Biological Inorganic Chemistry
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Lecture 23
K+ Channels

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Hello, everybody. So, good morning once again, and we will just again, talk about the business involving the two fundamental metal ions, the sodium and the potassium ion, what we all know chemistry wise from our school days. So, in this Module number 5, we are talking basically on ion channels and the pumps, and these ion channels and pumps are basically, we are focusing our attention only right now on two like that of your sodium ion and the potassium ion, but we can have also afterwards and the dependence also with the calcium ions.

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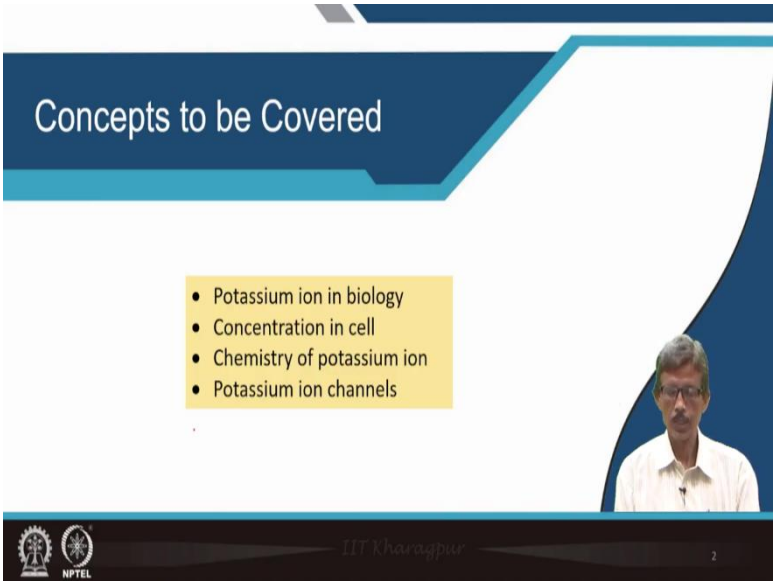

So, this lecture number 23 is devoted to only the potassium channels. So, let us see how we can understand regarding this potassium channel. So, a little bit we should know about the potassium ion in biology. So, the importance in the biology, even you go and search in the Wikipedia page, we will find that a huge page devoted to the potassium ion and its importance in biology.

Then the relative concentrations basically, that means, the intracellular and extracellular concentration of these ions, which are available within the cell and outside the cell that is also important to generate the corresponding electromotive force also. And, occasionally, we will compare all these things to that of our typical reactions of the potassium ions chemistry wise. And finally, the presence of these potassium ions in the different channels, how the channels is going, and how the channel structure looks like, and all these things.

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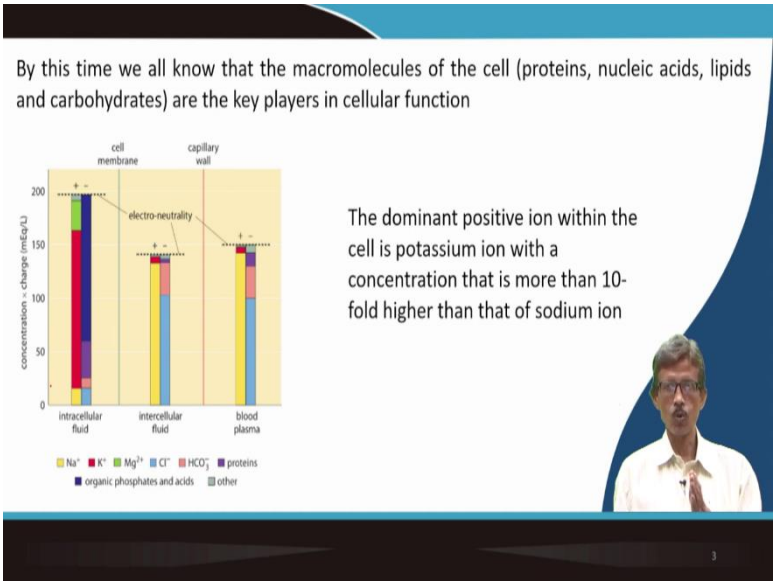

So, up to this point, basically, because we are talking for a few classes on these ions channels, and by that time we have accumulated some good information about the involvement of these macromolecules also within the cell. So, by this time, we all know that the different types of macromolecules, the bigger organic molecules within the cell, and they basically are very important. And also we can define them as the key players in the cellular function.

So, these are your proteins. And when these proteins are there we all know, and when they are interacting with the metal ions for their function for their typical structural function and the catalytic function, we know, we will be getting the corresponding metal of proteins. Then the nucleic acids, the DNAs and the RNAs. We all know the DNAs and RNAs also can directly interact with the metal ions.

Then we can have the lipids, the very basic idea about these lipids. Everyday we are talking now, about the cell, the cell membrane is a lipid phospholipid bilayer. So, the basic constituent of those molecules are again lipids and finally the carbohydrates. The carbohydrates are there at the cells and the carbohydrates are also there within the cell like glucose molecules.

So, how these cellular functions are basically going? And from a very useful drawing, what we find that the concentrations basically, because that is the most important factor what we call in terms of your chemistry wise that when we see that, if you typically identify the sodium ion or the potassium ion in the solution.

Suppose in our college days or late school days, sample is given, white powder is given to you and you are asked to find out whether it is a sodium chloride sample or a potassium chloride sample, what you should do? So, think it nicely, how you have first identified that this white powder is sodium chloride and another one is potassium chloride. So, these are the identification only.

So, we know for many years we know that the sodium ions and the potassium ions are there for our survival and for the cell functions also. But we do not know much about the corresponding concentration. So, now, the picture is very much clear to us. And we all know that there is some differences in these concentrations depending upon the type of the metal ions what you have.

So, if we think now, the concentration wise the distribution of these metal ions, like our quantitative aspects. When you determine that your white sample is potassium chloride and another white sample is your sodium chloride then if I ask you that how much sodium chloride or how much potassium chloride is given to you not in the solid state also a solution is given to you, a fixed solution is given to you.

Like the solution what is present within the cell membrane, inside the cell and also the outside the cell solutions, the fluids what is available outside the cell, then you should have some mechanism such that you can have the typical determination of these ions in aqueous medium or in the water medium.

The way we know that in our drinking water you had the sodium ion and you have the potassium ion. So, quantitatively, if you want to measure that concentration in those solutions of drinking water. Say I have taken one drinking water bottle from one company and another drinking water bottle from another company and try to compare the relative concentrations of those ions, because those are presenting a particular unit of concentration what we call the PPM level, the parts per million level of concentration are there.

But within the cell, we have, we just typically write, if you see the y axis is the milliequivalent per liter. So, that particular concentration is important, and we know that you can have a scale on y axis that is 0 to 200. So, within that particular range, this is the typical range of those concentrations, what is available, where is within the intracellular fluid, in the intercellular fluid and in blood plasma also.

So, these are the main three fluids we can have in our body also there. So, that is why it is a very important information what we can gather. And right now, we are talking only on the corresponding ions are the sodium ion, which is yellow in color and the potassium ion which is red in color. But apart from that, you all know that not the sodium can present alone because, the way I am telling you that if you are supplied with sodium chloride, so when you dissolve it both sodium ion as well as the chloride ions will be there.

Similarly, the dissolution of potassium chloride also will result the corresponding ions as the potassium ion and chloride ion. So, definitely, the first thing that means, the light blue or the cyan color chloride concentration is always there. But interestingly you see that the intracellular fluid, the corresponding chloride concentration is less compared to your intercellular fluid. So, that is why there is some imbalance in the concentration of all these things.

So, if we see from this particular, this bar diagram that, if you compare the corresponding relative availability of these ions, just we focus here only about the sodium and the potassium. So, in one case it is higher in the intracellular fluid, but one case it is less so, that particular balance. And finally, what is there in the blood plasma because that blood plasma is your carrier thing. When you take the food material it goes to the blood ultimately, and it is carried from that particular blood plasma.

So, in the blood plasma also your sodium concentration is very high, and you see that the sodium concentration up to that particular point, and the amount of concentration what you can have the potassium is also less. So, these relative concentrations also tells us immediately which is the dominating concentration. So, the positive part in the cell, within the cell is potassium, which is more than tenfold higher than that of that sodium ion. So, you will have a concentration gradient.

So, we can immediately write the Nernst equation in terms of the concentration related to C1 and another concentration related to C2 and you have the membrane. Like your electro chemical cells also we know that we can put some diaphragm also. When we put the electrodes also we require all the diaphragm, so they allow the passage of the ions, passage of the protons also. So, these C1 and C2 values are important, and those C1 and C2 values will tell us that there will be some membrane potential, if they are separated or they are isolated.

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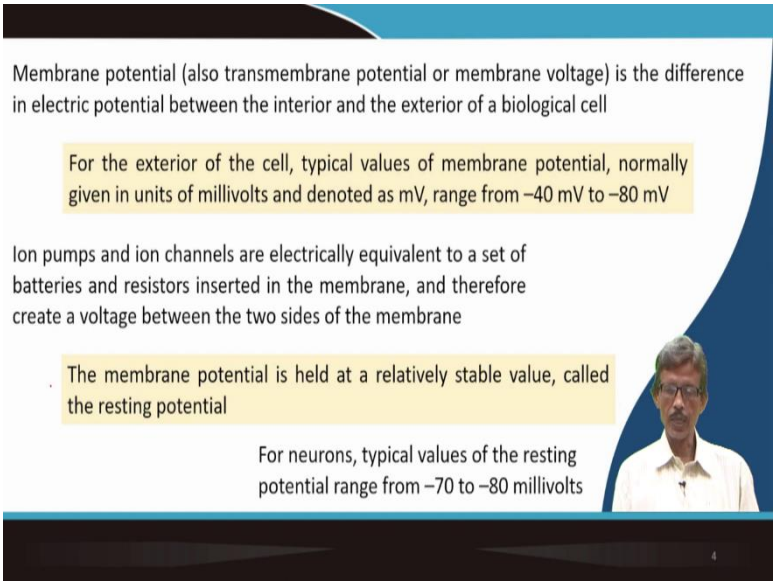

So, if you have two concentrations compared to your left-hand side to the right-hand side and it is separated by the membrane, we are able to develop, the cell is basically developing a transmembrane potential, which we also call as a membrane voltage. And that particular potential is very important for the passage of all these things. And once we discussed that, we are talking also in terms of this potassium channel or sodium channels with that of your pumps.

So, this difference that means the corresponding electromotive force or the EMF values, so the difference in electric potential between the interior and the exterior of the blood cell or any other cell or any other biological cell is important. So, for the exterior of the cell, typical values of the membrane potential depending upon these two concentrations C1 and C2 if we put that particular thing in the corresponding Nernst equation, and you can get the half-cell potential of all these things.

So, they are basically in which particular range, which particular unit that is important. When we talk in terms of the concentration in your drinking water, we are talking the concentration is in terms of PPM. When you talk the cell concentration of these ions, these are the milliequivalents. So, the scale is only in the mini scale. So, not that you are going for the nano scale or the pico scale. So, here also it is very important that the amount of this potential is also very high is the millivolt range.

We have seen in the physical methods of identification when we have studied the cyclic voltammetric. So, the cyclic voltammetric measurements also tell us the potential with regard to that of your millivolt potentials. So, you can have the electrode potential and we can

measure directly also by cyclic voltammetry or any other electrochemical technique, what is your cell potential or a model system you can build in the laboratory depending upon these two concentrations and you can measure it.

So, you can confirm these potentials. But only thing what we can understand now or we can remember also that the range, the window. Which particular range or window you can work basically, for all these things that are happening between the in this particular case. For potassium ion it is minus 40 to minus 80 millivolts, so you get a window. When you scan in cyclic voltammetry you scan from one particular potential to the other then you come back again. So, everything here also the to and fro movement of all these things can be within this particular potential window.

So, if you have those ion pumps and ion channels are electrically therefore, equivalent to a set of batteries, then. If we are able to produce some amount or some magnitude of your potential, so we can immediately correlate that to the batteries or the resistors inserted within the membrane. So, directly if you can put electrodes, you can find out that particular potential, so physically it is also possible to measure in your experiments. So, therefore, create a voltage between two sides of the membrane, so that is the thing.

If you have C1 and C2 from the membrane on the left hand side on the right hand side or the upper side or the lower side, and you can have a very stable potential value which is called as the resting potential. If something is not happening that means, the static potential the corresponding thermodynamic potential for this particular variation in these two concentrations will give you the corresponding potential as your resting potential.

Then, if you move from the cell to the other part of our body for neurons, basically, you see the typical values for those, and when we talk about the resting potential not your exciting potential or other potential the reversing potential and all. So the resting potential for this case is little bit bigger in the terms of the minus range that means, instead of minus 40 millivolts it can go down to minus 70. So, minus 70 to minus 80 millivolt range, only those smaller ranges basically, we see all these functions.

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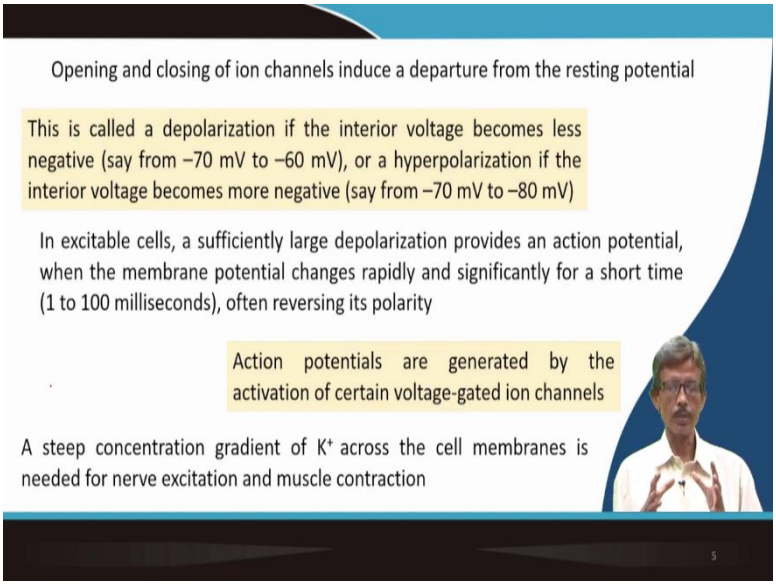

So, whether these potentials or the resting potential can have some role to play on the opening and closing of these ion channels. So, definitely they are gated, the gate is there. You have seen like your tube well valve, it can open in one particular direction and then you can close it. So, if you apply some voltage over there, so the resting potential, so that will be, that is the power basically. The opening and closing of the gate will be powered by that particular potential.

So, if you have that opening and closing of this thing, what you can say about this is that, the gate is there and the supplied voltage can open that particular gate or close that particular gate. So, these will be termed as the voltage gated corresponding channels. So, it is called a deep polarization.

When we consider that the interior voltage becomes less negative, so it is not much negative, so, it is less negative say minus 70 to minus 60 millivolts, if it is there, we can call it is a depolarization of the corresponding voltage within the cell. And if it goes from minus 70 to minus 80, then more negative. Some is less negative, range is minus 70 to minus 60 and some is the more negative which is minus 70 to minus 80 millivolts, we call that is therefore, due to the hyper polarization.

So, the cell which we can excite, you can get the electrical excitation. So, those cells which are being able to be excited, so you get the corresponding excitable cells. And in these excitable cells a large depolarization not polarization is depolarization provides a action potential when membrane potential changes rapidly.

So, if you have a membrane potential due to C1 and C2 then you can have the corresponding polarization or depolarization potential. And within a very short time these particular changes can take place in milliseconds range, and the range is also 1 to 100 only. So, we are talking in terms of the millivolt range, we are talking all in terms of the millisecond range, which is a pretty very fast one, because our conventional cyclic voltammetric measurements we basically do per second.

Some voltage the millivolt we can scan 50 millivolt per second or 100 millivolt per second to up to 1 volt per second. We can scan the to and fro movement for the cyclic voltammetric measurements. But here you see the measurements would be using some things, some oscilloscope one other thing not that your computer terminal or xy recorder can record all these things. So, these are basically within the range of only 100 and less in milliseconds. So, you can have the resting potentials.

Now, if you go for this excitation, the action potentials you can have and these are generated by the activation of certain voltage-gated ion channels. So, if you are able to excite these voltage gated ion channels that can be done by using of these potentials, which we are able to generate through the placement of the different concentrations within the cell and you have the membranes.

So, that is why we have the nature has devised such a useful mechanism that is why we get a good substrate to study, and we also try to learn many things out of these, why nature has taken these thing and the membrane they port and the two different concentration with respect to sodium as well as with respect to the potassium also.

It is not that only in case of potassium, you have the differences that C1 and C2, but you also for the potassium, which is in the reverse direction one is less another is higher, because all these things are for that you have the potential, and which can be used for your muscle contraction. We know that we can have the muscle contraction when we talk about all these muscles on the face, the facial, muscular things are also moving, so muscle contractions, the movement and the nerve excitations. So, these are all dependent on these small voltages.

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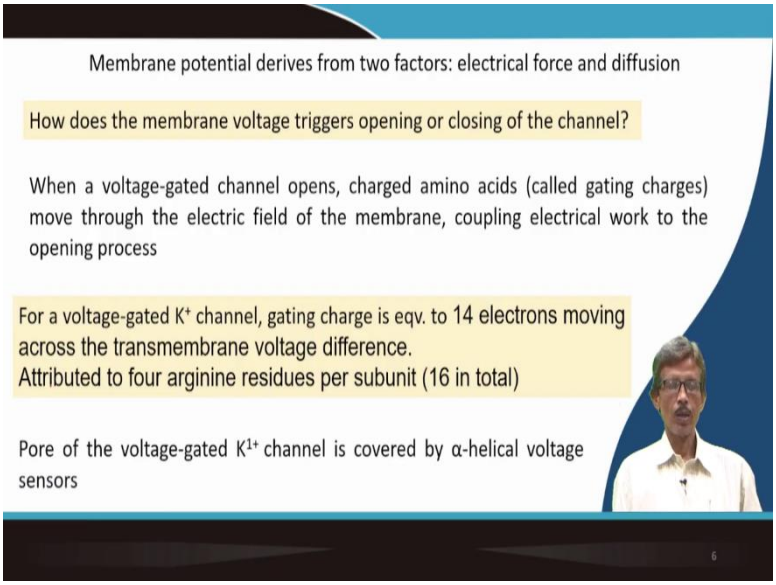

So, what do you see now that the membrane potential derives from two factors, the electrical force as well as the diffusion, because everything is also diffusion controlled. So, electrical force is there, which can go against the naturally occurring diffusion process. So, one question we can ask at this point that how does the membrane voltage triggers opening and closing of the channel?

So, that is why you are studying all these things, that you have to have the corresponding membrane voltage available, and how it can basically push or you can just go for the corresponding opening and closing of the channel, which is the most important thing.

So, when it is opening, the charged amino acids, which are known as the gating charges. If you have the gate, so gate is there, so gatekeeper is not there, but you have the gate. So, you have the gating charges the charged amino acids. How you get the chargedamino acids because you have certain amino acids, which can be protonated and which can also be deprotonated. So, either it is positively charged or it is negatively charged.

Since, we are talking about the positively charged ions, the movements of the potassium ions, so, it is the negatively charged amino acid residues like the carboxylates or the phenolate groups should be there, and move through the electric field of the membrane coupling the electrical walk to the opening process. So, by doing so, you can open up the corresponding gate.

So, for this particular case for a voltage-gated potassium ion channels or k plus channel getting charge is equivalent to 14 electrons moving across the transmembrane voltage

difference. So, it is some quantity, just only try to remember this number. People have identified that thing, people have established that thing, so all these things are very good. Amount of research work involved and people identified it, published in papers also and verified it also nicely. So, if you have 14 electronic equivalent of this particular gate for the transmembrane voltage, how it can attribute it per subunit if you have some arginine residue, arginine residues is we know the guanidine and basically that can be protonated also.

And always the amino acid residues, if the carboxylate end is not involved in peptide bond formation, if you have more number of carboxylate groups sometimes amino acid residues can have 2 carboxylates. One is engaged in peptide bond formation, so other one is also there available as the dangling one. So, the pore, the pore size, the passage. The pore of the voltage-gated K plus or K 1 plus channel is covered by alpha helical voltage sensors.

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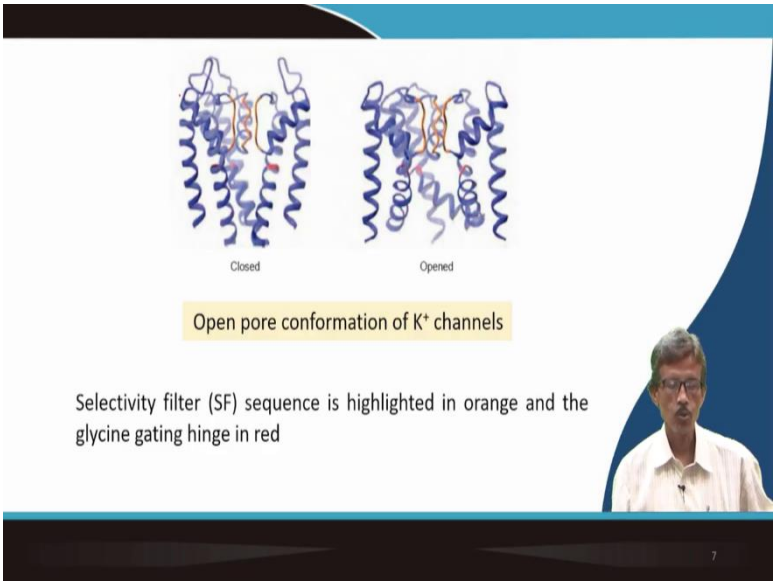

So, they are these proteins are voltage sensors, and that is how they areassembled. So, the assembly process and all these things. Again, we basically rely on the x-ray structure. So, this is the finding. Forget about all other things that where we can talk about in a biophysical way all these reactions, all these equations, putting, bringing Nernst equation and all these things, but the very first thing is that what we should do is the structure.

So, protein crystallography plays a very important role in all these cases, at least to see the two forms, the closed form and the open form of all these cases. So, protein crystallography basically defined all these things, and open pore conformation of the potassium channel. So, you can have the pore, pore is basically open, but the gate is maybe closed or open, so you have the closed gate and the open gate.

As a result, we can have something, the gate we can call also the selectivity filter. So, we know the filter paper, how we go for the filtration in your chemistry classes, we all know. Now, it is not only filtering, but it is selectivity filtering. That means, if you have the pore size of a particular type, only it can allow depending upon your charge or the charge by radius ratio of the particular ion, you can pass or allow it to go through that.

So, the sequence what you can identify from the structure, which is very difficult all the time, if you do not have the middle ion first, but if you have metal ion trapped in it you will be able to determine the x-ray structure nicely. So, it is highlighted in orange, so what you can have is the orange part and the glycine gating is in the red part. So, one is the red the lower end and have the red part, so red end is the glycinate. So, you see that the glycine end is also, not only

the arginine end, but the glycine end are also available and they are lined up within the channel.

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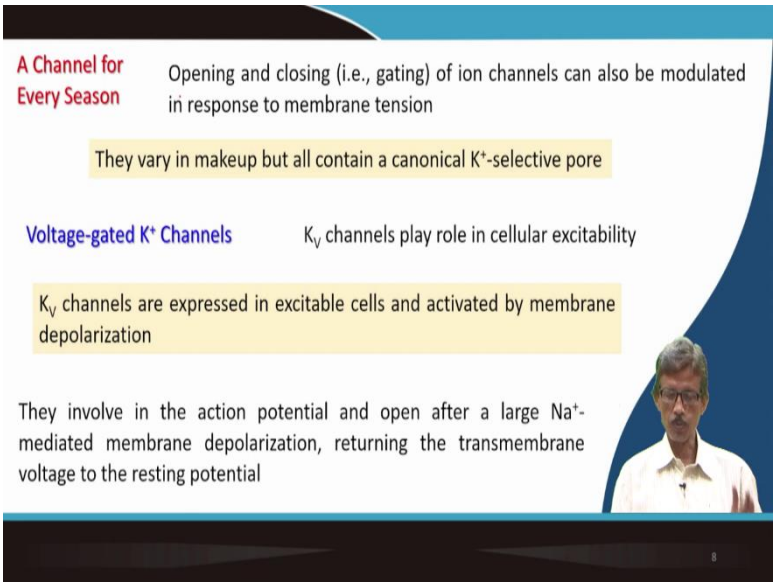

So, every time, everywhere we get this particular channel, so that is why we can consider it as a channel for every season. And we are just talking about the gating process, nothing else, and we are discussing all these things in a very lucid way that how you can think of all these things and involvement of the potential and involvement of the corresponding movement of the ions.

So, you can have also at some time the membrane tension. So, membrane, if it is in a stressed condition, if it is a membrane. So, if the field volume is more your membrane is in the stressed conditions. So, this particular ion channel closing and opening can also be modulated in response of the membrane tension also. And they vary in makeup, but all contain a canonical K plus selective pore. So, you have only the K plus selective pore.

So, you get the voltage that is why we can have the voltage-gated channels. And these voltage-gated channels when you apply to K plus we get the Kv, which is nothing but Kv is the subscript which is capital V do not forget it in writing in that version, this is not a small V it is subscript typical it is a subscript on K.

So, KV is your voltage gated potassium channel, and it is responsible for our cellular excitability. And these KVs are basically it is like your it is also easy to remember also your Kendriya Vidyalaya when we call is KVs so what is a subscript KV. Expressed in excitable

cells and activated by membrane depolarization, not polarization, but it can be activated by the polarization process.

So, when you have the resting potential, then the action potential. Action potential is different from the resting potential, and open after a large sodium ion mediated membrane depolarization. Because you can have some time because both these two are interrelated. When you talk, the potassium case you cannot talk in isolation with that of your sodium ion because these are interdependent when all this pauses here.

So, returning the transmembrane voltage to the resting potential. So, the movement from this particular resting potential to the action potential, you can have all these changes.

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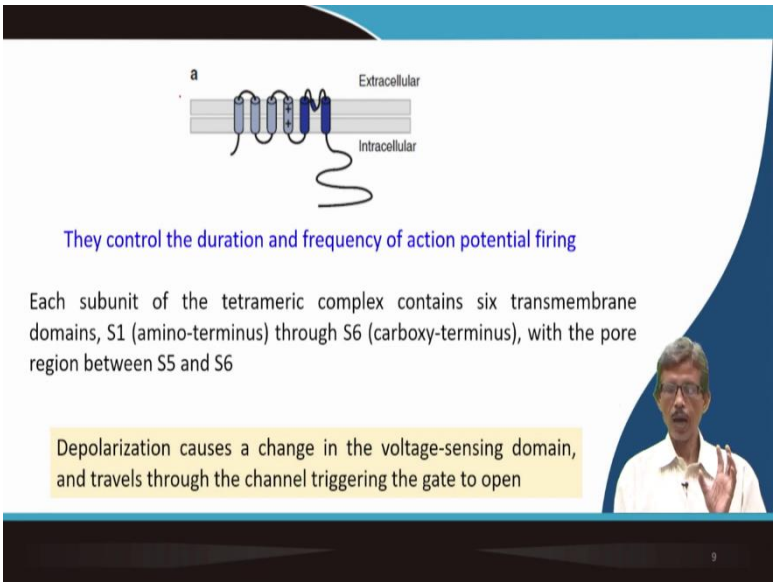

So, you have two separate things and you have the membrane, nothing else. Then how you like, that electrical engineers write as the capacitor. So, these are the corresponding diagram. The cylinders are nothing but your capacitors. So you have in your ceiling fan, everywhere in your household things also we have the capacitor.

So, drawing up all these things basically tell us that you place one after another. So,we have the domain, so you have the subunits, and you have the tetrameric complex from S1 to S4, then S5 and S6. And this S1 can be of amino-terminus and S6 can be carboxy terminus, like we know the polypeptide chain.

The amino acid residue have the carboxy end and the amine end, and they form the corresponding polypeptide chain also even 2 glycine units when they are coupling together.

What do you get? In between you have the amide bond, but at one end, you have the amine function, and another and you have the carboxy function.

So, if you go for the third one, if you go for the fourth one and so on, what you get, you ultimately get a polypeptide chain. And that polypeptide chain will have one end as the amino end and another end as the carboxy end, and the pore region basically that is why these 2two are differently colored, the S5 and S6 you have the pore region.

So, then, the electrical engineering part is going on there, the depolarization pauses polarization and depolarization. So, depolarization process here again causes a change in the voltage sensing domain and travels through that channel triggering the gate to open. So, this particular process, the gate is opening, and that opening of the gate is important. So, you can think of how we can correlate so the depolarization of this particular case with this particular diagram, the depolarization is responsible for your opening up of that gate.

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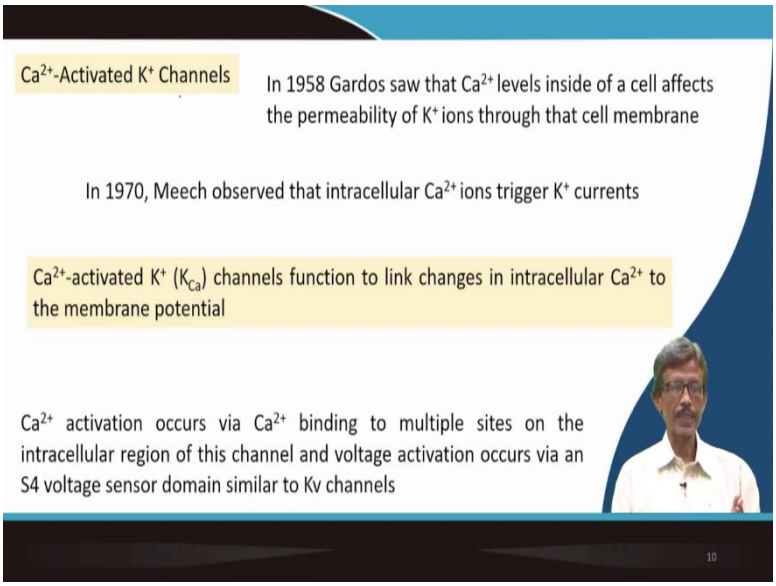

Then, some very useful understanding over here that, whether you have something, because I told you that you can have these 2, these 2 concentrations from left to right. You have the sodium concentrations and the potassium concentration. Now you bring another metal ion, as the calcium. And so the bivalent metal ion is of different type and different nature. Whether we can have the activation corresponding to the presence of calcium ions in the solution also.

So, the scientist Gardos in 1958 you see almost 50 plus 20 almost 70 years is the case. So, that is why is almost 70 years, we are talking about all these things. So, he found basically the

calcium 2 plus levels inside the cell and showed that it can affect the permeability of the K plus ion through the cell membrane.

So, other ion basically interacting or interfering the corresponding movement, where we know that when you determine the presence of say one ion in presence of the other, if you have the interfering ions, we know that even the detection of the other one is difficult in presence of the other metal ion.

Then afterwards another 12 years gap you have the Meech, scientist Meech observed that intercellular K Ca2 plus ion triggers basically the K plus currents. So, they basically activate all these things. So now you can have which one can be activated by presence of the bivalent calcium ion, you can have the K again subscribe Ca channels and to that of your function with that of your membrane potential.

So, the activation due to the presence of calcium ion you have some multiple binding sides. So, calcium binding proteins you can have. And now you have S1 to S6, now you see that again S4 is involved, and it can function, this S4 can function as a voltage sensor domain similar to your KV channel. So, you have the Kv channel, then you have your Kca channels also.

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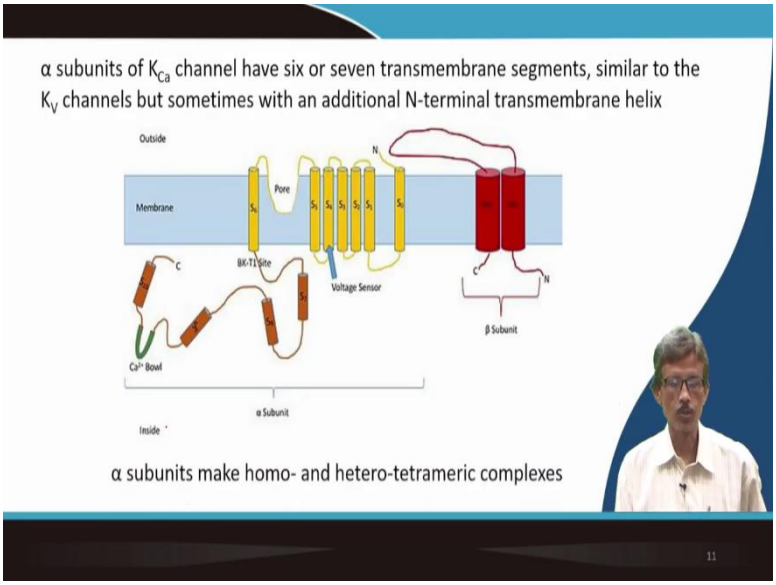

Then, the alpha subunits of these Kca channels have 6 to 7 transmembrane segments, similar to the KV channel. So, is it has the similarities, only that at certain point, calcium can come and can trigger the function of the corresponding potassium voltage channel.

So, you see in a bigger way, you can have more number of all these things. So, N-terminal transmembrane helix are there, so, you have at some point, you see that green part which is your calcium 2 plus, and we consider shape of this. So, protein is there, so it is basically functioning as a bowl, which we know that if you have a bowl in your kitchen, you can hold that particular metal ion.

So, holding that particular metal on within this bowl is important, so it is there. So, calcium will be sitting on that bowl and then it can pass and the dependents are there, and you can have the beta subunit also. The beta subunit can also play some role also for the function of this alpha subunit. So, the alpha subunits make homo and hetero-tetrameric complexes. When it is homo it is all are of similar type, when it is hetero all are not of the same type.

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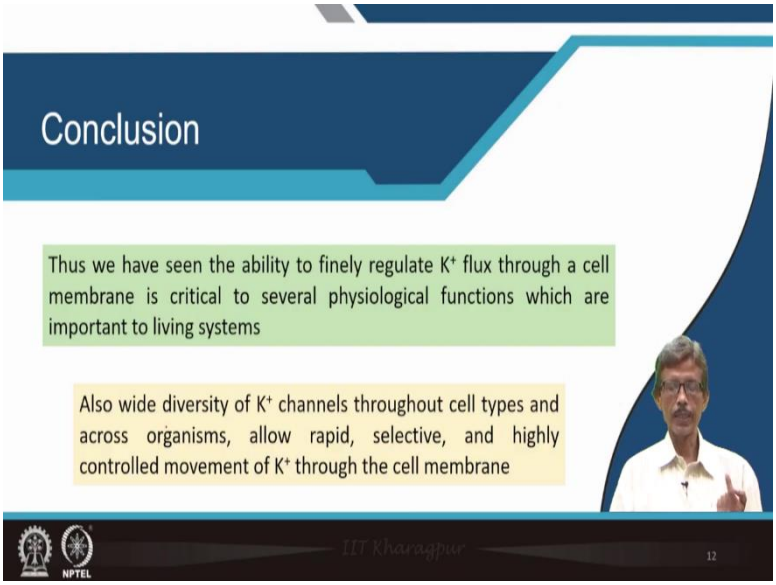

So, we have reached to the end basically in that way. And what we have learned so far, you can try to recap which a little bit in that way that, we are talking about the presence of the potassium as well as the presence of the sodium, and along with that you can have the corresponding calcium ions.

So, what we have seen therefore that, we can regulate or sometimes finely regulate because these concentrations are very less. So milliequivalent concentrations, say 5 to 140 milliequivalent of these concentrations are there, but you can have the corresponding potassium ion flux. And that potassium ion flux is important because you have the voltage, the voltage-gated thing is there through the cell membrane.

So, we have to pass this everything through the cell membrane. And therefore, we all knows and we should also remember it nicely that it is critical to several physiological functions, which we require for our hand movement and all these things, which are important to the living systems.

And also, we find that there is wide diversity of these K plus channels. We have seen that the voltage-gated K plus channels, then ligand-gated. When ligand is sitting on it that we will see obviously, for another example. Already we discussed a little bit for the, in our next class about the sodium channels, we will see, how that other innovators we discussed at some point, again, we will discuss a little bit.

Throughout the cell types, you have the diversity of these, and across the organisms, different types of organisms from plant to the human being, or the mammals. They allow rapid, selective and highly controlled movement. So, thing will be very rapid that is why we talk in terms of the milliseconds timescale or the time domain, they are selective is allowing only the movement of the potassium ion, not the sodium ion or not the calcium ion. And therefore, we have the highly controlled movement of these potassium through the cell membrane.

So how, the machineries are available to this particular movement, what we do not get for any artificial such membrane, like a parchment paper or any other membrane, what we can have, for that particular thing we do not get.

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So, again, you just try to go to the page, which is potassium in biology page in Wikipedia, and also the book, what we follow every day. And that particular book is basically to us is the

biggest help for us. And most of the things we basically adapted from that particular book such that you can have the book in your hand, and you follow it, and you go back what I am telling and what I am explaining basically that you can correlate also.

Then the third one, I am just giving today is that is the Encyclopedia, is the very big one. Encyclopedia of Metalloproteins is a compendium in 2013 basically, and it has huge information. So, all the information related to the metal ions, what people can think of related to the different metal of proteins. So, thank you all for your presence.