Biological Inorganic Chemistry
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Lecture 56
Brain & blood-brain barrier (BBB)

Hello, students. Good morning, everybody.

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Hello students, good morning everybody. So, we will reach to the module 12 where we will talk about the interesting area, obviously, we are not going beyond our metal ions, which is the integral part of your biological inorganic chemistry. So, today we will be talking about the brain, where your metal ions can be there and blood brain barrier, which we abbreviate as BBB, which is a very important component of our brain.

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So, we just only want to see the way we know about what are the primary metal ions which we have in our body, in our blood, similarly, what are the metal ions we can have in our brain. Then how these, movement of these metal ions are localized, that means there are certain pockets where one particular metal ion can have a huge concentration and other is not. Then what is the barrier which can control or compartmentalize these concentrations in the different small, small pockets and which is directly related to your particular area of research, area of interest, and is a very huge field which is growing very fast also, which is metalloneurochemistry.

So, the neurological functions which can be dominated by the chemistry, like that of your biochemistry, but which is based on the different movement of the metal ions, their functions, and if the metalloenzymes are also in involved. Then we will talk about only the chemical signaling, not way we have seen earlier as the electrical signaling or the other signaling, but we will talk about the chemical signaling and if we have some mismanagement of the normal homeostasis of the metal ions within the brain.

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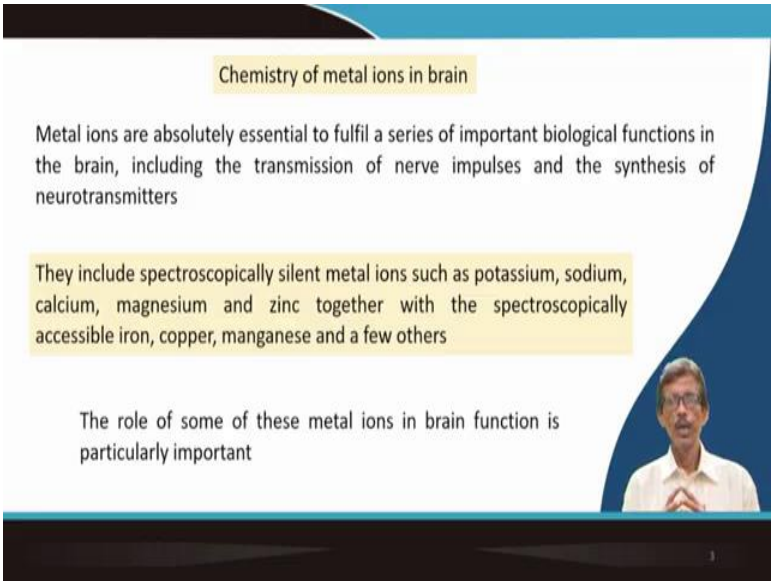

So, basically what we are looking for. We are basically looking for the involvement, the presence, identification of the metal ions within the brain, and what sort of chemistry it can go or it can do for us. Because we all know that these are the very essential components for many important biological functions, but now we will talk about the different biological functions which are originating from your brain. So, we can have the nerve impulses or the nervous impulses as well as the synthesis of the neurotransmitters. So, metalloenzymes can be there if we talk about the corresponding hydrolases, the peptide hydrolyzing enzymes, we think that we can have the corresponding breakage.

Similarly, different neurotransmitters we can synthesize, but many times we will find that MIs that means your metal ions are involved. So, what are those metal ions basically? So, they are basically starting from potassium to zinc. And when we consider about potassium, sodium, calcium, magnesium, we all know these are the main group elements and as well as the zinc which are spectroscopically silent, because when we dissolved these salts in a test tube in your laboratory class, we know they are giving you a colorless solution.

That means not only your eyes, but that your spectral eyes, as a spectroscopic eyes are also not able to find out these metal ions in solution whether you have a sodium ion or potassium ion or the zinc ion. So you must have some other different technique which can nicely detect the presence of these metal ions.

Along with that what we can have. We know that the color solutions. Those color metal ions like that of your iron, copper, manganese, and all other few. So, what are the roles basically? So, when we talk about the roles of these metal ions, so definitely these metal ions are again in the hydrated form if they are not bound to the protein chain. So, they are usually will be important for your brain function. And that is why they are very much important in understanding the corresponding metalloneurochemistry.

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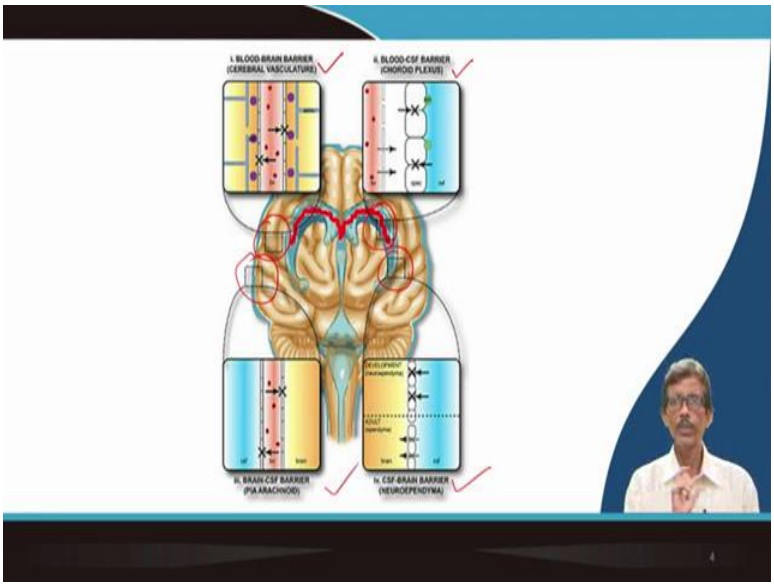

So, roughly, if we see about the huge structure of our brain, means the human brain, we are directly talking about the human brain, but we can have the model of the rat brain, the guinea pig brain or any other thing people can go for. These are the laboratory animals which can be studied nicely. So, ultimate goal is that how we can understand about our brain. So, it can have four different areas basically. You see the areas which are basically marked over here by the four squares. And these fours squares basically giving us that particular thing that this is one particular area, this is another particular area. So, is basically a huge structure and within which we can have, the top one is your blood brain barrier, so which we call as the BBB.

So, we are having many things like your hormones, like your toxic metal, heavier metals ions like cadmium, mercury and all. They are flowing in your blood. When you take the food material or body digest everything and then ultimately it goes to our blood. But that will not tell you that that can also reach to your brain. So, we must have some barrier, so we must have some layer

where the components which are present in the blood cannot directly reach to your brain. So, you can have the blood brain barrier.

Then blood CSF barrier, the cerebral spinal fluid, we know the corresponding spinal cord we have and within which we have the cerebellum or the cerebrum and within that you have the corresponding fluid. And that can also have some compartmentalized thing that we can separate it out. So, you see one layer and another layer. So, you have these layers, because the movement is restricted and here is also the movement is restricted. So, if you have the flow of the blood is not that the all the areas will allow you to go for these metal lines. So, if your body is absorbing the metal ions from your food material is not that it will reach your brain.

Similarly, that number three is your corresponding brain CSF barrier. So, blood CSF barrier, then brain CSM barrier, and finally, the CSF brain barrier. So, these are the basically all four areas where the corresponding movement of the metal ions as well as many important molecules can take place.

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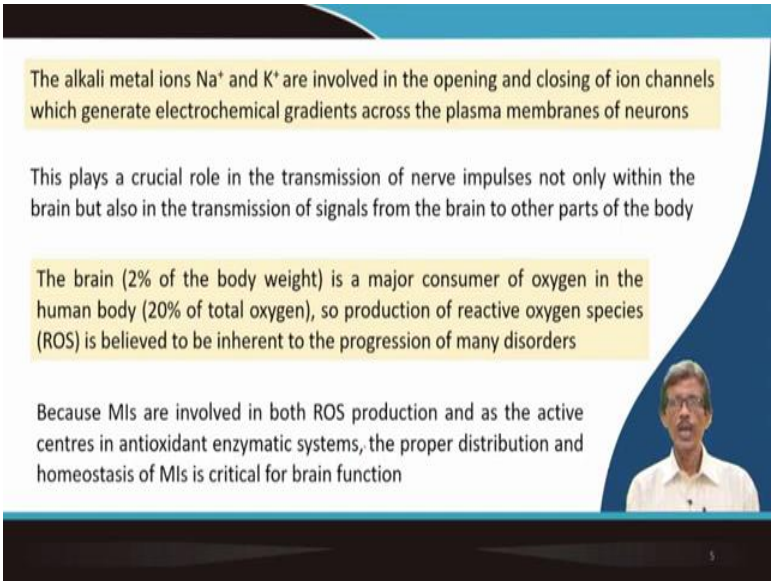

So, if we just simply talk about because we have discussed all in detail like that of your corresponding transport of the sodium ion and the potassium ion, their corresponding ATPases and the corresponding sodium ion and the potassium ion pumps and there we have seen that it basically used for opening and closing of the ion channels and they are moving from one part to

the other that is why within the cell we have one particular concentration of sodium ion and outside the cell we have a different one.

And while moving they are giving us some electrochemical gradient that means the charge is transferred across the membrane, the lipid membrane or the corresponding cell membrane. Similarly, if your neurons can have some such membrane, we are talking about the layer, we are talking about that membrane, we are talking about that barrier. So, that barrier basically if it allows or selectively it can allow to pass certain metal ions, then only we can have the enrichment of that metal ion in the other side.

So, we see that this particular transformation of this particular electrical gradient is very much useful on basically plays a central role or crucial role in the transmission of nerve pulses and not only within the brain, but also in the transmission of signals from the brain to other parts of the body. So, nerve directly related to your brain and all these impulses and all these things and also the final stage, the diseased conditions, that means you have the normal brain and you have the abnormal or the diseased brain so how to monitor these things. Because people tried a lot how to identify these diseased conditions, because we will be talking in other classes also that you can have the Alzheimer's disease, you can have the Parkinson's disease and all these things and out of that people are ultimately dying.

So, if you have a body in your hand, a dead body in your hand, you can scan the brain again and look at all these things, how the brain looks like and how these positions of the barriers and how the concentration of the metal ions so far accumulated in this diseased person's brain. So, we can have all these information. So, nicely these things can be developed. And we can understand many things from this. So, we know that about 2% of your body what is your brain weight, brain means inside, not the skull, what is the brain or gray matter we call, so which basically consumes a huge amount of oxygen compared to our body. So, 20% of the total oxygen is being consumed by our brain. Is body weight is comparison, if you compare it is very small, but your amount of oxygen consumption is very high.

So, the once you consume oxygen, you can go for its reduction to superoxide or peroxide that means or sometimes the free radicals are formed. So, the reactive oxygen species are forming readily over there and therefore it is believed to be an inherent part in the progression of many

disorders. That means you have the ROS and ROS is very beautiful oxidizing agent in terms of our chemical synthesis what we call. That means it will try to oxidize many things, it will try to oxidize the corresponding sulfide residue in the cysteine amino acid part, giving you the sulfur-sulfur bond, which we all know, if you have many sulfur-sulfur bonds, your protein can go for aggregation or agglomeration.

So, that basically create a different structure. So, because of these that metal ions MIs are involved in both ROS production that means we know that we can have iron, we can have copper and we can have our zinc and manganese in our brain so as the active centers also as antioxidant enzyme systems. That means we know that superoxide dismutase, it can be copper zinc based or it can be manganese based. So, that superoxide dismutase will try to destroy the accumulation of superoxide ions in our body, in our blood, in our corresponding cerebrospinal fluid as well as ultimately in the brain.

So, the proper distribution of homeostasis of these metal ions is critical for our active brain function. So, many diseases basically the huge amount of neurochemical knowledge or neurochemistry we all know. The neurotransmitters are nothing but your neurochemicals. And when we talk in terms of those neurochemicals, it is the subject which can be considered as the neurochemistry and when the neurochemistry is finally controlled by the metal ions, we call it as the metalloneurochemistry.

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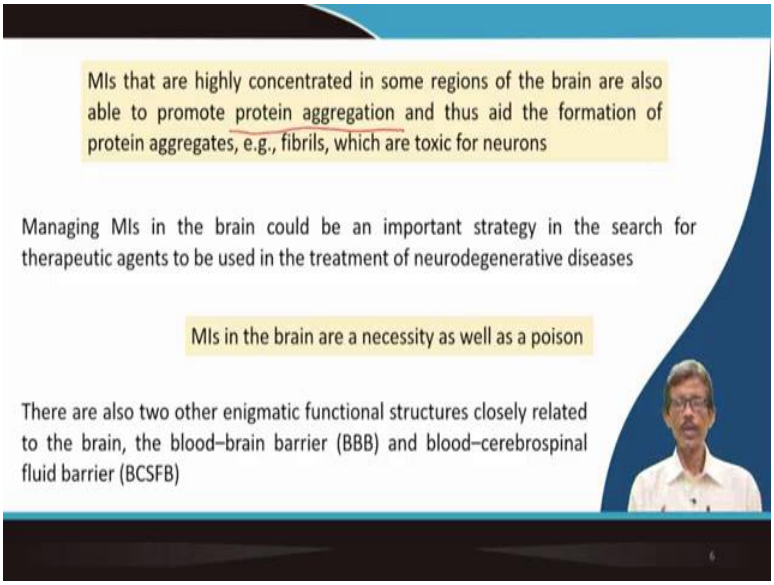

So, what we see there is that these metal ions are concentrated in some region. That means way we know that when on the earth surface the metal ions are flowing through some water stream and it is getting deposited under the corresponding earth surface and ultimately we get the corresponding mineralized form. Similarly, within the brain, in the solution form also, you see that it is compartmentalized. So, different compartments are available to keep the different types of metal ions and also not only the different metal ions, but also in different concentrations, because these range of concentrations are important.

And due to these basically we have seen that if you have iron, we know that iron is very much popular and well known to ask for their Fenton chemistry that means the radical formation chemistry. So, the Fenton chemistry if it is there and if it is operating, what we find that we can have the corresponding ROS formation that is reactive oxygen species are forming readily out of that particular reaction where hydrogen peroxide is produced in the medium from the oxygen O2 as well as the redox of the ferrous ferric system.

So, if we go for that and if ROS is involved and the concentrated metal ions are also involved, we can have certain thing which we call as the protein aggregation, which is a very important area of research. People are working on these. This is the protein aggregation reaction. What is that aggregation? We know the protein can have the structure, the primary structure, secondary structure, tertiary structure as well as the quaternary structure. We know one particular basic unit of myoglobin can give you a tetrameric form of hemoglobin. So, hemoglobin can have a quaternary structure.

If that particular structure is changing and we find that due to this oxidation or some other involvement of the metal ions, because the metal ions can also interact with all these proteins and the proteins are basically accumulating at a very small space and they are going for the aggregation, and finally, we get these we known as these the protein aggregates for the formation of the fibrils, is fiber like structures, this string, string structure, the fiber like structure and sometime we ultimately find that we can have the corresponding plaque, is a scale, like a dental skill is basically getting deposited, some hard material is getting deposited out of those proteins basically.

So, protein is getting drying up, giving the fibers, the fibrils and ultimately the plaque. So, definitely that will disturb some things say solid deposition of these aggregation of the proteins can be toxic for your neurons. So, how to manage these metal ions? That means to keep the concentration in right form and also the homeostasis. So, the strategy we must have in search for therapeutic agents, whether some problem is happening. We are having that Alzheimer disease, we are having the Parkinson's disease and all these things. If we can find out the cause of these diseases, we will try to avoid that particular route. If it is due to protein aggregation, how to stop that fibril formation, what are the reagents we can use, what are the ligands we can use.

If the metal ion concentration in higher amount is responsible, we have to take out that metal ion concentration, we have to reduce the metal ion concentration from the body, that means from the brain. So, for the neurodegenerative diseases, some therapeutic agents we can think of and we can understand these things nicely. So, different metal ions in the brain are therefore a necessity as well as a poison. When you cross the concentration not that your methyl mercury is reaching to your brain, we know that is due to the Minamata disaster from the fish cycle from the aquatic, we just basically, people who are consuming those fishes they are contaminated by methyl mercury ion, MeAg plus which can cause this BBB that means the blood brain barrier and ultimately reach to your brain.

So, not only that methylated mercury even the mercury ion itself can be a poison, but the other metal ions like which are beneficial for us, which are necessity for us like your iron, like your copper, like your zinc, but if you have some elevated concentration that will definitely be poison for us. So, we can have two other enigmatic functional structures closely related to the brain. Basically, we have the BBB, already we have seen, and also the blood cerebrospinal fluid barrier BCSFB. So, we have for compartmentalized things and we can have one after another if we include blood. So, blood with this barrier, blood with the another barrier, another barrier with that of your brain also.

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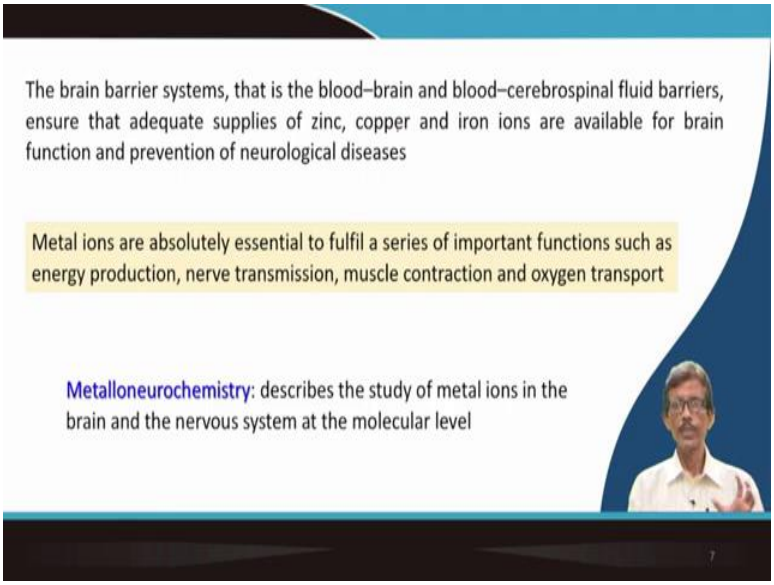

So, four such things, we have seen that you can have the barrier and these blood brain barrier and blood cerebrospinal fluid barrier ensure therefore that you can have the compartments, adequate supplies of zinc, copper and iron should be there for proper functioning of the brain and which can also control the corresponding development of the neurological diseases, because we can restrict the concentrated form of these ions in that particular region.

So, basically, these are essential to fulfill a series of important functions, because we know that metal ions are required for the corresponding cytochrome c oxidase function which we ultimately use for consuming O2 for your water formation, for your glucose oxidation. So, we are producing large amount of ATP molecules. So, depending upon your corresponding change in free energy, we can have the corresponding change in the E0 values and that E0 value can be correlated to the magnitude of your delta G values, delta G0 value. So, energy production will be directly related to your corresponding management of these metal ions.

Then nerve transmission or the signal transmission, nerve signal transmission or nervous signal transmission is also dependent on these particular metal ions. Then muscle contraction, we all know that the corresponding signals, the electrical signals out of that of your sodium and potassium ion we required the metal ions and also obviously the oxygen transport in myoglobin and hemoglobin. So, a particular area of understanding or particular area of the subject or the research people can define it as your metalloneurochemistry. By definition what is that.

It describes the study of the metal ions only in the brain and in the nervous system at the molecular level that means what is happening. The way we know that you have a metal ion, when you dissolve the metal ion in your test tube, you have the corresponding solution in the test tube. Similarly, if metal ions is there in our brain and having a solution there so that will immediately we can compare with that of your test tube metal ion, that your iron if it is there that iron will be in the hexacoordinated form if it is not disturbed by six water molecules. So, those metal ions are doing something or some beautiful reactions or the chemistry which we can see for that all these things.

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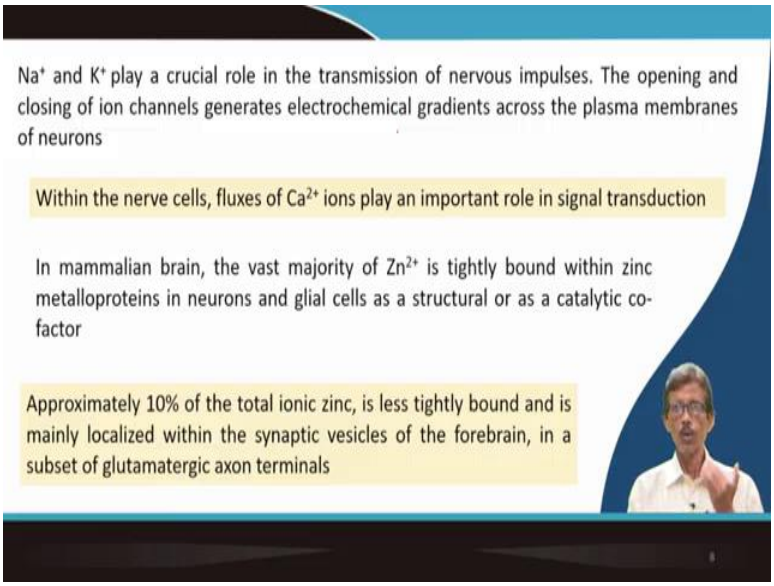

So, already we have seen that not only you can have the corresponding sodium and potassium for your transmission of nervous pulses, it can also give you the opening and closing of the channels, electrochemical gradients are there, and which across the plasma membrane of the neuron. So, earlier we are talking about the blood, we can have the stomach and is going from liver to some other parts or the whole body, but brain itself is a different part only typically and the neurodegeneration because the aging process as people are older and older that your neurodegeneration process is taking place and that is due to the corresponding involvement of the metal ions.

So, we see that within the nerve cell not only sodium and potassium, but you can have also the color, because the calcium channels are also there. So, they basically also play some important

role in signal transduction. So, this signal transduction is important. Whether this signal transduction due to the presence of the calcium ion or the presence of the sodium as well as the potassium ion what we find that we find that you can have the opening up of the channel and closing of the channel.

So, due to that opening and closing of these channels, not only the sodium and potassium or the calcium ion will pass through those channels, but your iron ion, copper iron and zinc ion can also pass from one particular site to the other. And if the signal is basically controlling the opening and closing of the gate, then the movement of these ions can also have some important role to play while you understand not only the free metal ion, but also its corresponding metalloenzymes and the metalloproteins.

So, in our brain, what we see, the vast majority of zinc 2 plus is tightly bound, is not in free solution that we call sometimes the extracellular zinc concentration. So, the extracellular zinc concentration if it is there, so intracellular what is there. So, zinc metalloproteins in neurons, so bound within the zinc metalloprotein so they are bound. Where they are bound? They are bound to the metalloproteins in neuron, not that zinc of your carbonic anhydrase, zinc of your carboxypeptidase is now we are bringing zinc to close to your neuron, whether that is in your spinal cord, whether that is in your brain and the glial cell, G-L-I-A-L and the glial cells one particular type of cell as a structural or as a catalytic cofactor.

We all know like your corresponding superoxide dismutase, we have seen that the zinc is playing the structural role, but when you go to carbonic anhydrase or carboxypeptidase as we all know that zinc is playing the catalytic role or catalytic cofactor assisting the real function of the enzyme where this particular zinc bound to water molecule or hydroxide ion and that bound water molecule or hydroxide ion can function as a good nucleophile to cleave your ester bond, to cleave your peptide bond or your peptide or protein molecule.

So, the total amount of zinc if you have, if we just simply consider that whether zinc is there, whether zinc is important or iron is important or copper, because zinc is a non-redox metal ion. That is why with sodium, with potassium, with calcium we are talking about zinc. So, 10% of the total ionic zinc that means zinc is present as zinc 2 plus is less tightly bound. So, only very small amount of this is not bound to the metalloprotein. And within the synaptic vesicles of the

forebrain, the front brain is the forebrain, in a subset of glutamate, glutamate we know. glutamatergic axon terminal so terms you will write nicely, so glutamatergic axon terminal. So, glutamate amino acid is there, the axon terminal is there. Within the forebrain you can have those zincs available.

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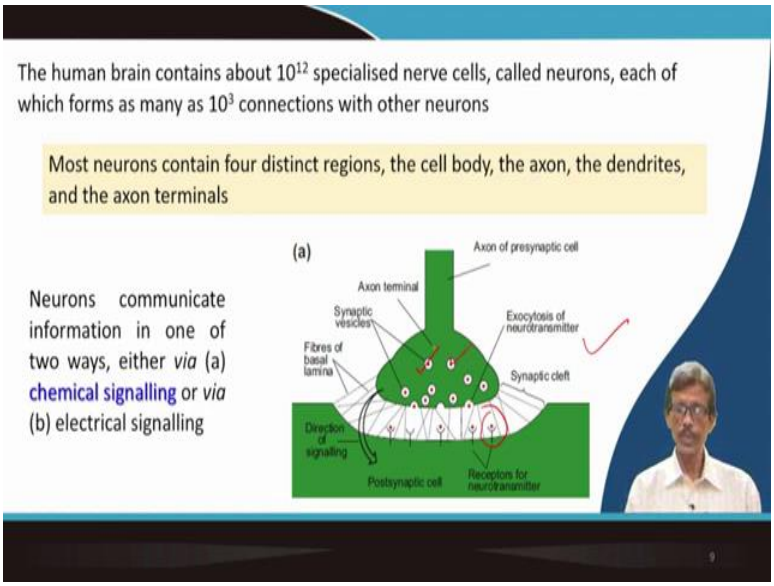

So, what we see now that your human brain basically contains about 10 to power 12 specialized nerve cells, a huge number of nerve cells. We can monitor nicely the electrical signal, the signal transduction, but is difficult to monitor which particular nerve cell is operating for what particular purpose. So, these all nerve cells, collectively, we call them as the neurons. And these neurons, each of which form as many as they can 10 to the power 3 connections that means 1000 connections with other neurons. So, is a very useful network, is very difficult to understand also by only look at the digit, look at that dataset, which will give you some understanding that how complex this area is.

So, you can have four distinct region within the corresponding nerve cell or the neuron that it has a body, we know the structure, the neuron structure, the axon, the dendrites and the axon terminals where you can have the corresponding hair like structures where the axon terminals are there, which can basically bind something and send something.

So, these neurons basically come and communicate information in one of the two ways either via chemical signaling or via electrical signaling. So, we are chemists. So, we are very much

interested to know about the chemical signaling. We are not electrical engineers or other electrical people who are talking about these electrical signals. So, when we talk about the electrochemistry, we talk about the electrical signals, but right now we do not have that much time. We will talk about or confine our attention on chemical signaling.

That means some good molecules, some good neurochemicals are available and those can give now signal and those signals are like that of your electrical pulses. So, only see that, already we have seen that you can have the four distinct components, you have the axon terminals, you have the axon of the presynaptic cell so is a huge one so is basically a loop of this covering thing and the bottom you can have. So, you can have the fibers and all these because you can have the presynaptic cell and the postsynaptic cell on the top and the bottom.

So, exocytosis of the neurotransmitter what is that. So, this particular part will be involved for exocytosis mechanism for your neurotransmitter. So, it is basically the corresponding dotted lines are giving you the corresponding directions of the signaling and that signaling will tell you that okay you can have some receptors point. We know this is the receptor and on this receptor your thing is something on sitting on it. That means the corresponding, the neurotransmitters are coming so these are all your neurotransmitters. So, these neurotransmitters, hormones and all are neurotransmitters also. They will come and bind to those positions sitting on the corresponding receptors and the corresponding give you all these results.

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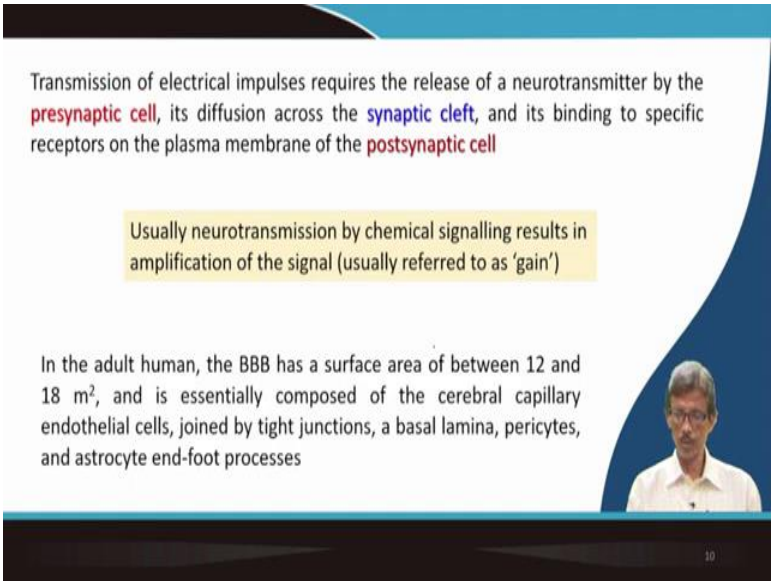

So, electrical impulses on the other hand can go for the corresponding neurotransmitter, where neurotransmitter is sitting, your presynaptic cell, your synaptic cleft as well as postsynaptic cell all are activated. So, receptors and the plasma membrane basically all are getting activated. So, you think about the corresponding neurotransmission, so signal transmission by chemical signaling results in amplification of the signal. Basically, we can go we know that radio transmitter, how we go for the transformer, we can signify the corresponding increase in the signal intensity. So, amplification of the signal is also required such that you can do something very useful work.

So, the BBB, the size of BBB, the area-wise is a huge one. So, it is 12 to 18 meter square in amount. So, you can have many such junctions, so you can have the barriers, so if you open up these things, it will cover a huge area of 18 meter square, up to 18 meter square area. And these basically can have the endothelial cell that joined by the tight junctions, basal lamina, presides and astrocytes end-foot processes. So, many things, many complicated things, we do not understand all these things nicely, though you can take help of the biologists. But do not worry for that we are talking only about the BBB in this particular class.

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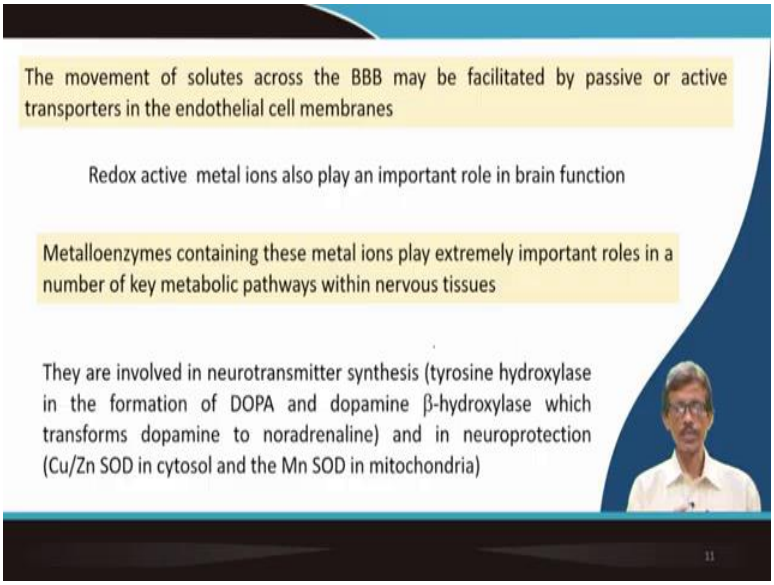

So, the movement of these solutes across the BBB may be facilitated by the passive or active transport of the endothelial cell membranes. And if we bring now the redox active metal ions for this particular purpose as well as the metalloenzymes, so if the metalloenzymes are there having

copper and iron, what thing we can have. So, we can have the metabolic pathways within the nervous tissues also because the nervous tissues are also getting all these things, but we will be able to produce, due to the presence of these redox active metal ions, the neurotransmitters.

We have already seen, we have already learned it all this thing now you try to correlate it where do we have seen that DOPA is there, dopamine beta hydroxylase for the copper and we all these things because the dopamine can be produce for the corresponding production of the noradrenaline and in the neuroprotection, the neuroprotection is the superoxide dismutase activity on cytosol or in mitochondria.

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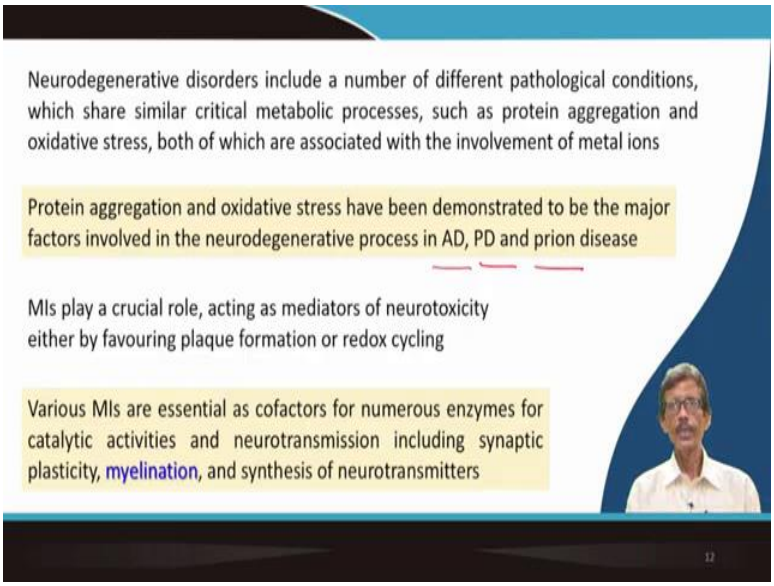

This neurodegeneration, the disorder basically, and basically a particular type of pathological condition and we can go for the involvement of the metal ions, the protein aggregation and oxidative stress. So, we are talking about this simple protein aggregation only. So, definitely it will be correlated to the production of the ROS and then we can have the AD, the Alzheimer disease, the Parkinson's disease. So, three diseases we are talking about. Afterwards we can talk all these. And also the prion disease.

So, metal ions play a crucial role to go for a mediator of neurotoxicity either by favoring plaque formation or redox cycling. So, metal ions are also responsible for plaque formation, is also responsible for AD, PD and prion diseases, because these are involved in neurotransmission, not

only synaptic plasticity, but myelination, because this coating of the corresponding fat molecule on your neuron and the synthesis of different neurotransmitters.

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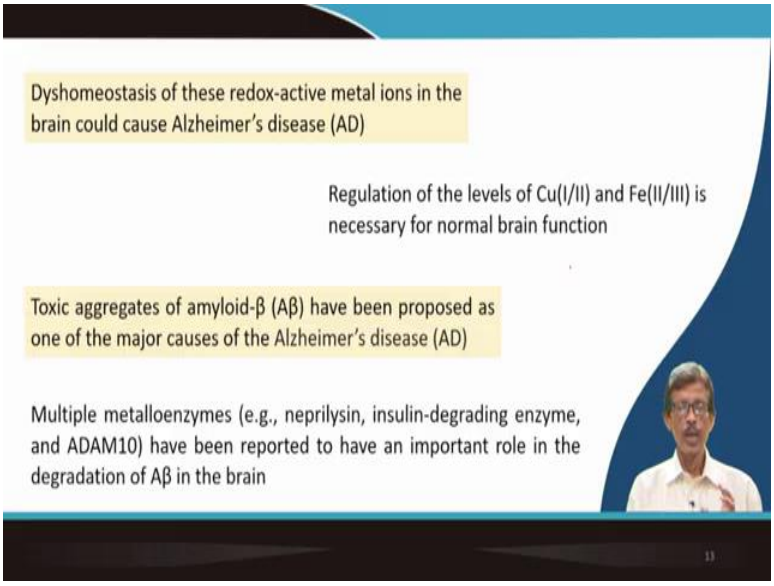

But this homeostasis is important and this homeostasis and some redox active metal ions like copper is the corresponding, crucial thing which can go for the regulation of the different metal ions and will be useful for your normal brain function. Otherwise, you have the aggregation. That aggregation is known as amyloid beta formation. And that amyloid beta formation can be correlated to your Alzheimer's disease or AD. So, there are different metalloenzymes. If time permits definitely in our feature classes we will talk about these metalloenzymes which are important for your insulin degrading enzyme. And there are some ADAM type of enzymes are there which can be useful for your A beta formation.

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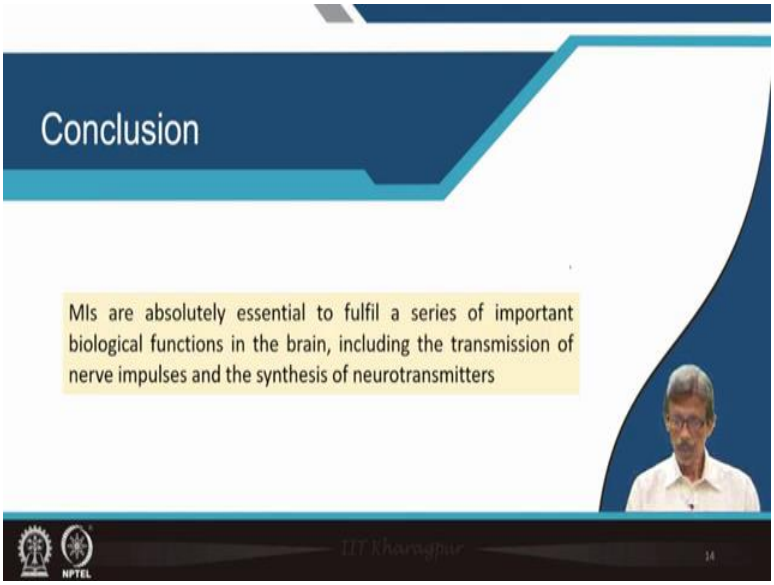

So, what we have seen therefore that the involvement of the metal ions which are important and which are absolutely essential to consider or to fulfill a series of important biological functions, not only your nerve impulse, your movement of the metal ions, your activation of the metalloenzymes and then ultimately the deposition, the protein aggregation, is not that the metal ions are storing as your corresponding biomineral formation like your hematite or magnetite formation or any copper based mineralization, but it is the protein aggregation.

So, metal ions are basically triggering that protein aggregation. So, the normal functioning of the brain, the knowledge of the metal and function is important. And therefore, the transmission of nerve impulses and the synthesis of neurotransmitters all are dependent on the availability and the function of these MIs that means your number of many such metal lines.

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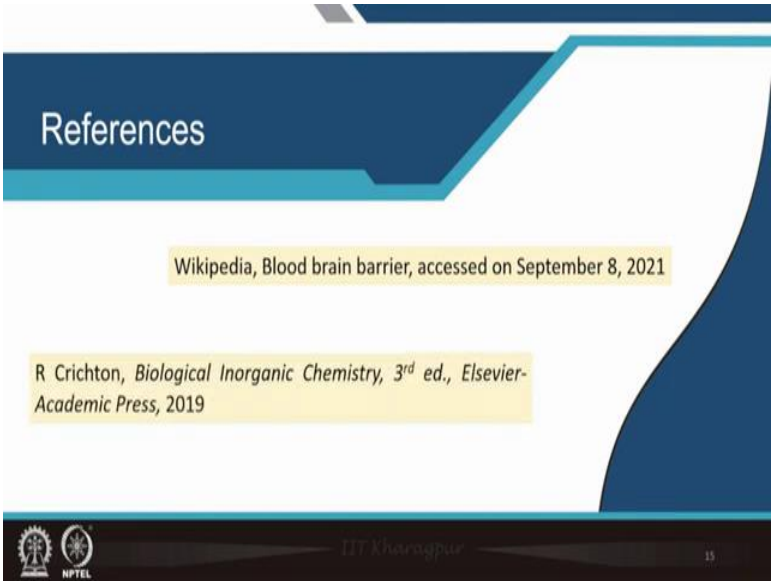

So, you can go for the blood brain barrier part from the Wikipedia page and the book of R. Crichton, Robert Crichton. So, thank you very much for your kind attention.