchange between the two metal ions

already we have seen that we have the corresponding pumps for sodium ion. So, how the calcium pump will also work.

So, if you have the exchange at which can transport calcium two plus with lower affinity in exchange of another ion. So, you can have the movement of sodium ions as well as the calcium ions there. So, for that particular purpose, what we can have we can have the calcium channels at the plasma membranes, what are those types, there are four types. Already we know these things that is why we can quickly pass on this particular part that we can have the voltage gated one CFE channels, we can have the ligand gated channels similar to again like that of your sodium channels and palms.

And they are all we all know that if you have the interaction, but the mechanism is still there is not that whatever we have for sodium will be available for calcium. So, the nature has devised that particular mechanism in such a way that we can have the thing for the calcium as well. sodium and potassium then stored you have the storing mechanism that where you can store the uptake and the storage of calcium on the store operated calcium entry that how much we have already stored and whether it will allow the entry of the calcium ions or not that type of channel is SOC channels.

When you have the remove up all the stored calcium ions, that means, you are emptying your cellular calcium stores, then only your store can tell no you do not have any calcium in the system. So, you will let us try to have more calcium from there. So, that will allow basically these channels to open to take up more calcium to store.

Then last type is the transient receptor potential channel. So, you have can have the acceptor potential like electrical potential which can be modulated or controlled or regulated by interaction with some other environmental agents or the environmental signals or the signaling process.

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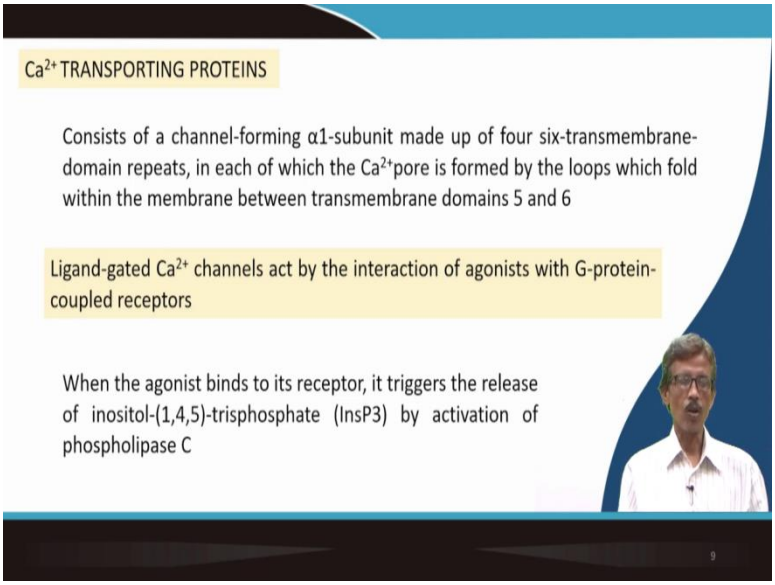


Then finally, we can see the transporting proteins. So, you can have the channel forming already we have discussed in detail for your sodium as well as the potassium channels can you can have the alpha one subunit. So, let us get to that basically where we have seen 1, 2, 3, 4, 5, 6 these are the bundle proteins that are available. So, here also six transmembrane domains are there and those are the repeating unit 1, 2, 3, 4, 5, 6 then another bunch of 1, 2, 3, 4, 5, 6 you can have and they can also form the loops, which basically go for the folding and in a particular domain such as domain five and six can go for this particular type of folding.

When you get the ligand which is following or which is controlling the gating mechanism, one particular protein we all know that G protein so, G protein can be coupled and you can have a different type of reception and G protein basically if it is available, it can only allow that particular channel to open and pass the corresponding calcium to go through when we can have some agonist which basically go against or sometime it can help antagonist go against basically antagonist and agonist is the helping thing while binding we can release some inositol or inositol triphosphate InsP3 to go for the activation of the phospholipases.

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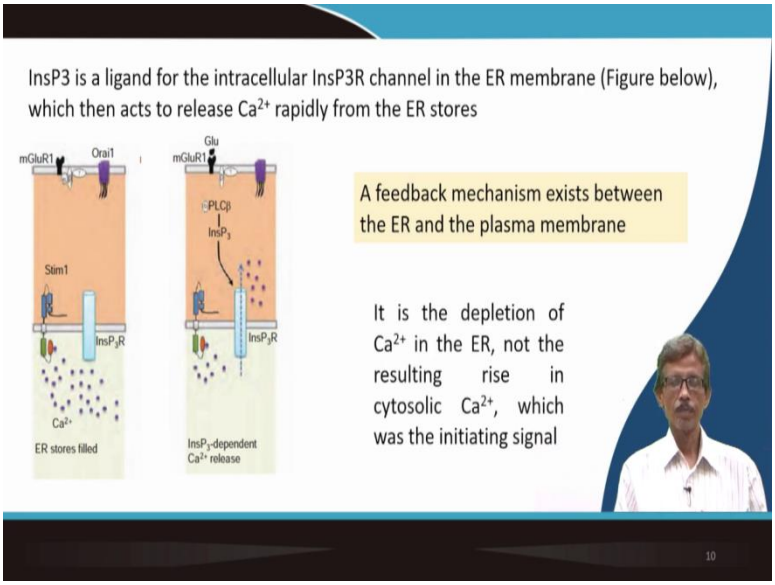


See so, one another group of important molecule. So, InsP3R channels there are and it is there in the (())(27:41) thing for the membrane thing which then act to release the calcium two plus rapidly from the ER stores. So, if you have the ER store there and which is filled, then InsP3R will be available. So, InsP3R is the channel which will allow to pass these calcium ions from one side to the other.

And while doing so, you can have a feedback mechanism and that mechanism is basically responsible for modulating your ER mechanism or you are storing it in the plasma membrane which is available. So, you see we are emptying this group. So, you are having this calcium at the bottom part and those calcium have been moved towards the top and you can have the corresponding mechanism where you can have InsP3 is working and they are for the calcium release.

So, this particular calcium which is there in ER and rise in the cytosolic calcium two plus and that basically initiating the signaling process or the signals.

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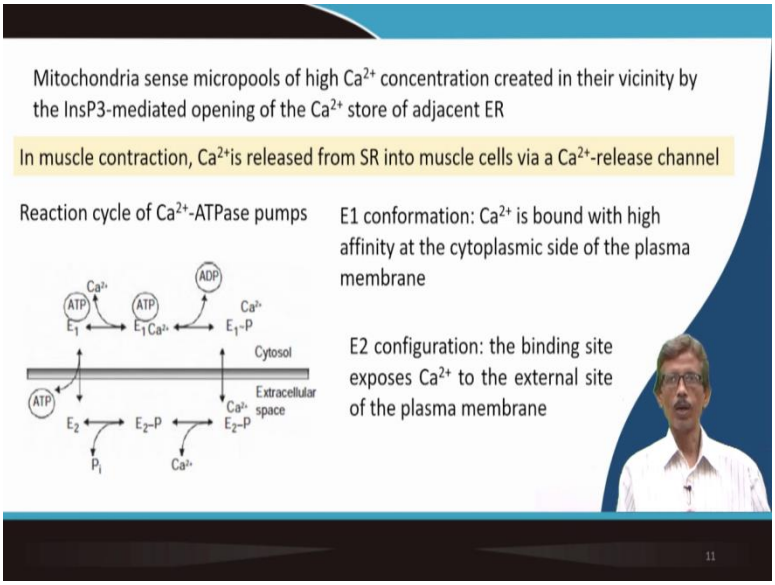


So, mitochondrial sends high concentration of calcium and your corresponding place where you can store is mediated by some other important molecules, then for muscle contractions also we release some calcium ions and the calcium ions can sense and we can have the sense for the corresponding muscles, then the reaction cycle for ATP as pumps also we can have you can have this channels like E one and E two and E one and E two already we are discussed somewhere earlier that similar type of thing we can have for these types of cytosol and intercellular space and the other part.

So, one particular conformation which can be modulated by calcium coordination and which can have the higher affinity you want is one particular confirmation which can have high affinity for calcium binding while the other the two may not have. So, if it is not their calcium binding potential is less. So, it will release the calcium ions and the external site is there and in the through the calcium plasma membrane it will pass.

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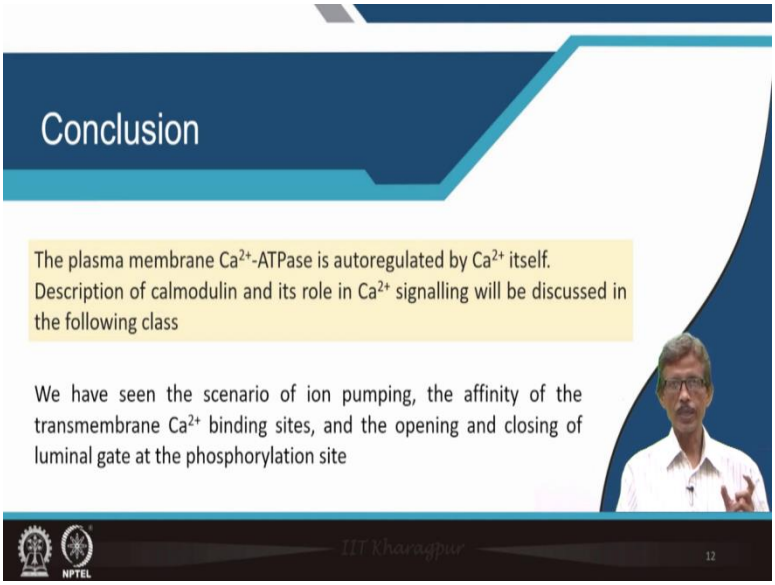


So, by studying all these things, what we have learned from this particular class is that, that you had the plasma membrane and calcium two plus ATPases are all parroting and they can monitor the corresponding calcium two plus concentration and one important group of molecules that we will discuss in our next class next day that calmodulin calcium related some biological protein molecules. So calmodulin and its role what is there for calcium signaling and in the following class definitely will discuss and the scenario for iron pumping we have seen and the affinity for the transmembrane calcium two plus binding sites, we will also see an opening and closing of the luminal gate and the phosphorylation site.

So, here also like your sodium and potassium, the phosphorylation and that a corresponding release can also take place, but if you focus your attention more on the calcium function, we can little bit ignored about that phosphorylation process because that we have already studied earlier.

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So, references just you go to the page of Wikipedia for calcium in biology page, and then the book of Crichton. So thank you very much for your kind attention.