**Biological Inorganic Chemistry**
**Professor Debashis Ray**
**Department of Chemistry**
**Indian Institute of Technology, Kharagpur**
**Lecture 22**
**Ion Channels and Ion Pumps**

(Refer Slide Time: 00:28)


Hello everybody, So, welcome back to the class where we are continuing our particular Module number 5, where we have briefly discussed in previous class that ion channels and the pumps, which are very much specialized one for these two ions. We are considering only these two and not the other ones. So, in this lecture we will talk about the two things very clearly that ion channels and ion pumps.

(Refer Slide Time: 00:54)

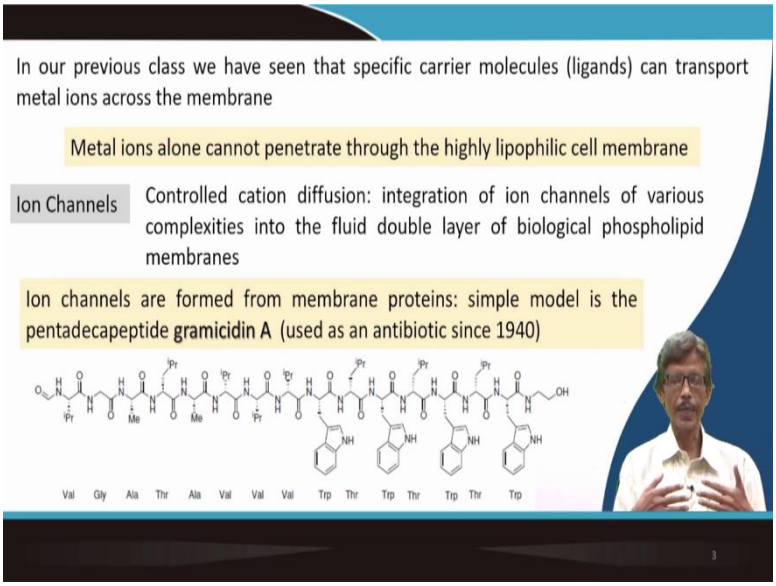
So, based on that basically what other things we can consider that, ions to know and the properties and functions. Already we know that we are talking all in terms of your sodium and the potassium ion. But if we can know something more than that, that when you drink water, so the water what we consume we can have both.

It should have the sodium ion, it should have the potassium ion, is not that we are not taking the extra salt as potassium chloride. So, these are they are and how these can also be assimilated from the simple drinking water. So, the next four concept points are basically your four bulleted points are all based on you see ions.

So, never forget that, whatever we are learning, whatever we are seeing in these particular classes, all these particular classes, they are based on ions. So, whenever you have the metal, it is definitely the metal ions, that is why, I have abbreviated as MIs. So, we only talk in terms of MIs. Whether it is a potassium ion or it is the iron ion or a zinc ion.

So, we will consider channels, we will consider palms, we will consider transporters. And finally, a very important aspect, whether we will be able to block these channels by something, such that, due to that blocking we get the benefit. So, what is that benefit also, we will see.

(Refer Slide Time: 02:18)



So, in our last class, what we have seen that, the specific carrier molecules you can have and we can designate these as ligands, like your crown ethers. So, they can transport metal ions across the membrane. So, metal ion, the bare metal on or the hydrated metal ion cannot move from one side to the other of the membrane, but if we can have some ionophore type of molecule, which can bind or which can coordinate to the metal ion center, such that, you can have a different lipophilicity of that particular complexed ion, and you can be able to pass it through that particular membrane.

Because the metal ions alone cannot penetrate through the highly lipophilic cell membrane. So, cell membrane will basically stop the movement of all these ions. So, that is why this elaborate mechanism has been devised, such that you can trap those ion, and selectively, you can move from one side to the other, it is not random.

Our body machinery is basically controlling, will control the movement of all these ions, such that you can reach a particular concentration from one side to the other. And also, while moving those things, your concentration at one side is going down. So, that concentration should not go to a certain limit also, so we will have always a limit. So, within this limit, all these processes are taking place, and we have these ion channels, and they control the cation diffusion.

Why I am particularly mentioning this particular thing that means why it is cation diffusion? We have seen that we can have the chloride ions because thechloride ions are there also in our body. That is why the very basic question we should ask every time from our school days also, why you are taking only sodium chloride, not sodium bromide or sodium iodide because sodium iodide nowadays we take for as the iodized salt, because we require the iodine requirement, but that is a different story.

But instead of sodium chloride, if you take other salt, like your sodium nitrate or any other thing what is the harm in it? Because not only the sodium ion, but also the chloride can also some good role to play in our body. So, these ion channels, we are not talking in terms of is whether it is a cation or anion.

So apart from these metal ions, if you have the nonmetallic anon like chloride ion, we can take care of that chloride ion also. So, the anion binding receptors, we can call ions the receptor because it is not metal ion, so anion binding ligands basically, you can have and that can trap those anions and move from one side to the other.

So, within this phospholipid membranes, we can have these ion channels from a number of these particular groups can attach, so ion channels are formed from membrane proteins. So, how these channels are formed? It is not that you can have the civil engineering channels you make some, such that your water can pass from one side to the another, so what you require. You require the placement of the bricks.

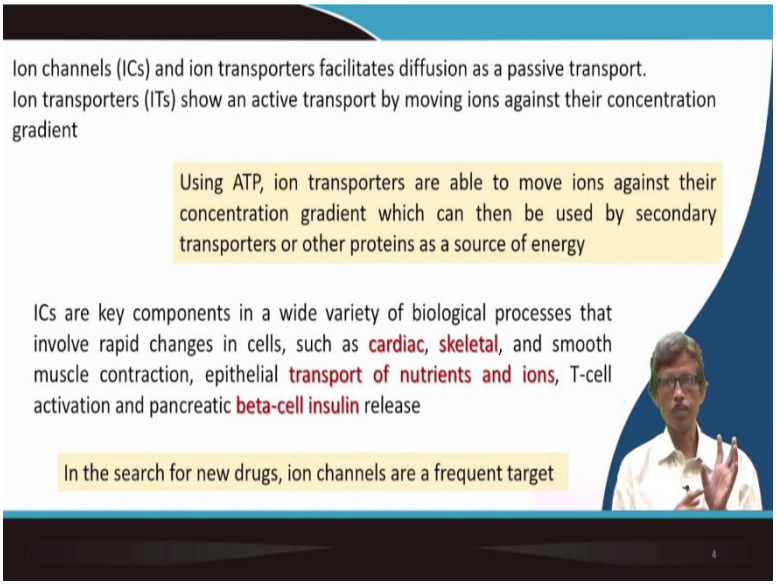
So, bricks are there, then you cement it also or sometimes it is not required. So, you have the brick such that you can guide some parts, such that water can flow through that particular channel. Similarly, here we have, we will take the help of the proteins as bricks, and you can have the channel where you can pass selectively some ions, whether you can have the sodium ion or the potassium ion.

So, we have been studying all these things during the last say 80 years that is from 1940. So, during the last 80 years, we have been studying it when it was first discovered or first identified, but the knowledge whatever we have gathered so far for during these last 80 years is not very big. Only during the last 10 or 15 years, we are studying all these things, and we basically point out all these and their functions.

So, do not worry about the huge molecule because already I defined it. If it is there, if you consider that you read it, that is the pentadecapeptide. So, how many peptide bonds you should have? And pentadeca means 10 plus 5 is 15 numbers, those are 15 numbers. How you get all these things these are very simple molecules. So, you see that is why it has been discovered 80 years back. So, on the bottom we have written all the amino acid residues.

So, valine, glycine, alanine, thionine, alanine, valine and all these things. So, it is not the genetic coding type of thing, but is a straight way is a pentadecapeptide molecule what you get it through the incorporation all the different amino acids. So, whether that can basically be available for binding all these metal ions or these two types of metal ions.

(Refer Slide Time: 07:14)




So, now, I categorically abbreviated it as the ICs because I am an organic chemist. I always abbreviate my subject as IC is inorganic chemistry, but that can also be applied to your ion channels. It is not that is a misnomer what I am applying from one point to the other. But whenever you are talking about this sodium ion and the potassium ion and that ICs is not your inorganic chemistry, but it is typically pointing out for your ICs as ion channels and ITs are ion transporter, because we all know what we see as ITs.

So, these ion transporters basically can control every time we see the transport, as well as the diffusion, and you have the concentration gradient. So, these are the key things what you can consider, and we basically use ATP. So, ATP is there and ion transporters are able to move ions from one point to the other. Again, we know that the concentration gradient, and the secondary transporters can also be available, there are other proteins as a source of energy.

So, how this energy can be used is due to the corresponding transporters, which are available, which can be able to move ions against the concentration gradient, that means, it is in the opposite direction it is trying to move, so you need a pump and you need some energy.

So, these ion channels are key components of so many things, for the different types of biological processes. So, that is why how we can correlate all these things to the final thing that how these studies and all these things can be beneficial for our health, for our diseases or whether we can have some drugs or medicine molecules out of these information, out of these studies.

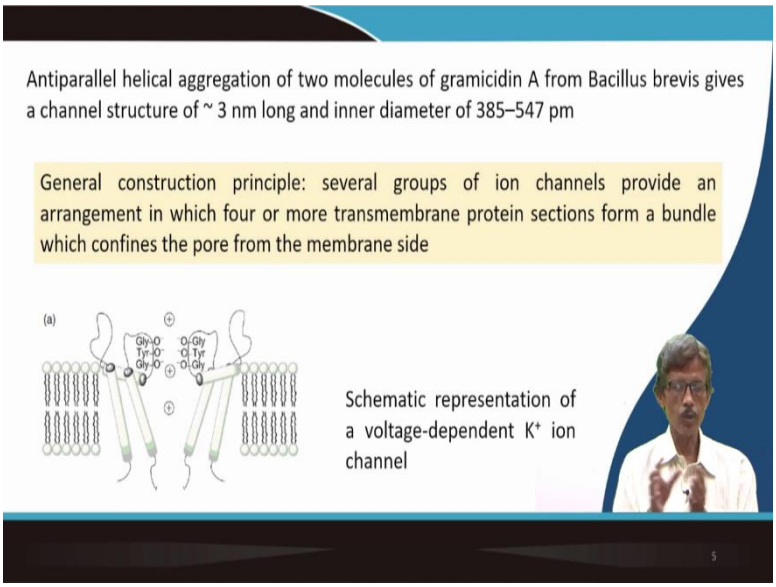
So, the rapid changes in the cells, what can happen due to these ion transport. Such as, your cardiac, skeletal, smooth muscle contraction, epithelial transport of nutrients or ions, T cell activation and pancreatic beta cell insulin release. So, all these things, all these are different processes basically, what you see, they are controlled by all these ion channels.

So, you see that the civil engineering channel what I was discussing that is allowing only the water, but along with that water you can have the other species, that means, if the water is our drinking water, with sugar, with salt and so many things, they will carry all these things.

So is also used for the transport of nutrients as well as the ions of different types, can be cations or can be anions also. Then for our immunity boosting, that means, the T cell activation. So, ions are also there for boosting our T cell. And then obviously, the very simple thing that the movement of the insulin to take care of your glucose concentration.

So, that is why, all these studies can be directed finally to the development of new drugs, these ion channels are frequently the target. So, if you target the ion channel, you can have the blocker development of the blocker studies of those blockers and you block the channel such that you can get something, which is beneficial for your life.

(Refer Slide Time: 10:31)




So, this helical aggregation. So, antiparallel not of the same type is the antiparallel so, one is up another is down. So, antiparallel aggregation of two molecules of gramicidin, gramicidin A which is we are getting from Bacillus brevis, which basically gives the two of these basically giving the channel structure of only three nanometer long.

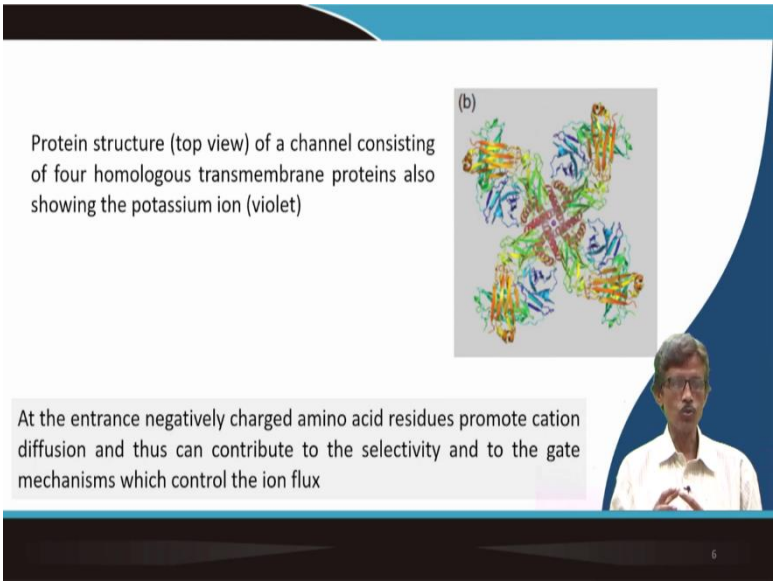
And with having an inner diameter ID is again, we are going to a picometer scale because this thing is very small. The digit, instead of remembering it is point 384 or 3.85 or 38.5 is easy to remember 385. So, you change the unit from nanometer to picometer. So, that is the idea that how easily or how quickly you can remember these things.

So, how you basically construct the structure. So, several groups of ion channels provide an arrangement. So, they are coming and they are fixing where four or more transmembrane protein section form a bundle. So, four or more, so is basically as an aggregation type of thing the way we know our hemoglobin has 4 units of myoglobin part, having around say 153 or 154 amino acid residues.

So, that bundle type of arrangement, so that bundle type of arrangement is always easy to have it such that finally you get something which is your channel. So, is the voltage dependent potassium ion channel, how it looks like that we can see, and is basically this particular case. So, you can have. So, all the amino acid residues are there, so amino acid residues are basically showing some groups to then, and these positive charges, these positive charges are for your product ion.

So, you have the lipid bilayer on the left hand right, and you have the channel in between. So, channel is basically not that you do not have the lipid bilayer and it is sitting inside, it is on the bilayer. So, on the bilayer surface is basically it is showing. So, to get a clear picture or get a clear scheme, what you get, so you remove that particular point as the background, but the background the bilayer is there. So, on that bilayer background you have this corresponding channel. So, that channel how it grows in that particular aggregation finally gives you the real structure.

(Refer Slide Time: 12:54)




So, you see, immediately if you see you can look at it out that if you can have these things, not that you have to draw it nicely and all these things, but the spiral thing and the spiral drawing you can have what we stock it as a cartoon diagram. So, what basic and the fundamental thing you can have from this particular point is that you can have four such units, one here, one here, one here, one here. Not the four directions what we can have, the east, west, north and south, but is the agonal directions. Probably, you know all the names of these what we say all the time in Bengali also, but you have the northeast you have the southeast and all.

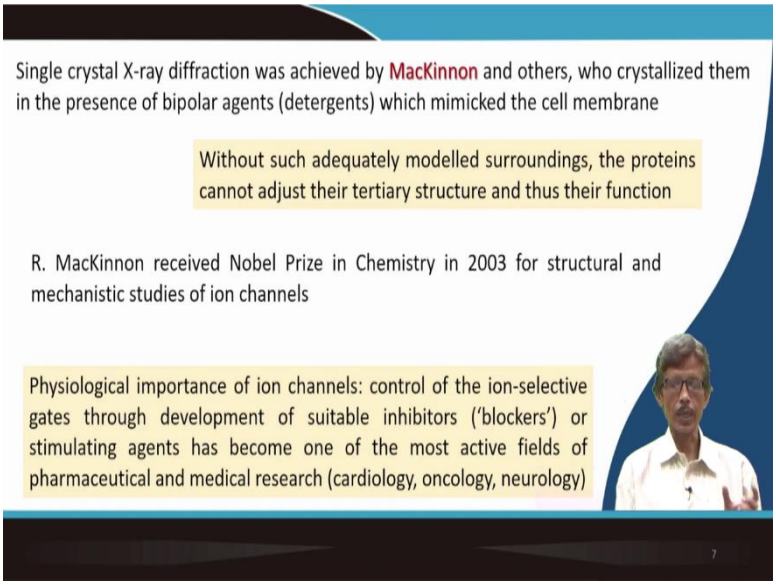
So, if you put in this figure, so, four units you have to draw first, then you have the spiral moment at the center basically. So, center again, it is having a C4 symmetry the fourfold symmetry within this particular, basically a square type of arrangement or a diamond type of arrangement. So, either a diamond or a square, having both these two have the C4 symmetry.

So, within that particular, so you get a protein structure, structural views you have consist of four homologous transmembrane proteins. Like your hemoglobin molecule you can, it is easy to remember also that hemoglobin also has the four units, but here also you can have the four homologous of same type homologs are there.

So, transmembrane proteins and showing the cavity where the color is violet at the center only. So, at the center you have the potassium. You see, such a huge arrangement considered in terms of your huge ligand, so all these four things are required to only take care of potassium ion. So, this is basically, so that is why it is only allowing through that particular channel, potassium can only move from one side to the other.

So, when it is entering there you have the negatively charged amino acid residues, so carboxylate ends or the phenol ends, you have the negatively charged, such that it can attract the potassium ion through electrostatic attraction and promote then the cation to diffuse and basically that can also contribute selectively the gate mechanism and which is basically or finally controlling the ion flask.

(Refer Slide Time: 15:13)




So, we get the ion flux from there. And what are MacKinnon, what our MacKinnon did all these things finally did a single crystal X-ray structure. And before that, when you go for the single crystal X-ray structure determination, what you need? You need the good single crystal, this term is single, one crystal single crystals, not as a multi-crystals or the amorphous powder.

So, he crystallized all these mechanisms applied, so is a bipolar reagent as detergent, only in presence of detergent, because the detergent can mimic the cell membrane. So, the bipolar agent is required so that bipolar agent or in presence of the detergent, he and his team basically the research group could crystallize it for its good crystal for its structure determination.

So, that adequately model surroundings what we can have for this particular protein. So, the four units, the four units basically like your hemoglobin again, because we will discuss afterwards do not worry, I am going from periodic table starting from sodium, potassium and all these then we will definitely move to iron.

So, here you can have that particular aggregation of four such units like your hemoglobin, giving you the final tertiary structure. So, not only what we know that the hemoglobin has a tertiary structure four such units are there, and which is required for binding four centers of iron.

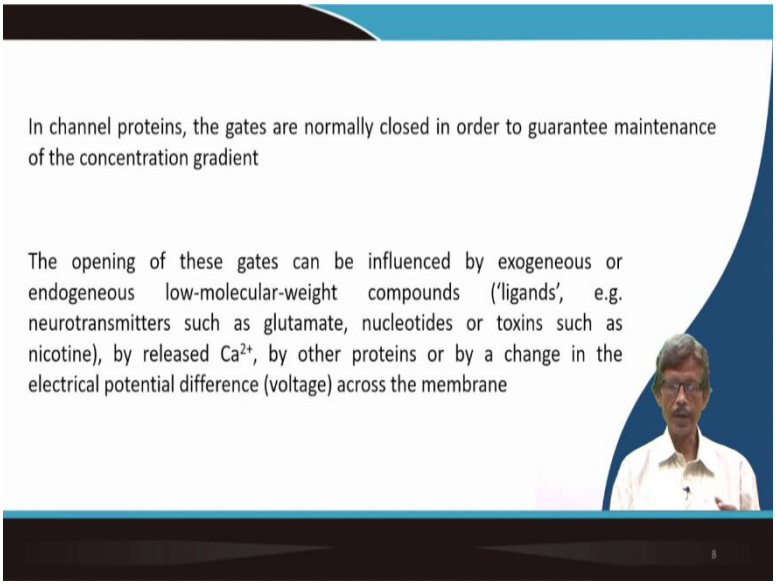
But here you see that the tertiary structure is only controlling that particular entity basically, controlling one potassium ion or one K plus. So it is not very old story, only because he is working for a long time, but he got the Nobel Prize in 2003 for the structure and for the mechanistic aspects.

So, if we consider now that, okay, we can have this importance of these ion channels. Definitely they are important, and for our physiological thing also, is that, that how the bioinorganic chemistry or the biological inorganic chemistry, how much you know about the biological sting.

When you know about the biological thing in detail, then only you can think about what is the abnormality there, what is the disease conditions and how we can remove those conditions, the diseased conditions and all these things. So, you will have definitely in terms of those the physiological importance of the ion channels.

So, it can control the ion selective gates by giving some inhibitors, and those inhibitors, which inhibits the function we can consider them as blockers or sometimes can stimulate the agents. And most of these fields are of not only the physiological importance, but also pharmaceutical importance, as well as people can do in the medical research in the areas of cardiology, the heart related thing, then oncology, the cancer related thing and the neurological thing in terms of your neurology.

(Refer Slide Time: 18:16)



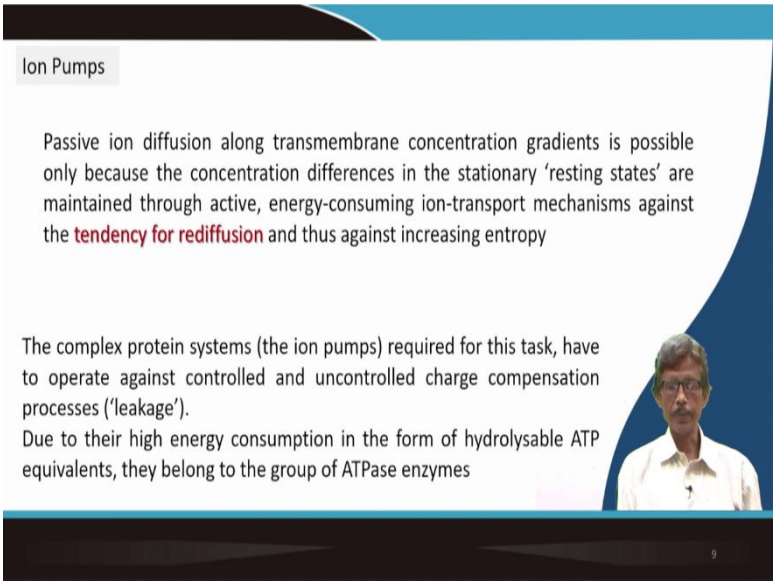

So, the medical thing is also very much benefited by knowing the channel properties of all these gates and pumps, such that, you can have the proper maintenance of the concentration gradient. So, when we open up these things, we know that the groups like the exogenous and endogenous, the exogenous are coming from outside, low molecular weight compounds what we call as your ligand.

So, these ligands can also be your neurotransmitters. When you talk in terms of the neurological thing or neurological disorder or neurological problems, then you have to identify the nature of those neurotransmitters.

Those are small organic molecules sometimes, some amines only or catecholamines also. So, these catecholamines are small organic molecules, but when they are functioning or they are disrupting or enhancing your sending signals, the neural signal, what you find that neurotransmitters like your glutamate. Glutamate can also be a neurotransmitter or a neurochemical, then sometimes the nucleotides or sometimes simple toxins the nicotine.

The nicotine can stimulate us. We all know, the nicotine can also blocking some points. So, the nicotine itself can be a blocker then. Sometimes it can also release the calcium ion by other proteins by changing the electrical potential difference that against the voltage control. So, not only the molecule itself, but the voltage control of this movement can also be achieved since we have identified these two types. The one is ligand gated, another is voltage gated thing.

(Refer Slide Time: 19:59)




So, now, we quickly see the ion pumps, the passive ion diffusion what we can control, what we can monitor. So, now we can have a very good idea about what are pumps such that you can have a stationary resting state, and energy consuming ion transport can be achieved against the tendency for diffusion. So, if you have the diffusion from left to right, you can have the transport from right to left.

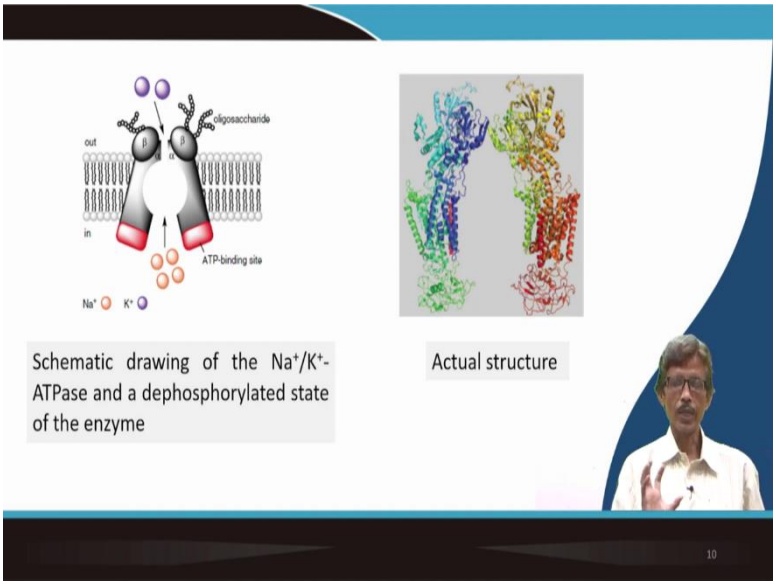
Then we can have some point, the leakage, the complex protein system or the ion pumps, which basically requiring for this task, have to operate against control or uncontrolled charge compensation processes. What are these? That you have to have the corresponding charge compensation, the positive charge is being compensated by the negative charges available over there.

So, you have the very complex protein system. Just now, we have seen, the bundles of these proteins then again you have the tetrameric form. So, the ion pumps basically functioning or doing that particular task and they operate against the charge compensation. So, the charge compensation is required for the moment, but when you disrupt that thing we can consider it as a typical leakage.

Leakage of your washbasin, leakage of your some pot, such that, the ions are moving out through that leak. So, due to their high energy consumption in the form of hydrolysable ATP, the ATP should be hydrolysable. Some metal ions you should bring will bring magnesium we all know that magnesium is required for your ATP hydrolysis.

So, hydrolysable ATPs are they are there. Not that all ATPs are getting hydrolyzed, and they all belong to the group of ATPase enzymes. So, sodium and potassium ion pumps are required for your ATP hydrolysis and your energy delivery.

(Refer Slide Time: 21:50)




So, if you have the dephosphorylated state of the enzyme, so, you have these. So, this is the chain thing, and now, we are leveling these two ions together now. Sodium ion as well as the potassium ions. So, on the bottom you have the sodium ions the smaller sodium ions and the violet big spheres are your potassium ions at the top.

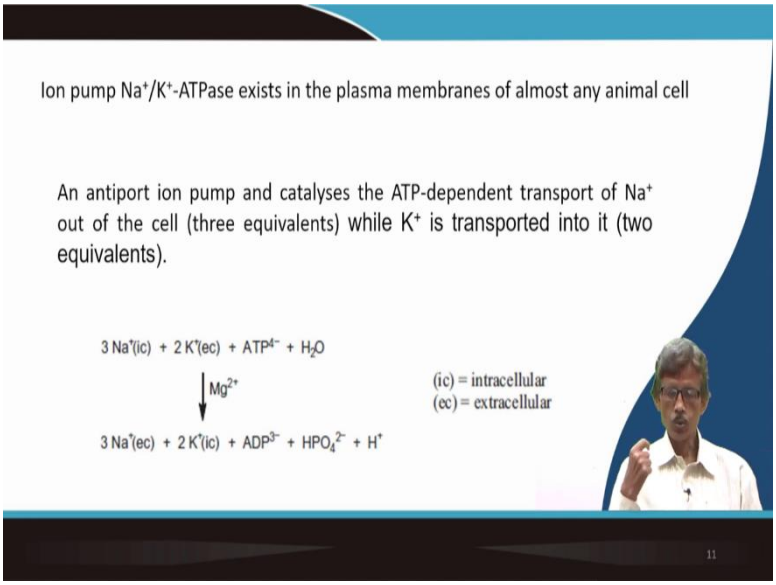
Then you have all these parts, you have the oligosaccharides and all these things. But since these are four bundle type of things, so like your hemoglobin you can level it as 2 alpha, 2 beta, alpha, alpha, beta, beta orientation of these groups. So, these basically is giving that particular entity, so this entity we have, so if you can consider 1, 2, 3, 4, 4 such units, so, this is the bundle arrangement, and you allow something to pass over there on this particular lipid bilayer.

What is that actual structure? So, actual structure is this now. So, for the ATPase do not worry, we will again come back for these particular examples in some other discussions, that this bundle pot is again similar object type for the potassium channel, but these are ATPases, not that your potassium channel only.

So, they are also 4. So, 4 number the number 4 is very important, and you can have occasionally find from hemoglobin to these ATPases how the proteins are assembled, is because most of the time we will take the help of only cartoon diagram, we are not doing the

corresponding protein crystallography, we are not determining the whole structure up to a particular resolution, say 2.4 angstrom resolution or 2.2 angstrom resolution, but we know the cartoon structure, because you have the ligand environment, we know the environment. And by knowing that particular environment, you can only see that how these metal ions can pass through all these cases.

(Refer Slide Time: 23:14)




So, the ion pump like your ion channel of these particular sodium and potassium ase, ATPases are there, and plasma membrane of almost any animal cell. So, wherever you find any animal cell, you will find all these there. And then one symport, which is helping the port the movement, you can have also the antiport then the reverse direction.

So, antiport ion pump there, is there and which catalyzes the ATP-dependent transport of NA plus out of the cell, three equivalents of sodium ion can be moving from the cell, while potassium is transported into it of two equivalents. So, more and more potassium will be entering the cell and more and more sodium will be coming out from the cell. That is why this equilibrium is again achieve such that you can reach a concentration where your sodium concentration outside the cell is higher compared to your potassium concentration, which is highly concentrated within the cell.

So, what we see here is that, you have the corresponding intracellular and the extracellular corresponding channel or the pumps whatever you consider. Since, we are talking in terms of the 3 such or the 3 equivalents or 3 miliequuivalents of these ions of sodium. So, when you write the corresponding, always, the chemists always tempted to write the chemical equation.

Here you have the biochemical equation. So, you always try to have a scheme, the reaction scheme or the chemical reaction. We write in this particular fashion such that you can have a very good idea what is happening for this particular reaction from left to right or from top to bottom, hence the arrow is your downward arrow.

So, the corresponding intracellular sodium channel, so sodium channel or sodium ion pump, what is there. So, in this particular case it is the pump basically, the ATPases are the proton pump, sometimes we have the proton supply also, because you see that proton we are producing from the reaction.

So, 3 is to 2, the combination is 3 is to 2 only. For sodium as well as the potassium because you always go for these such that you move 3 sodium ions and you move 2 potassium ions with that particular thing. So, what we get from there is that, during that moment you write now ATP 4 minus that all the phosphate groups is a adenosine triphosphate.

So, if you have these, all these 4 phosphate groups because they are phosphate esters, but it can go for different levels of deprotonation, it can be protonated. But the most important thing is the 4 minus charge. So is the charge is quadruple charge, a 4 negative charge on the phosphate anions and those negative charges along with these charges what we get from the sodium and the potassium ion, but the side by you have the magnesium, but that magnesium we will see when we talk about the magnesium. The magnesium is binding on this phosphate group.

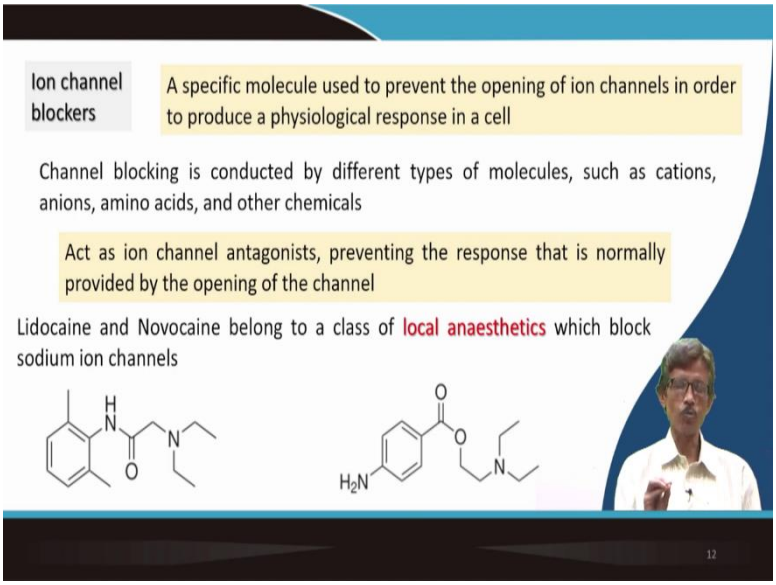
So, if you have a diphosphate, so 2 have the phosphorus oxygen bond, that means the 2 of the oxygen ends up those phosphorus oxygen bond are available to bind your magnesium. So, many number of these bidentate parts of the diphosphate groups can come and bind to the magnesium because you have to go for the strain on that particular bond such that your good nucleophile.

Water is your good nucleophile, and the good nucleophile H2O will come, and that nucleophile will attack that particular bond and you can be able to clip that particular bond giving you the hydrolases. And you produce HPO42 minus. So, you will be able to take up that, as HPO42 minus, and along with that, you can have the H plus. So we will be liberating the corresponding proton from that particular medium.

So, from this particular reaction, we can see that you can have these iron pumps, which is taking care of not only sodium and potassium, but also the presence of magnesium because it

is a ATP-dependent thing. ATP will give you the corresponding energy for its hydrolysis, and that energy is basically, not your electrical energy to run the electrical pump, it is that energy from the ATP due to that hydrolysis, which is basically running the pump for the sodium potassium pump to give it energy to run that thing and to give these reactions from movement of, only the movement, what we are getting, like a pump moving the water from one side to the other.

(Refer Slide Time: 28:30)




Then finally, quickly see, heard about, we know about the ion channel blockers. We know that the channels are there and the channels we have developed by the placement of these proteins. So, if we now see like your nicotine. I give you the example the nicotine molecule. Similarly, some other specific molecule, which can prevent the opening of some ion channel, we require in a regular fashion like your gate or your door or a window, we open it as and when required.

These ion channels are also there. So, ligand gated channel or the voltage gated channel, as we need we can open it up and then we can close it up, close it down also. So, if the nicotine is there, and that molecule is there, and which can prevent this opening in order to produce a physiological response in a cell. So, we have taken that nicotine. If we consider that it will have some drug like or the medicine like effect on the system, so it will just sit over there and will closed that particular channel.

And whether that particular closing will have some benefit to us or not. So, the channel blocking is basically is conducted by different types of molecules, different anions, cations and anions, amino acids and other chemicals, and they act on ion channel antagonists. We

know this against that means it will close the channel or channel blocker. Sometimes it can assist the opening up of the channel also that we will also see at some point. Then it prevents the response of the normally provided by the opening of the channel.

So, when we get the function when the channel is open only, but when it is not there, we do not get that particular thing, 2 such molecules these are drug molecules, these are generic name basically not the commercial name basically, Lidocaine and Novocaine, the caine is the common term, the suffix basically on these thing, they function as local anesthetics. We all know a little bit on that only.

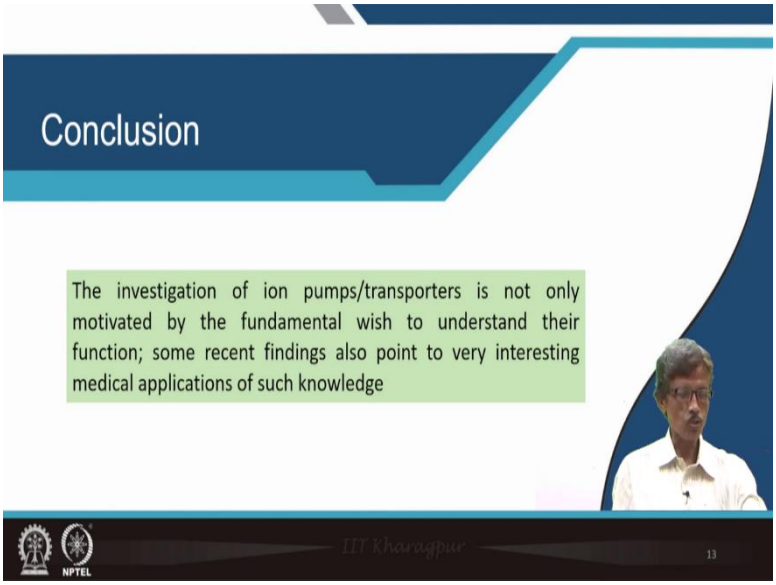
But if we now correlate that we have learnt a lot about the sodium ion, as well as the potassium ions and know about the channels. So, why they are functioning as local anesthetics these molecules? Because they can go, and they can basically block those channels of sodium such that you can see the corresponding effect as the, is an anesthetic effect of those particular drug molecules.

It is a very simple molecule not a very big molecule. So, you have a mild backbone in it. So, is amido amine type of thing and on the right hand side you have the amine function, but not the free NH2 function, but it is substituted. So a diethyl amine part. So, one amide part, one diethyl amine part and two substituted, double substituted phenyl ring or the benzene ring.

The next one, the Novocaine. Novocaine is of similar type, but now you have the ester function. So, you see, these are the two basic things, the drug molecules are basically, we all know that the nitrogen bearing molecules are our drug molecules basically we get, but they are modifying. If one is obtained first, we try to modify it, particularly the naturally occurring molecules like your nicotine and all these things, so you can have this similarity.

So, you see the tail end of the n diethyl part is same, only the amide part has been modified with a long chain, and you have the substitution not only the 2 methyl functions on the benzidine, but paramine function as the substitutions.

(Refer Slide Time: 32:13)




So, now, definitely we should conclude this particular talk or the lecture here is, by saying that, whatever studies and whatever investigation or whatever thing we are studying here is due to the pumps of ion sub-sodium as well as potassium and the transporters. Basically, we can this particular studies can modify the fundamental ways to understand. What we basically we like to know or like to understand, and like to believe it.

And finally, we can apply it they are functions. So, the recent research and recent walks basically also find that very interesting medical applications of such knowledge. So, that is why, we definitely conclude on this, why we should study the sodium and potassium ion channels, because every day we are consuming sodium ions and the potassium ions directly as the salt or directly from the food material, but we should know about their function for our medical applications.

(Refer Slide Time: 33:14)


And the references that again, you simply start with the ion channel, and then, the other related thing, it will be highlighted in the Wikipedia pages, probably you know, and you can get the other things if you start with this particular item of ion channel and the book of Robert Crichton. Thank you very much.