Inorganic Chemistry of Life Principles & Properties
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Lecture – 17
Role of Alkali, Alkaline earth elements in life – continuation

Welcome you to the next class of the Inorganic Chemistry of Life Principles and Perspectives. Let us just have a recap of what we were doing in the last class. In the last class I was explaining you about the metal ion binding affinity of alkali alkaline earth ions towards the cellular kind of a proteins, we have seen calcium 2 plus mines much more stronger and the magnesium 2 plus, which is which binds stronger than the potassium plus which is in turn greater than that of the sodium plus.

So, above all these 4 sodium plus is the weakest and calcium 2 plus is the strongest and their affinity would make a difference in activating the proteins accordingly and that is what we have seen in the previous class.

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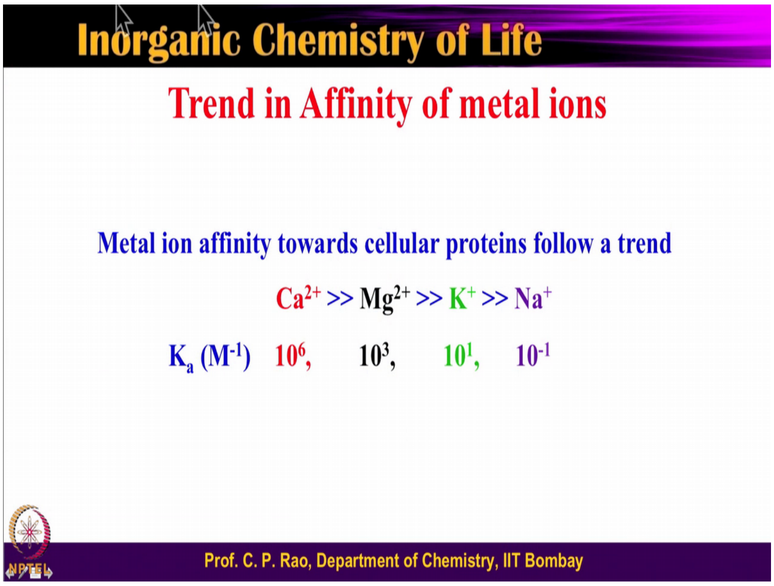

So, calcium amount in the range of 10 power 6 mole inverse 10 power 3 for magnesium, 10 per 1 for this and sodium 10 power minus 1. So, about 1000 fold, a 100 fold and a 100 fold difference.

So, you have a quite a large fold difference between sodium and calcium and accordingly this thing will reflect in their activity of the enzymes.

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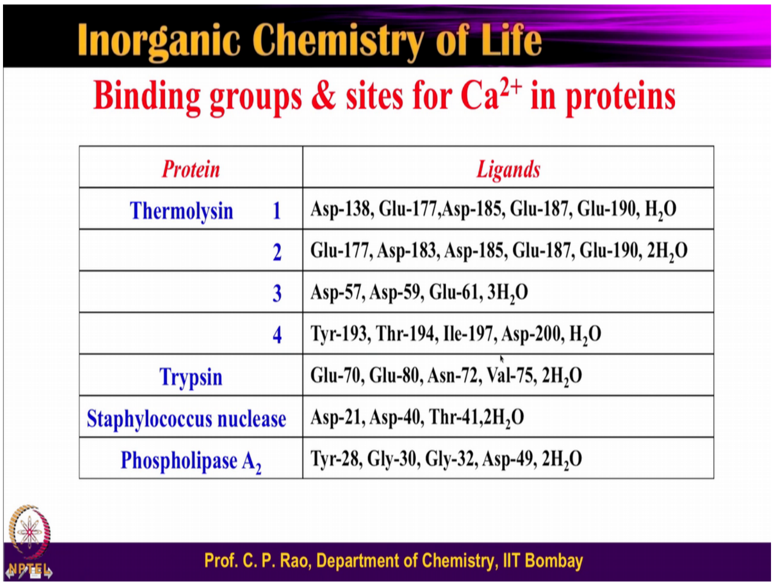

Now, next point, let us look at a few proteins of calcium; let examine how these are bound calcium 2 plus is bound. So, here is a table where I have a crystal structures of a different proteins or the calcium proteins. So, and in this you can see 1 2 3 4 refers to calcium site 1, calcium site 2, calcium site 3 and calcium site 4. So, there are 4 calciums are there and if you try to examine this, you would say aspartic, glutamic, aspartic glutamic water aspartic glutamic like that.

So, many things so, if you go to the trypsin glutamic glutamic aspergin etcetera and you go to phospholipase. So, this is the one where you have a less number of a aspartic or carboxylic.

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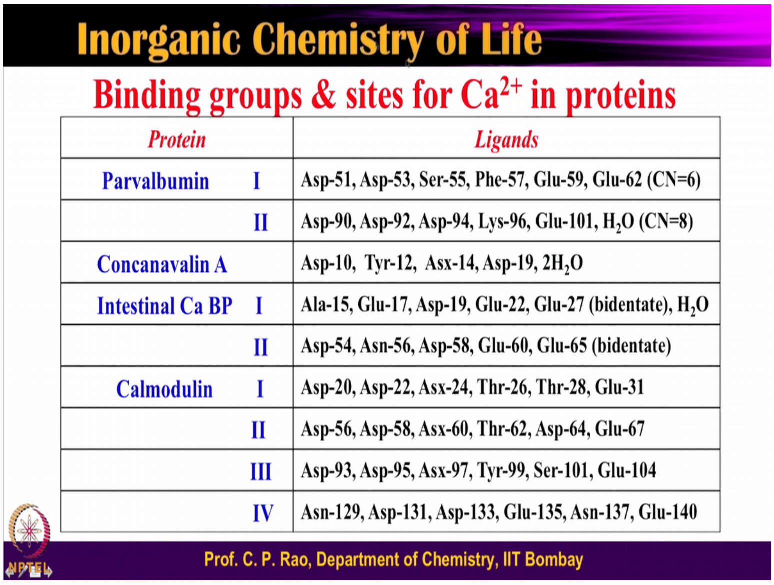

Protein		Ligands
Parvalbumin	I	Asp-51, Asp-53, Ser-55, Phe-57, Glu-59, Glu-62 (CN=6)
	II	Asp-90, Asp-92, Asp-94, Lys-96, Glu-101, H_2O (CN=8)
Concanavalin A		Asp-10, Tyr-12, Asx-14, Asp-19, $2H_2O$
Intestinal Ca BP	I	Ala-15, Glu-17, Asp-19, Glu-22, Glu-27 (bidentate), H_2O
	II	Asp-54, Asn-56, Asp-58, Glu-60, Glu-65 (bidentate)
Calmodulin	I	Asp-20, Asp-22, Asx-24, Thr-26, Thr-28, Glu-31
	II	Asp-56, Asp-58, Asx-60, Thr-62, Asp-64, Glu-67
	III	Asp-93, Asp-95, Asx-97, Tyr-99, Ser-101, Glu-104
	IV	Asn-129, Asp-131, Asp-133, Glu-135, Asn-137, Glu-140

And look at the other a table the continuation of the table parvalbumin, there are 2 couple the calcium centers aspartic aspartic etcetera etcetera aspartic aspartic aspartic glutamic and concanavalin. So, you have. So, we have seen several calcium 2 plus binding proteins; proteins like thermolysin, trypsin, staphylococcus nuclease, phospholipase and then we have also looked at parvalbumin, concanavalin, intestinal calcium buffer protein and calmodulin.

So, we have seen good number of proteins to judge and justify the kind of a binding that we have. So, what is the majority you see among this? So, the majority in all this is calcium 2 plus is bound to as many number of carboxylic groups as possible and some water and a few peptide carbonyls primarily these are the ones. So, you can also see some of the cases that coordination numbers here, coordination number 6, coordination number 8 is the same, protein 1 center is coordination number 6 other center is coordination number 8.

So, you have coordination number 6 7 and 8 mostly that is one carbon point. The second carbon point is that the carboxylates are the major binding residues. So, carboxylate is is the one which is stabilizing the calcium that is what we looked at or the why the magnesium 2 plus is not able to activate, the proteins of calcium inside the cell in spite of the fact that the calcium 2 plus concentration is low and magnesium 2 plus concentration is very high still they will not better of the proteins of the calcium because of this particular reason.

The reason we have already seen that earlier aspartic glutamic, you have a post translational modification of introducing carboxylic groups and such carboxylic groups are responsible for binding to calcium. And we could see here example from all these 7 8 different proteins that we have examined, several calcium centers we have examined the maximum binding is from the carboxylate and sometimes carboxylate may be more in dentates sometimes it may be bidendate those kind of interference is possible, but nevertheless this is the carboxylate rich.

So, therefore, the carboxylate rich is the main point to differentiate the calcium verses the magnesium. Therefore, the magnesium ions cannot activate the proteins or calcium. I hope you understand the difference between the magnesium and calcium. Then let us look at the some proteins in little more into calcium modulation.

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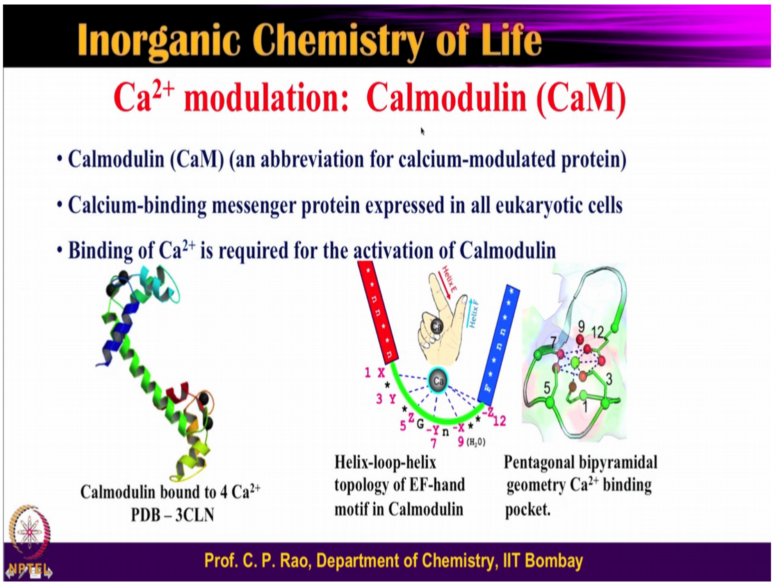

So, cal and modulation is modulin, so, Calmodulin. Calmodulin is nothing, but the modulation of the calcium or control of the calcium ok.

So, calcium modulated protein ok. Calcium binding messenger protein expressed in all eukaryotic cells that is the absolutely present in almost every eukaryotic cells. So, binding of a calcium 2 plus is required for act the activation of the Calmodulin this is important. Just look at a one of the Calmodulin over here . So, the Calmodulin over here you have a calcium binding center here and there are other calcium binding centers over there and if you open up this region at C is which is shown over here, the this is 1 helix this is a helix.

So, helix, helix the red helix, the blue helix and the green is a loop the green is a loop. So, in this loop you can see count 1 2 3 4 5 6 7 coordinations are directed towards the calcium. So, it is a 7 coordinated calcium in the loop region of the Calmodulin and that is an important parameter to be noticed. Now you can see the same in a little better clarity your calcium is here in the center, they are all this reds the fine in 1 plate and 2 in the other it is called pentagonal bipyramidal.

So, in Calmodulin calcium is bound like a pentagonal bi bi pyramidal kind of a structure. So, I hope you understand things in these. So, how the calcium binds to the calmodulin; because in turn the Calmodulin is involved in a interacting activating various enzymes as well and let us see in the next slide.

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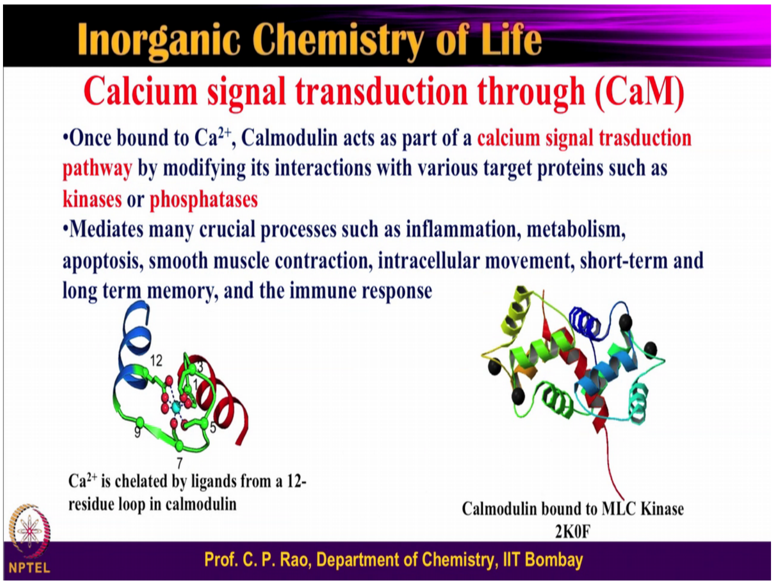

See once bound to the calcium 2 plus the Calmodulin it is a part of part and parcel for introducing the signal transduction pathway.

So, therefore, the calcium introduces the signal transduction pathway, and how it does that? It does because it modifies it is interactions with various targeted target proteins.

What are the kinds of proteins that it gets it is targeting? It is targeting in kinases targeting in phosphatases. What will happen, what is the kinase, what we learned kinase means? Kinase means phosphorylation. So, phosphorylating enzyme, phosphatase means phosphate hydrolysis phosphate removal hydrous enzyme.

So; that means, when the calcium binds the Calmodulin and it brings a kind of a signal trans transduction pathway by interacting with a variety of target proteins and these target proteins are nothing, but kinases and phosphatases; that means, entire business here is adding a phosphate, removing a phosphate phosphorylation dephosphorylation; phosphorylation dephosphorylation; why you think? Means when you phosphorylate a protein, the protein conformation will change in protein properties will change. When you dephosphorylate similarly the protein conformation and the properties subsequently or consequently changes.

So, that is what is an important aspect therefore. So, though the calcium is binding to this, it creates all these impulses kind of thing. So, that is signal transducing pathway ok. So, as a result of such a kind of a manipulations done by the calcium concentration or calcium binding to calmodulin. So, there are variety of processes in our body, which we are aware of inflammation we know metabolism, apoptosis, muscle contraction, intracellular movement, short term and long term memory and the immune response.

So, for all of these functions of a body, the calcium Calmodulin role is very important via kinases and phosphatases via kinases and phosphatases ok. So that means, the signal transduction is takes it is own path going via kinases and phosphatases . So, here is the one where the calcium 2 plus is chelated by the ligand of the 12 residue loop, we have seen in the previous slide you can see once again over there and this is the calcium. And this protein now it can activate kinase we said it will activate kinase it will activate phosphatase, it will deactivate also when it comes out.

So, let us say kinase MLC kinase MLC is not important it is a kinase. So, the kinase how it is? Now look at this very carefully, there is one alpha helical a loop alpha helical, a loop alpha helical, a loop alpha helical that is your MLC. And you see inside there are 2 dark spots here and then alpha helix green alpha helix, red alpha helix blue and this particular 2 ions this is nothing, but Calmodilin. So, this Calmodulin just embraces with that of the kinase.

Now, the kinase gets activated. So, you understand there are 2 proteins in this, one is you just follow what I am showing here, this is one protein and the that is the Calmodulin and the outer is the other which is the kinase. So, kinase and Calmodulin interact together to activate the kinase part of it with this, that is how they modify they target the enzyme such as kinases and phosphatases. As a result of that kinase will do phosphorylation, phosphatase will do dephosphorylation and then. So, that is that is where the properties of the proteins will change basically essentially I hope you understand.

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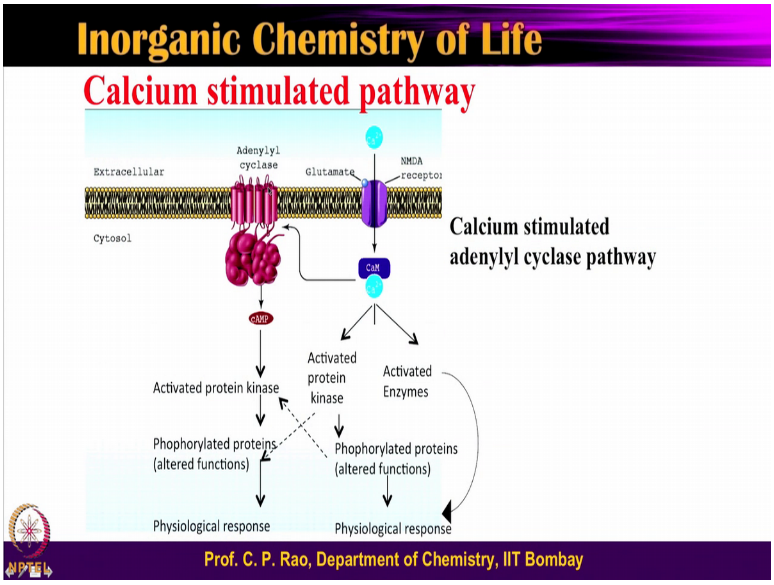

. So, the same thing let us see in a slightly different way. So, when the calcium binds into these things, then it will activate activated kinases or activated enzymes. So, once that kinase is activated, it will add phosphate groups to various proteins. When it adds the phosphate group groups to various proteins the protein functions will change. So, therefore, the entire story of this not necessary to understand each and every part of this, whole all that you need to say is that the calcium through the Calmodulin interacts with these proteins called kinases and a phosphatases that will induce a path of a reactions. So, therefore, calcium these are all called Calcium stimulated pathways.

So, in this particular case example is Calcium stimulated adenylyl adenylyl cyclase pathway. So, like that you have several; what one needs to understand from this? It will activate a kinase the carries will add a phosphate group to proteins and the phosphate group is added, then the properties will changing and some other proteins let us say a phosphate proteins if they do it that; that means, phosphorylate a phosphate hydrolysis will be activated that will be in some other case.

So, example is just shown over here, this is what we were talking about calcium signal transduction pathway. This whole thing is calcium signal transduction pathway via are activating deactivating the kinases and phosphatases.

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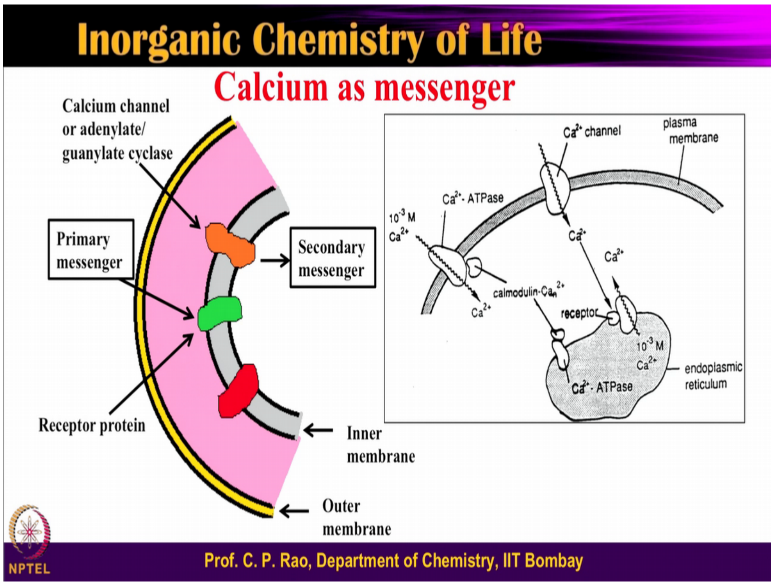

Now, let us look at a calcium where it binds, there will be some change. So, where it binds if the change transfers from there it is the primary kind of a messenger. At the other hand the calcium binds here and then it is transported to this and then there is some signal comes out or some message comes out or some response comes out then that is called secondary messenger understand that.

So, binding is over here, response is coming from over here. So, that is secondary messenger that is because, this binding of this will go through some transformation, that will activate one more thing and the signal comes. It is note that direct binding of the calcium bringing the signal that is called primary messenger part of it and if it goes through via cycles and then gives the response, there it is the basically the calcium as a secondary messenger. So, primary is coming activating this one secondary giving a signal or of this one.

So, actually it enters here, it activates here and gives the signal. So, therefore, entry and the signal are 2 different process that is the secondary messenger. So, you have a outer membrane is a yellow portion, that the inner membrane you have the gray kind of a portion such that you have and that is what refers to. So, when you have an interaction the calcium at the outer membrane and if the signal comes from the inner membrane that is what is the secondary messenger of the calcium.

So, calcium can give a strike straight away response, it can also give a response through which is called secondary messenger properties. The same thing is shown over here where you have a calcium entering into that, calcium goes through all this that gets into endoplasmic reticulum. So, therefore, that is where a thing. So, all that we understand from this is, calcium can act as a primary messenger it also can act as a secondary messenger. So, therefore, now you have seen calcium can activate Calmodulin and do a large number of phosphorylation dephosphorylation kind of things, calcium can give a primary messenger output you can also give secondary messenger output.

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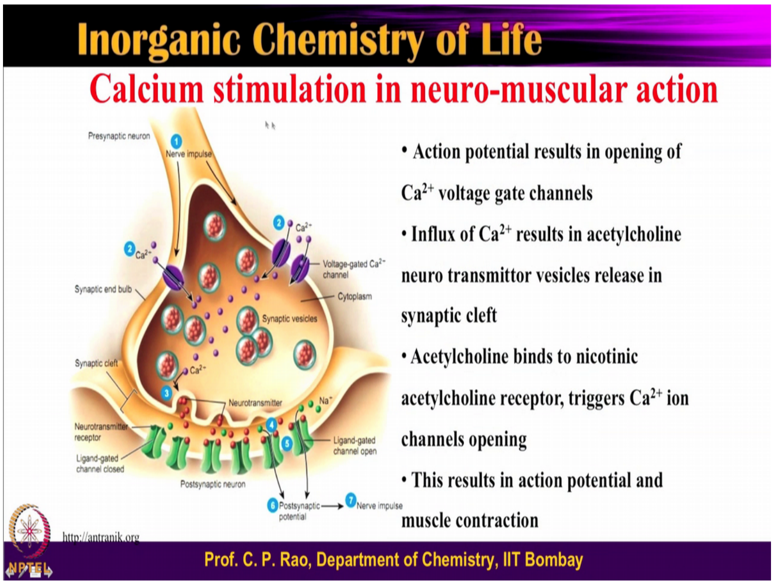

Now, if you put all of them into one action you will get an example, example of calcium stimulation in neuromuscular action. So, neuron versus the muscle interface. So, at the neuron versus the muscle interface, the calcium plays a role in terms of the calcium in terms of the muscular contraction or muscular activity. So, this is because there is some action potential, which results in opening of the calcium 2 plus gate channel and once that is opened here is a here and that will do bring an influx or the calcium 2 plus, and this result say this brings in influx you see that these are all calcium coming in and this influx of the calcium 2 plus results in the acetylcholine neurotransmitter is a acetylcholine is a neurotransmitter and; that means, it generates the signal of the acetylcholine.

So, that is the primary and then vesicle these vesicles are release in the synaptic cleft. So, this part is the synaptic cleft. So, so you have a calcium coming in, then the acetyl choline neurotransmitter coming in and that enters into the synaptic cleft and then something comes out. So, acetylcholine binds to the nicotinic acetylcholine receptors here at this stage. At this stage it will bind to the receptors, acetylcholine receptors and that triggers the calcium 2 plus ion channels to open.

So, the all these results in a action potential and this whole thing will result in a muscle contraction. So, now, you understand a primary signal effect and the secondary signal effect, primary messenger secondary messenger. So, calcium coming into that releasing the acetylcholine the acetylcholine reaching this region of the synoptic region and where this will basically bind to the receptors of the acetylcholine and that will result in flow of the calcium ions, this and which will change the potential or a action potential and that will make the change in the neuro muscular aspect or muscular a contraction.

So, this is just to demonstrate how a primary and secondary you know signals, a primary and secondary messenger signals released by the calcium binding or calcium release is to demonstrate that this example is taken not to teach the biology of neuro muscular action.

The idea is not to teach the biology of nuclear neuro muscular action, but to say how a metal ion flow or metal iron concentration can trigger many things. As you can see here the initial input of influx of calcium generates the acetylcholine neurotransmitter, and the and this neurotransmitter will bind at the synaptic cleft to the receptor, and this will open the gate or channel and that will change the concentration of the calcium and thereby you have a action potential changing .

So, you can see that primary messenger effect as well as the secondary messenger effect, this is very interesting there are hardly a examples of this kind in the bioinorganic chemistry or biological inorganic chemistry of life at all.

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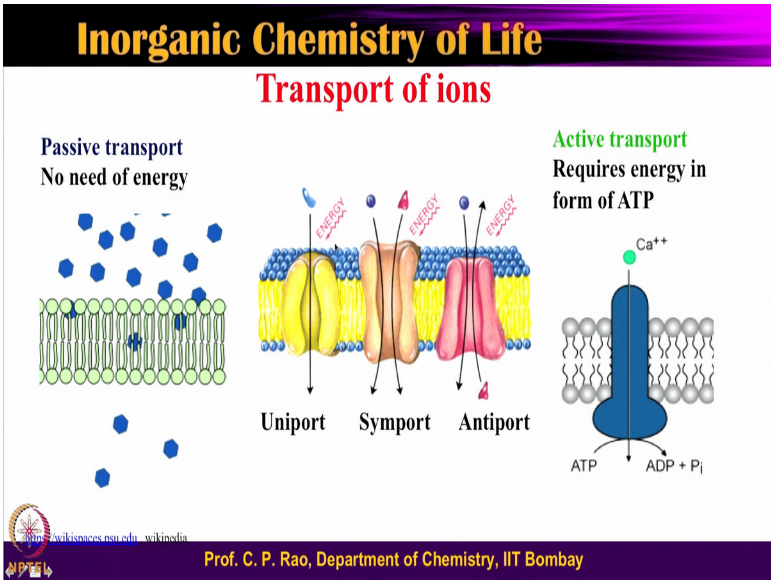

So, this brings into the arena where we have seen the ions going through. So, the ions going through or are giving some messenger properties. So, therefore, one needs to look at the transport of ions also we have seen earlier the concentrations of the sodium outside inside, concentrations of the potassium inside and outside, concentrations of the magnesium inside and outside similarly calcium.

So, that also we understood that one needs to have mechanism in the biological systems to to maintain their concentrations. All this brings it a phenomena called transportation of ions transport of ions. Now let us look at the transport of ions particularly the transport of alkali and alkaline earth ions. When you transport something do you need energy or not, I am sure you know when you want to transport anything you need energy. So, you hire a vehicle the guy will use the petrol and then transport your things from one place to the other obviously, like this.

Ah suppose you know how to pay for it you want to carry yourself, but your body energy also is there. Now take another example take a there is a there is a quite a good flow of water and you keep a tire and sit on this and that moves do you need energy there, no there is no energy required there. So, there is certain transpose. So, you are, but you are moving from one side in a river to other side as per the flow of the river. So, therefore, there is no energy put by you, but in the other case when you carry something you are putting your body energy of biological energy or when you carry it by a transporting vehicle, then you are using in the form of fuel.

So, therefore, you have transport processes, where energy is involved and there are also transport process made energy is not involved. So, just now I said that there is a flowing water in river and. So, you just take a tire and sit on top of that. So, you therefore, you are floating because the tire and the water surface and the water surface you move, without any of your effort there is no energy that is being spent. So, similarly transport of ions in the biological system also has got both these kind of things. So, those which do not require energy, but ions are transported, those which require energy also ions are transported very important we have to look at it.

So, transport of ions is the biological systems can be done without spending any energy oh or can also be of course, done with the spending of energy. Whenever we say talk about the energy in the biological system it is ATP what is ATP synthesis; that means, energy is synthesized, ATP hydrolysis energy is consumed. So, whenever you have used your energy; that means your ATP is hydrolyzed and whenever you have gained your energy means you have synthesized the ATP.

So, ATP synthesis ATP hydrolysis in fact, this kind of a thing, which also used in transporting or phosphorylating things is the maximum kind of energy that is being used in our body system. So, body continuously synthesizes continuously uses ATP ok. Now let us come to the how can you have a transport of ions without spending any energy. If it can be there that is called passive transport and if you require energy it is called active transport how can you have a transport without energy? I am sure you must have studied a very basic electricity experiment, that is you have 2 ends of the 2 rods connected by electrical circuit and where you apply a potential from one and one of the electrode and you can connecting in the connecting wire you put an ammeter you can see the current is flowing.

So, from a high voltage to low voltage with the current flows, similarly you take a huge rod heat on one end; let us say you have taken 1 meter iron rod and you heat only on one end, you take one end and heat it up in a in a flame and it is temperature is very high and you check on the other end slowly, you would start seeing the other end also start getting heated up even if you are stopped your heating on this side. So, this is. So, you are not heating that side, but the temperature is raised. So, how the energy heat energy is being flowing without putting any kind of energy barrier and that is because heat flows from high temperature to low temperature, current flow flows from higher potential to the lower potential.

Similarly, ions will flow from a higher concentration to lower concentration, after all ions having a charge higher concentration means higher potential. Ions which are having less number of ions less concentration therefore, less potential therefore, you have a greater potential, you have a lesser potential therefore, the ions are dragged or a from higher potential to the lower potential well that is what the driving forces. But no energy is spent, I hope in this example of the current flowing between the 2 you know systems, where the potential difference is maintained and also heat flowing between a 2 ends of a rod, where the temperature difference is there then this flows without any kind of energy.

So, similarly the ions which are having your greater concentration greater flux and these ions will move towards the lower concentration because that will be a lower potential. I hope you understand ions can flow without the energy of course, the ions can flow with energy for example, here example shown over the calcium going through all this how do we know it is it is having the energy? We know because we know because a ATP is used and ATP is hydrolyzed to ADP and phosphor inorganic phosphorus is referred as pi. In the entire course when I show pi means phosphate, it is roots it is also called inorganic a inorganic phosphate. Biological cab is generally referred to that as a foundly as a inorganic phosphate ATP to ADP 1 phosphate is less.

So, phosphate is hydrolyzed ok. So, that is we are thinking now. So, this we have started talking about the transportation of ions without the energy with the energy consumption. Now see some few things, there is some ion let us say here, this ion going through the membrane going through one side. Suppose if the only these ion goes from this to this it is called uniport. Uniport means one direction transport and here there is an example you will understand this by the there is an arrow for this, which is shown over this side and there is an arrow for this red one so, over this side.

So that means, as these species goes in this species will also go in. So, as the blue circles go in this red triangles will also go in so; that means, both are going from this side to this side that is called Symangistic transport either would in short form it is called symport symangistic transport called Symport. So, a is going in this direction b is also going in the direction, because of the a is going b is also going in other words the transport of a is coupled with b and such a kind of transports are called these imports.

Now, there is the next example exactly reverse this one is going in this direction, this red is going in the other direction so, but these are coupled this the a spherical one going in this way from outside. So, inside and this red one going from inside to outside these 2 are coupled and this is called antiport because the directions are different. Here symport because the directions are same and here only 1 ion uniport. So, you can have a uniport, you can have a symport, you can have a antiport ok.

So, these are all some things why I am telling is, all of these are observed in biological systems. Just you will see in a while the examples for a many of these or most of these are all of these ok.

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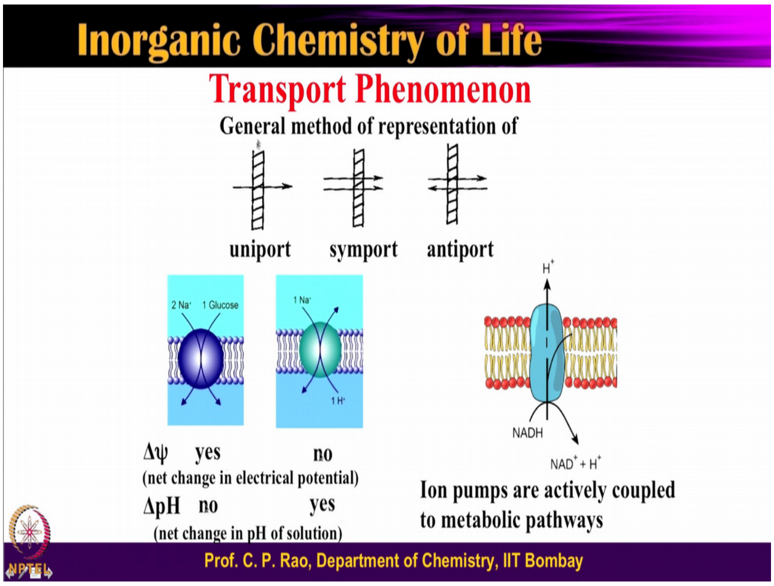

The same thing is shown over there in another depiction uniport this, you take this a hatched line as the membrane and a left side is the outside right side is the inside. Going from this to this one ion going uniport, 2 ions 2 different ions are going in the same direction symport, one ion going in this direction another ion is going in the other direction is called antiport it can be ion, it can be molecule, it can be any species it is not necessary only ion. So, this transport could be any of these things to.

So, same thing is shown over here, when you talk about the sodium ions going inside that will also take glucose. If 2 sodium go ions or goes inside it also takes 1 a glucose here this is a actual example, that change in the electrical potential in this and. So, then here you take one sodium inside and from inside you take one proton inside, what is happening? One positive charge came inside, one positive charge go went outside. So, what does this mean? The charge no change in the charges.

So, no a net change in the in the case of the this is no net change in the potential ok. So, 2 cations are coming inside one neutral molecule therefore, potential is changed because the si function will change here, 1 sodium cation came inside, 1 cation go went outside. So, therefore, no change here there are no protons changing. So, no pH change; here the protons is changed. So, pH is change. So, these also got in interchanged ok. So, what we have to say here first this thing is yes and this is no, and this is no and this is yes ok. So, you can understand you can change even the pH 2 o, it can change the potential only the ions which are showing that we will we will have this one.

So, 2 ions going in one glucose molecule therefore, the potential is different. And a one ion going in this direction another equivalent charged ion going outside no change, but since it is a proton which is going outside the pH will differ from inside to the outside ok. So, therefore, so ion pumps are actually coupled to metabolic pathways, which I will explain later on when I come to the sodium potassium at pH etcetera or calcium magnesium (Refer Time: 30:02) ok.

So, there is these are a energy coupled processes ok. So, here it is idea is to say no change in the potential, no change in the pH there is no change in the potential sorry. In the first one change in the potential, no pH change the second 1 no change in the potential, but change in the pH.

So; that means, this ion transport is not just a simple phenomena and this particular phenomena is taken, which brings a lot of changes in the properties of this and therefore, the properties of these things are vanished in this ok.

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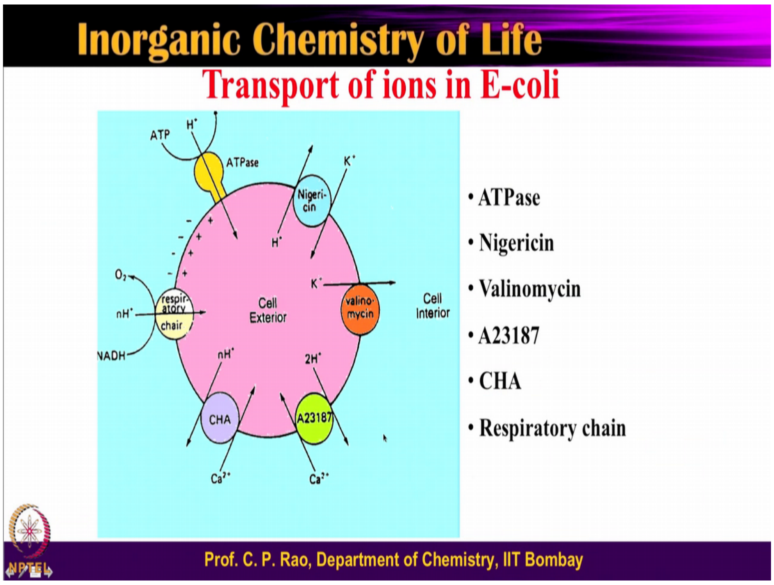

So, you can see coupling in E-coil simple a simplest organism E coli. So, in the E-coil you can see let us say this is a E-coil surface, then you can see here a something coming in here the H plus is coming in here.

So, you can call this as a uniport and here H plus is going out K plus is coming in what is it what do you call this one? It is called antiport it is called antiport. So, potassium is going out what do you call this? Uniport and here 2 protons are going out a calciums are going in. So, this is again antiport and charges 2 charges in 2 charges out no net change in the potential, but because 2 protons are going on this process can change the pH similarly calcium with this. So, different processes that you can talk about .

So, as you can see some other process will change the potential some of them will change the potential, and the pH some of them will not change the potential, but changes only pH. So, therefore, if you have a system where all of these are coupled together, you you can see how complicated an ion transport or molecular transport system in a human. This is only for one cell is a E-coil small cell.

So, the ATP is nigericin valinomycin A 2 3 1 8 7 cha respiratory chain these are the items that you have, all that you need to know is what is going in what is coming out what will happen? Will there be change in the potential, will there be change in the ph. So, that is what I explained you can do your own exercise. So, after this we will continue with the transport phenomena in the next class.

Thank you very much.