Biological Inorganic Chemistry
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Lecture 24
Na+ Channels

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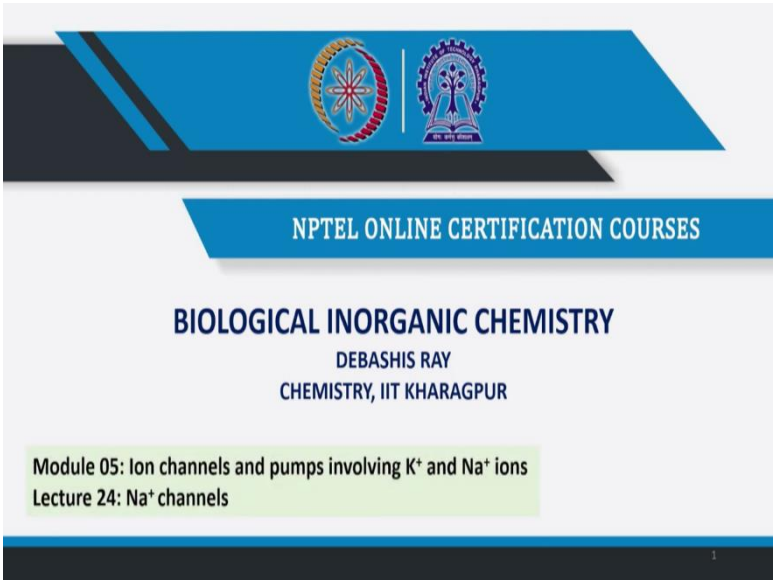

Hello everybody. So, welcome back to this class again where we are talking and after potassium, we now go in lecture 24 to the sodium channels. So, bigger ion I have considered so now we just talk about the sodium in a different course or in a different direction, so where we can have.

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So, little bit always, if you know about the sodium, try to learn it from the what you have learned so far from your school days. So, atomic radius and all these things you go to the atoms first. You have the corresponding hydrogen atom, then you go for the sodium atom. So, learn first nicely about the sodium atom then you try to get the corresponding ion, and then the typical salt every day, every time we use it, and in your home also try to love that iron also like your sodium ion, as the sodium chloride which is present in it.

Then how much you know about the sodium ions in biological world. So, that is why the course is biological corresponding biological inorganic chemistry can be biological metal ion chemistry and the biological sodium ion chemistry, because we are talking everything in terms of that particular metal ion. So, it is there, where it is present, and how it is physically giving some very important role when they are present in the channels.

Then the different types of channels, already we know, you now already know all these things, the voltage-gated channels and the ligand bound channels and all this. And now, one more thing we will just see that we know that the opening and closing. Whether we can activate those channels, so what are the molecules what we can have such that we can activate those channels like your channel blockers.

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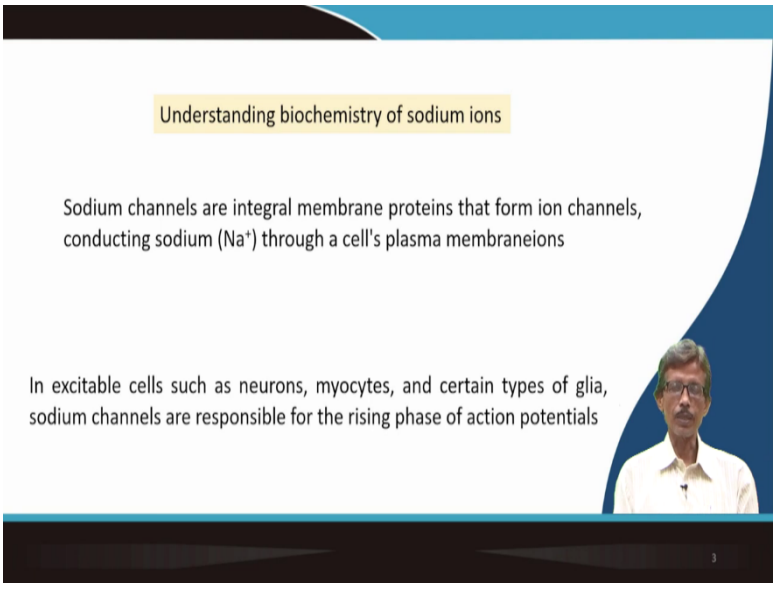

So, not only the chemistry just typically we can consider it as the biochemistry of these sodium ions. So, a good understanding of these biochemistry of sodium ions is important from the perspective of sodium ions only. So, what you know about the sodium ion, the sodium chloride solution in your test tube, so we do not have anything surrounding that. But

if you put some ligand say, EDTA, EDTA 4 minus, you know that it will try to interact with that EDTA minus 4 minus.

Then if we consider that, okay, you put some amino acid or a peptide or finally a protein. So, when you put that particular protein you get something that the sodium ion can interact with all these things. Even the protein side chain, if you have the carboxy end, we know the CO2 minus.

So, in that particular CO2 minus the carboxy end, if it is there. And if it finds that only through charged neutralization, that CO2 minus can go and come to that particular available sodium ion, so such that you can have the corresponding equivalent structure what we know and what we find in case of your sodium acetate. The acetate charge is balanced by the sodium ion.

So, this particular membrane part or the sodium channels, which are therefore, present with that of your membrane protein and then from the channels and conducting or transferring or moving sodium through the cells, plasma membranes also. So, you can have the plasma membrane, and the plasma membrane basically carrying all these sodium through our food material absorption is taking place and absorbs so not only for your carbohydrates, lipids, fats and all these vitamins and other minerals, but also typically for the sodium ion.

So, when we have all these cells, just in our previous class, we are talking where we were discussing and we came to know that we can have the different cells, which you call, which could be able to excite it, so they are excitable cells. So, these excitable cells are basically the neurons, the myocytes and certain types of gila, sodium channels.

In all these cases, all these three categories basically, sodium channels are responsible for the rising phase of action potentials. It is not the resting potential, but you have to go, the rising phase, the rising. You rise the potential for its action from that resting potential to the action potential. So, you have to move that particular potential. So, again in a similar fashion similar mechanism, you can have to get that potential and through that potential to basically generate these channels.

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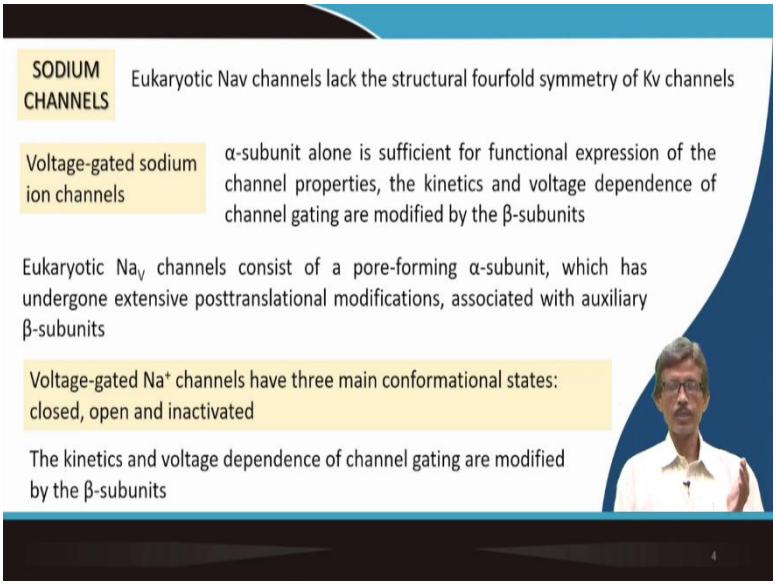

So, that type of channels basically the sodium channels what we can find in our hand then the cells are from say eukaryotic cells. So, eukaryotic NaV channels, NaV is not, it should be subscript. So, V is capital V is your subscript. So, NaV channels, lack the structural fourfold symmetry of KV channels.

Now, if we have the structure of these, because, why we have studied potassium first, because during the last 50 years or 60 years, we know much about the potassium channels because the structure is known. When you synthesize a new molecule in our laboratory, as a synthetic inorganic chemistry or coordination chemist what I can say to you is that, that until and unless something new is happening we can have some good idea that how the ligand can bind to the metal ion.

But since the protein, the protein macro molecule is a huge one, and it can have several donor points, and it can bind many number of metal ions, particularly, when the binding is for sodium and potassium which are very weak in nature not like that of your transition metal ions like copper, nickel or zinc.

So, what we find that, this determination of the structure is a difficult task. So, that is why initially we get the structure for the potassium channel, then we go for the sodium channel and people identified these sodium channel. And once you have these two structures, so structurally, how the protein folding is there, how the folding is basically helping the movement of all these ions.

So, those channels, there is a channel, only the channel part, because we are focusing again our attention on that particular part, we are not talking about the other bigger part of the ligand or the protein part what we are leaving behind.

So, again you bring the V, that is, your voltage-gated thing. So, you have then again from the protein part the alpha subunit. So, alpha subunit basically is we know that the whole structure, we know the alpha-alpha subunit and the beta-beta and all these things, so only we are considering the alpha subunit and the beta subunit.

So, it is basically only important for your functional expression of the channel properties. How the channel is working, the kinetics and the voltage dependence of the channel gating and modified by the beta subunit. So, the primarily it is the alpha subunit, which is important to control this function of the sodium ion within the channel and within the passage, then it can be modified by the beta subunits.

So, for these NaV channels, what is available for your eukaryotic cells. So, eukaryotes we study first, these are again modern substrate, and what we can study in detail from that. So, you can have the pore forming alpha subunit. So, since alpha subunit is the primary thing, which is controlling for the generation or the structure forming pore formation, which undergoes then the right amount of post translational modifications. The amount of post translational modification, which we are looking for then you bring the beta subunits, and the beta subunits are therefore ancillary or supporting or auxiliary to the alpha domain or alpha subunit domain.

So, what we can have now, not that we can have two things that means, it is opening and closing, opening and closing, but you can have the voltage-gated sodium channels, you can have the different conformational states. So you see now, the channel will have more power. It is not that the metal ion is there, and it is therefore coordination is taking place and it is closing that part it is not that.

Since the voltage is there, and the voltage is basically activating the channel passage or the channel path or the channel gate in such a way that, that particular voltage is basically will control the opening up of that particular channel gate, also the closing of that channel gate and at some time in the dead condition or the inactivated condition. So, at that point it is neither opening nor closing. So, it is the inactivated state.

Then, how fast the thing is happening, the kinetics, and the voltage depends. So, definitely like your electrochemistry we put the voltage and we see the electron transfer within this particular voltage window. But how fast this movement is taking place that we are not able to monitor from there, but depending upon your scan speed, how quickly you can scan it and how quickly the electron is going from one point to the other that we can monitor. So, the kinetics and voltage depend, so these are the two path factors basically.

The voltage is the thermodynamic property, and the kinetics is the red property of the channel gating are modified by the beta subunits. So, if the beta subunits are not present, will not be the modification you get, what you expect, it will be dependent only on the presence of your alpha subunits.

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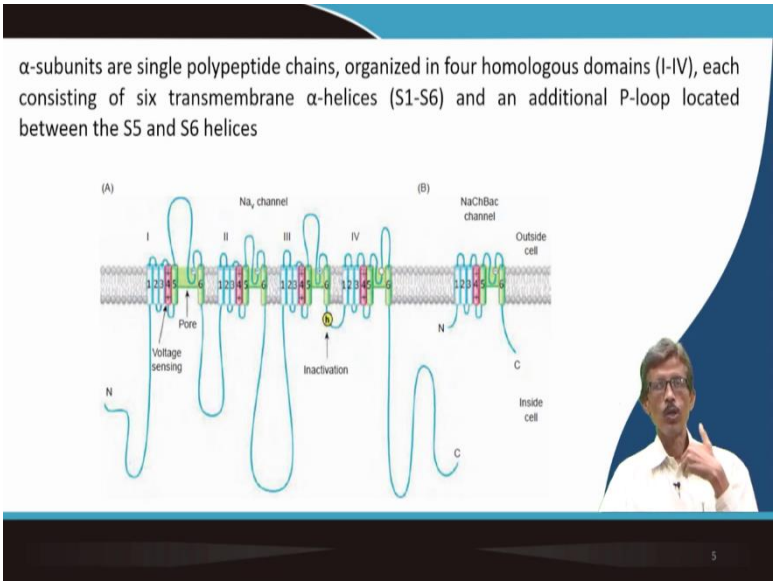

So, what are those basically? So, these alpha subunits, again, I am talking to you, is that, in the fashion that you try to remember as more number of amino acids you bring you get the mono peptide dye peptide and tripeptide chains. And these polypeptide chains when they are organized in homologous domains, say 1 to 4, 1, 2, 3, 4, and each of them are having 6 transmembrane alpha helices from 1 to 6 basically. So, 4 homologous unit within S1, 4 homologous domains in S2, 4 in, so you get a cylinder type of arrangement, and an additional P-loop.

So, if you can have a loop, we have seen for the calcium. We have seen that you have a bowl-shaped structure, but sometime you can have the loop also. So, at the end basically, so S1, S2, S3, S4, S5 and S6. So, between S5 and S6 you bring that P-loop and such that you can connect that, that is why you get 6 sorts of arrangements.

So, what you can have? You can have, in A is a sodium and it is a voltage-controlled or voltage-gated channel. So, something is there. So, something is the number 4 is basically sense, voltage is sensing then you have the pore and you have all this loop. And one point you written it is in this A diagram left hand diagram is A.

So, you have N, so N is your N-terminus thing and your C is your C-terminus thing. So, this is your C-terminus thing. So, you have many channels, and you have this. Again, the same drawing, I am showing you every day, so you try to now master enough for these things is lipid bilayer.

So, these all things the base is your lipid bilayer. So, on these lipid bilayers, so they are at certain points only, they are at certain channels only. So, you have this pore, you can have and some point which is h is written as h is the inactivation part. So, between 3 and 4, you can have some point, you can have the inactivated part, so when the gate is there and is not opening up you can have the corresponding inactivation state.

Then NaChBac, what is that? So, it is again the sodium channel Ch is your channel and Bac is your bacterial part. So, like we all should be master enough to know about these abbreviated forms. Because like us, people have designed these things and people have labeled these also, but we know nicely the symbols, instead of writing the sodium, S-O-D-I-U-M we typically write the Na only, the symbol is fine for us, we can read it nicely.

So, similarly, for this biochemical world or the biological world these abbreviations are important. And when you tick all these things, so on the diagram you do not write so much on this diagram or the figure, you read the sodium channel and which is of bacterial origin. So, the bacterial cells basically give similar type of channels, so you can have the inside, cell inside and the cell outside and how you move.

So, sodium channels we all know that is important is the sodium concentration is higher outside the cell and lower inside the cell. So, do not forget that anytime that what we are looking for and what we will be seeing.

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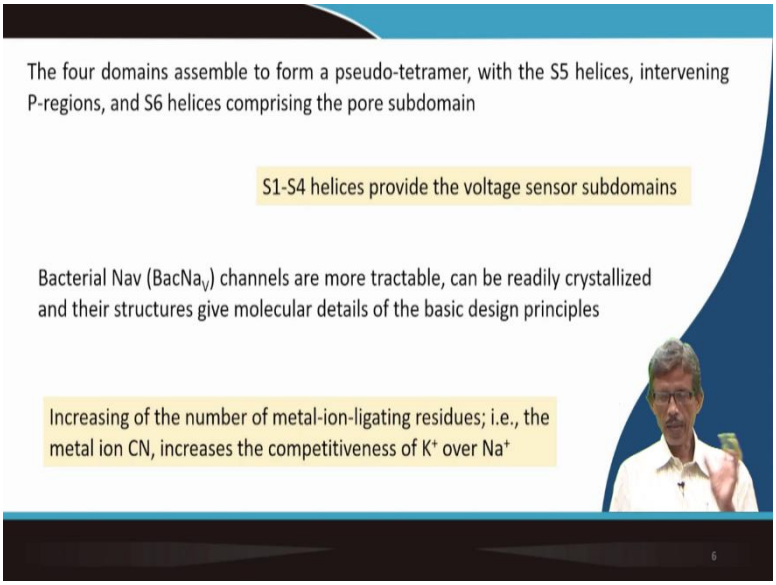

So, what you get now that, that you have the four domains and forming a tetramer. So, how you assemble those four domains, so you definitely have the tetramer. And with the S5 helices, intervening the P-region, so P-loop is there and S6 helices comprising the pore subdomain. So, you have the pore subdomain is there, and you must have some voltage sensor.

So, subdomain is basically functioning as your voltage sensor, which can sense the particular type of voltage. Voltage is there minus 60, minus 70, minus 80, when minus 40 voltage millivoltage is there, but who can sense that. So, you can have this, after this eukaryotic cells, you can have the bacterial Na sodium cell, a channel the volt channel, which are more tractable and can easily be crystallized.

That is why we have studied it in detail and their structure gives the molecular details and the basic design principle. But, in all these cases, what we should try to find that where the metal ion is sitting, because during the structure solution, if it is metal ion bound species or the metal ion bound crystal, it is easy to locate the position of these metal ions, because that is the heavy atom species within all these cases compared to a carbon, hydrogen, nitrogen, oxygen and all these things the metal ion, sodium or potassium or calcium is the heaviest one.

So, it will try to detect the corresponding environment of that metal ion that means, the corresponding environment for that particular metal ion. So, if they are bound, we will be quickly find out, if the structure is not so good we are not able to determine the whole structure, but if we are able to determine only a part what information you will be able to get is the metal ion and its immediate environment, the coordination environment.

So, heavy atom method we determine for the structure solutions, the heavy atom method can help us in determining the metal ion, the presence of the metal ion, where the metal ion is present or not, and its immediate environment.

So, the metal ion coordination number that is why whether it is ligated to 1, 2, 3, 4, 5, 6 all these groups form the protein chain. It is not that water molecules is bound to the water molecule, and increases the competitiveness of potassium ion over sodium because the potassium ion is the bigger one. Having more number of coordination number, is that, it can go up to 6 to 8 compared to your sodium. So, we can compare these two sides by looking at the corresponding structures also.

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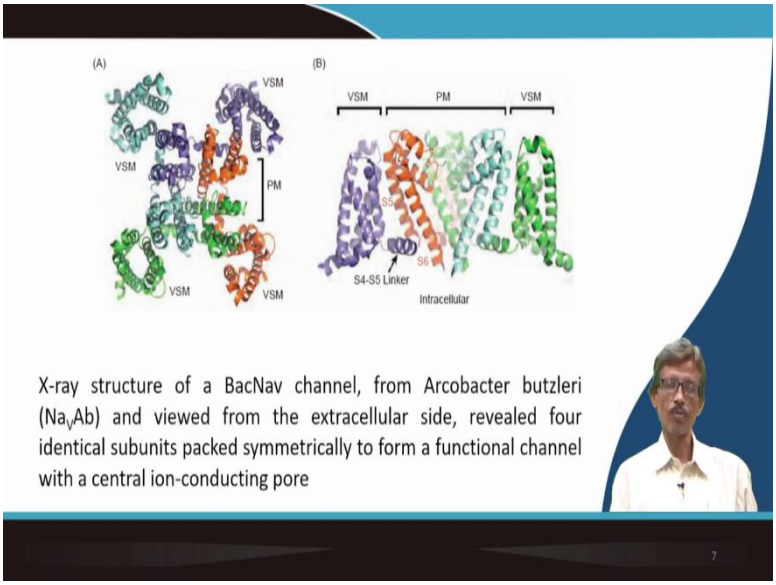

So, you see, the bigger structures, do not worry about these all are cartoon drawings. So, any kid we can ask and just ask you to replicate it, so it is a spiral things you draw and setting. This is like a drawing picture, drawing a picture, but these are the ultimate structures what people get from the protein crystallography.

So, you have again, the symmetry wise, immediately you look at the symmetry and the symmetry wise, what you find on the left the A drawing, drawing A, what is this is for the bacterial sodium voltage-gated channel from Arcobacter Butzleri, Arcobacter Butzleri that is why it is abbreviated as AB, and the extracellular side and the intracellular side, you view it. You it is a three-dimensional one.

So, when you publish it in some paper and you get it in the textbook from there you get in one particular view, but it is three-dimensional. You can rotate it in the computer screen, and

you can find out a good view such that you can then project it and you can find out the figure for that.

So, four identical subunits are packed symmetrically to form the functional channel what we are looking for. So, you have the C4 symmetry around the metal ion. And expectedly, immediately what you can have that if one subunit is giving one coordination number all are giving, so you can have 1 particular metal ion, and you can have immediately the 4 coordination numbers, but it can go beyond that. You can have 6 or from other point, it can go to the 6.

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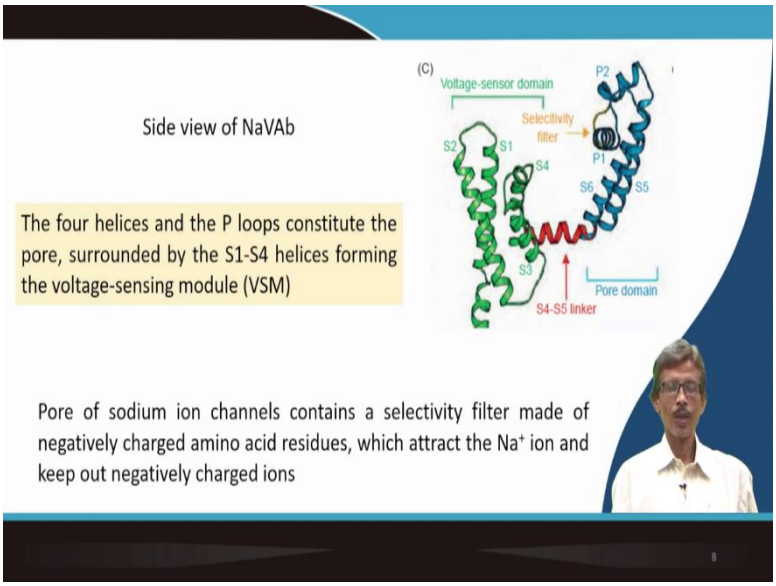

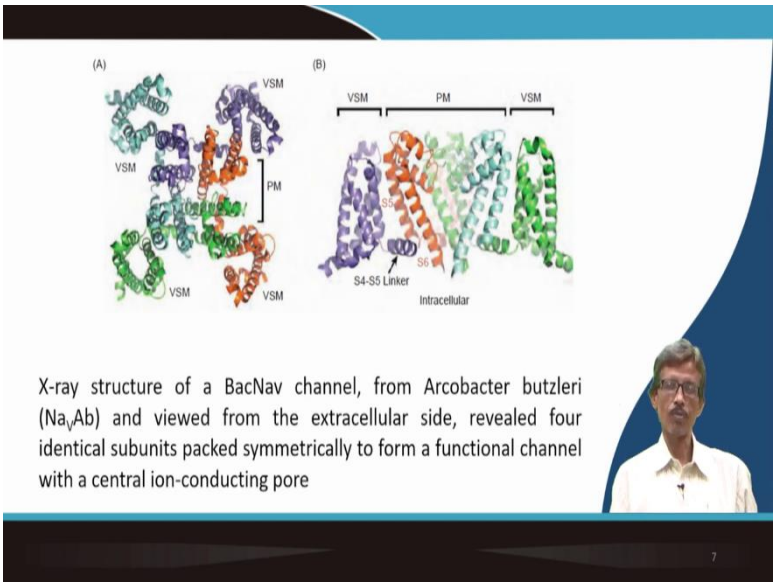

So, the other side you have the corresponding side. So, viewing through another axis and that gives you another drawing of another figure, so the hat side view also can give rise to this particular one is the some part, which is basically your, that one particular subunit.

So, you have the VS, the voltage sensor domain, the pore domain and all these things, so that is why you have this corresponding pore domain and the voltage sensor domain and all these things. So, basically, it is not looking from here. But if you go here in this particular drawing, you will find that this particular one, and then some spiral coil thing, you see, is written as the selectivity filter. We call as the VSF.

So, the selectivity filter is there, so that plays some very important role apart from your all these domains S1, S2, S3, S4, S5 and S6. So, you can have the S5, S6 linker and the pore domain. How you generate that particular pore domain that is important, and within that pour domain you have the selectivity filter, so and which can also sense the corresponding change in the voltage. So, how we can select the passage of your sodium ion compared to that of your potassium ion that is important.

So, the four helices and the P-loops, the placement of all these things has been determined. And VSM in the previous drawing, we are writing the VSM like a Vibrating Sample Magnetometer, you can also know is a very well-known abbreviation we use for studying the magnetic properties of some sample. So, it is voltage sensing module. Only the module, that part, or you can consider it as a domain.

So, that particular domain and also the corresponding sensing part or the filtering part is important. So, these pore of sodium ions basically, which are there in the channel, so you have the selectivity filter. And again, since we are talking, we are thinking for all these in terms of the amino acid residues.

So, amino acid residues must be negatively charged, like your carboxy end or the phenolate end, because we have to attract the corresponding sodium ion. Just I have discussed again and again that you have to trap or you have to attract the sodium ion, so your alignment of those amino acid residues is not that they are protonated.

So, in this particular region, pH is also very important. So, afterwards, we will also see about the corresponding role of the proton channels and the role of the protons. If the proton is competing with that of your sodium ion and the potassium ion you will have a real trouble.

Because if your proton is coming and sitting on this carboxy end, the carboxy end is getting protonated, so it will not attract your sodium ion and the potassium ion.

So, definitely, your local buffered conditions or the local pH medium of the place is in the basic medium what is above 7, or above 6.8 what is your average, our blood pH is 6.8, so average basically is going down and going up. We know in the stomach pH can go down to 2.

So, this particular one, so the pH is important and that's why the charge is important. So, the ligands are all in the negative side. So, the amino acid residues charge is important, which can take care of your corresponding sodium ion.

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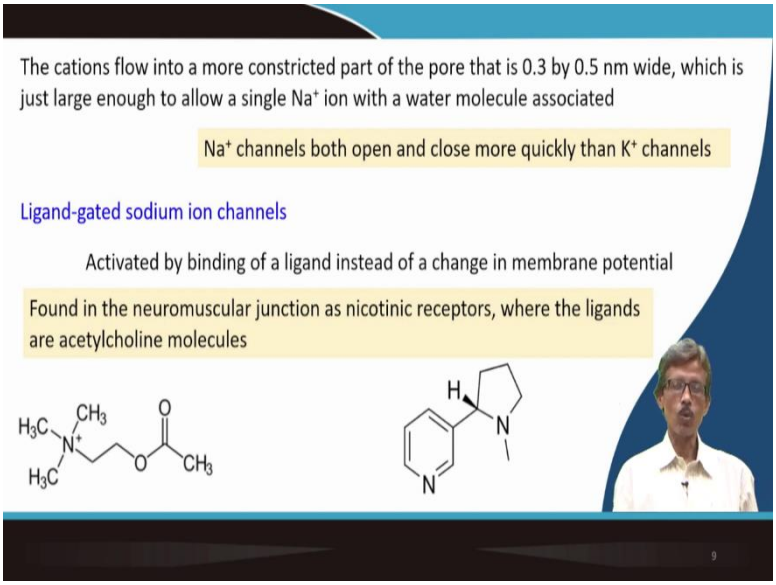

So, it is flowing. So, where from it is flowing, and which part is going? So, you have a part which is constricted part we call. And a single sodium ion can be taken care by these with a pore side your 0.3 to 0.5 nanometer. Now, you can think of there lies the answer that what is the corresponding ionic radii or ionic radii shop that one individual sodium ion and it is hydrated and is solvated also that is why.

So, size is there, and you can control, you can have 1 to 6 say water molecules around it, but if you find the channel is only 0.3 to 0.5 nanometers wide, so you can pass or you can push the corresponding sodium ion with A water molecule associated to it, that means, a single water molecule associated to it. Because during passage also it is removing that water molecules and after crossing that channel, it can take up again the water molecules and again rehydrate it.

So, these sodium channel close, open and close more quickly than your potassium channel. So, you see, since the ion is small, sodium ion is small and your voltage is such that is the corresponding function that the kinetic part is there and the kinetic effect of all these things is a very fast movement of these opening and closing.

Then we see in this last part of this particular class that how you bring the ligand, the most fascinated thing, what we call all the time to a coordination chemist or a bio-coordination chemists that you have the ligand, you have the metal line, so these things we are talking. So, we are not talking anything very much difficult, anything very much not understandable to you. So, anybody which can have some attention, you can understand it nicely from that particular fashion.

So, if you bring not only the protein part, you bring some other secondary ligand or if that ligand is sitting over there, we already know, we defined it at some point what is known as how you define it as ligand-gated, like voltage-gated thing, the ligand gated sodium ion channels. They are activated by binding of a ligand instead of a change of membrane potential. So, we do not need the corresponding help of the change in the membrane potential.

So, how you activate the excitation of the corresponding channel, is due to the binding of that particular ligand. So, it is, we get it in the neurotransmitter junction as nicotinic receptor. So, nicotine is there. We all know in the cigarette smoke is there, in many other places is nicotine is there, but it is naturally occurring molecule.

So, it has also the natural occurring and naturally it is available. Where the ligands are acetylcholine molecules. So, acetylcholine ester as we all know, you have read somewhere. So, acetylcholine molecule. What sort of acetyl function and the choline part is there? So, acetyl molecules are there, so in that particular neuromuscular junction where you can have the nicotinic receptors, that means, it can sit, nicotine molecule can come and sit on it.

So, the ligand what you can have, which can be giving you something what you can consider as your ligand-gated sodium ion channel Na plus channel. So, these molecules, so structurally it can be similar of that type. So, this is your acetylcholine molecule, so acetylcholine molecule you see that particular part the very basic backbone is NH2, CH2, CH2OH, how you can remember that particular thing.

So, if you can have from the lab, this NH2, CH2, CH2OH, which is nothing but your ethanol amine. So, if you have the ethanol amine function and this particular OH is now OCOCH3 is acetylated. So, the hydroxy group is acetylated and N is also not NH2, but it is methylated and further also, so it is ketonic thing.

So, trimethyl N function, trimethylamine function on the other side. To take care of the nicotine very simple molecule is a pieridine substituted molecule. So, nicotine is a very simple molecule that is why most of our drug molecules are nitrogen-based drug molecules and most of them are sometimes the pieridine-based also and the piperidines also is a substituted piperidines also.

So, this particular molecule when it is sitting the receptor molecules were there. So, the small molecules are playing some important role for this particular thing, but remember, the sodium ion is also the bigger players there.

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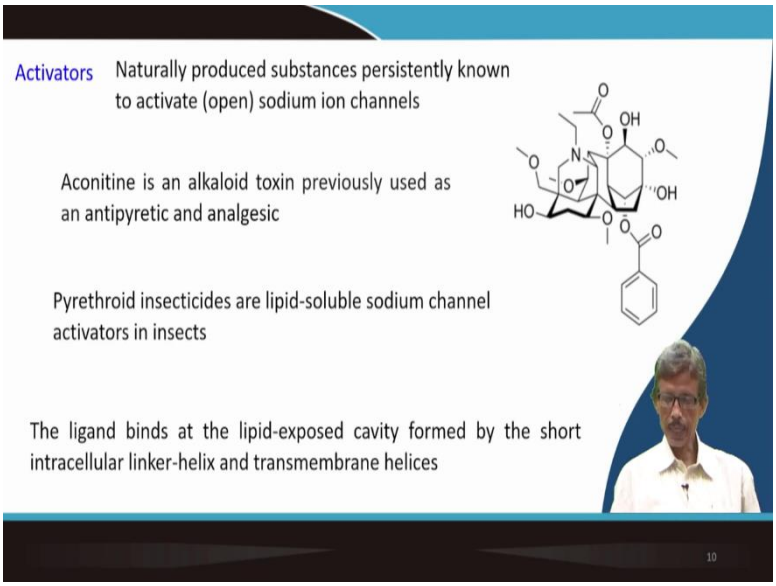

Now, we talk in terms of the corresponding activators where the activators we can have. So, these activators are basically more bigger and more complex molecules. So, natural products chemistry, we know, the organic chemists always use or find out the structure of some naturally occurring molecules.

So, nowadays, we are reaching that particular knowledge what people have identified long back say during the last 50 or 60 years that many such naturally occurring molecules are well known to us, we know all these things. And these molecules, if these naturally occurring

molecules are available to you, and if they can activate the sodium ion channels, that means, they are helping the opening up of all these things.

So, one such molecule like nicotine is the name is also very much similar to this is aconitine, is like nicotine is aconitine is a alkaloid toxin. So, nicotine is also definitely a toxic molecule. So, alkali toxin used for some time back as a drug molecule, the Chinese people are using for several centuries, the antipyretic and analgesic also. Antipyretic the pain reliever and analgesic. So, you see the big molecule.

So, these big molecules, if it comes and sit or bind at some point close to that of your sodium ion channel, and we find that due to that particular attachment, it can activate the sodium channel. So, definitely the poisoning effect or any other effect or the medicinal effect or the health effect, we can see, in with respect, in respect of your movement of the sodium ions.

Similarly, the pyrethroid, the pyrethroid insecticides well known for many years and which is also lipid-soluble sodium channel activators in insects. We can study all these things how the sodium channels in insects are looking for and how these molecules are functioning as insecticides.

So, they are basically activators, and sometimes they can damage all these things and that is why they can function as insecticides. So, we find that what are these activators basically? In this particular case for these insects also, the activator is a ligand, which comes and binds to the liquid exposed cavity formed by the short intercellular linker-helix and transmembrane helix. So, binding up all these particular types of insecticides are important, and they then finally disrupt the channels and the movement of the respective ions.

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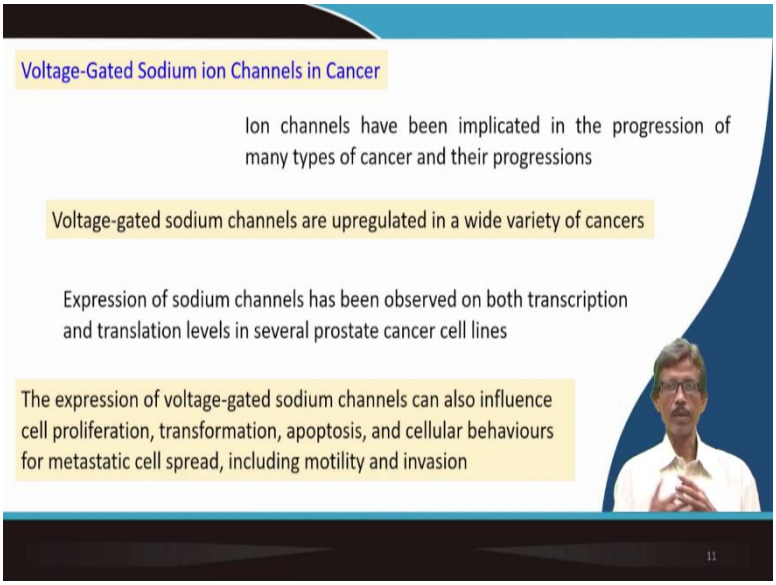

So, lastly, we will see that how it can be correlated to something deadly also, deadly disease also we know that cancers. Whether the sodium ions can have some role to play with regard to the cancer. So, definitely this channel, the ion channels have been implicated is a very recent story, and people have discovered it in recent time, that in the progression of many types of cancer and other thing other progressions also, because the cancer is a very long process, we all know that if the patient suffering from cancer can have these changes in all these ion channels, which are basically derived from our intake of sodium chloride only, and our concentration in our body for the sodium.

So, not only your blood pressure, what we see most of the time that we take most amount of the sodium chloride when people are suffering from hypertension. So, these voltage-gated sodium channels are up regulated in a wide variety of cancers. So, they are basically up-regulated. Expressions of these sodium channels have been observed, so it is a very recent discovery, but you see that what our particular study can be correlated to something else.

So, they are basically correlated to both transcription and translation levels, and in several prostate cancer cell lines also all these things have been found out. So, these expressions basically for voltage-gated sodium channels, not ligand-gated sodium the voltage-gated sodium channel can also influence the cell proliferation, transformations, apoptosis, cellular behaviors for metastatic cell, spreading, including motility and invasion. So, all these things are basically dependent on the presence of your sodium channels.

So, sodium channels are ubiquitous in nature. So, everywhere you have the sodium environment or the sodium channel environment. We are talking about some drug that is

functioning that is killing all this thing, but the cell processes such as the cell apoptosis, we call we know, then the different types of cellular behavior and metastatic cell spreads, we call metastasis for A cancer patient is spreading of all these things. Whether those things can be correlated to the knowledge what we are gaining through this only the studying of the sodium ion's movement through the channels and all these things.

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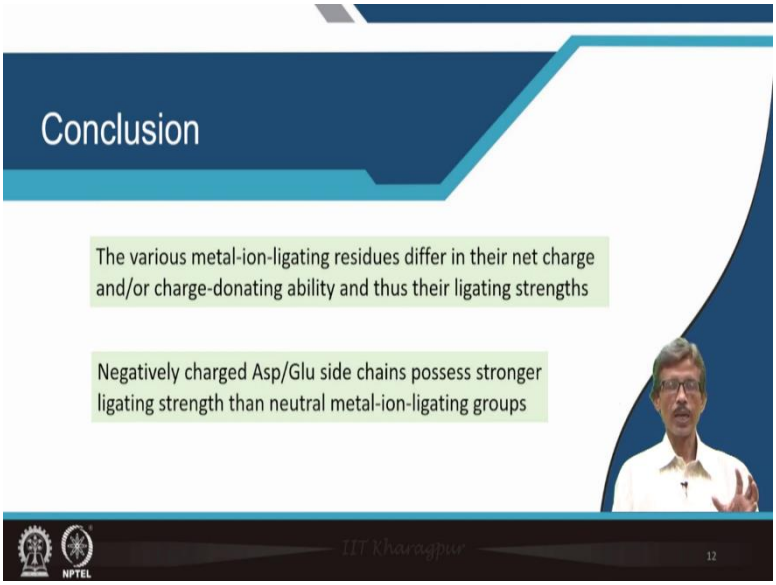

So, at the end, what we can now confer from these particular studies that the various metal ion ligating residues basically, they differ in their net charge that is why you have the sodium ions and we have the potassium ions, and the charge donating ability, how much charge they are donating, and thus, they are ligating strains.

Whether your carboxylate function is coming they are useful more than your corresponding phenolic residue and not, and what are the things we can be there. The carboxylate end from amino acid and the carboxylate end from the other amino acids because you can have the different amino acid residues in your hand.

Such as, we all know, that aspartate and glutamate these are the two commonly known amino acid residues. So, the negatively charged aspartate and glutamate residues, possess stronger ligating strength, not that the corresponding glycine residues. Then the neutral metal ion ligating groups.

So, if you have the negatively charged species, amino acid residues. And apart from these, you can have it from your aspartate and glutamate side chains, so you can have the stronger binding within these particular channels.

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So, references again, through that sodium channel in Wikipedia page and the book. Thank you very much for your kind attention.