Biological Inorganic Chemistry
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Lecture 58
Iron ions

Good morning, everybody.

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So, we have reached to the module 12 where we are talking about the metal ions which are present in brain and the use of the metal ions in certain development of medicine and drugs. So, after zinc and copper ions, today we will be talking about iron ions.

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So, how these iron ions are important, how the system can take out or sequester the metal ions like iron, then their involvement within the synaptic vesicles and cleft. We will talk about a little bit about the neuronal activity which is the dependent on the iron ion concentration or the deposition. Receptors and transporters are also important in this regard. And interestingly and most importantly the dopamine synthesis as well as the myelination of axons are dependent on the presence of these metal ions, particularly iron in this particular case.

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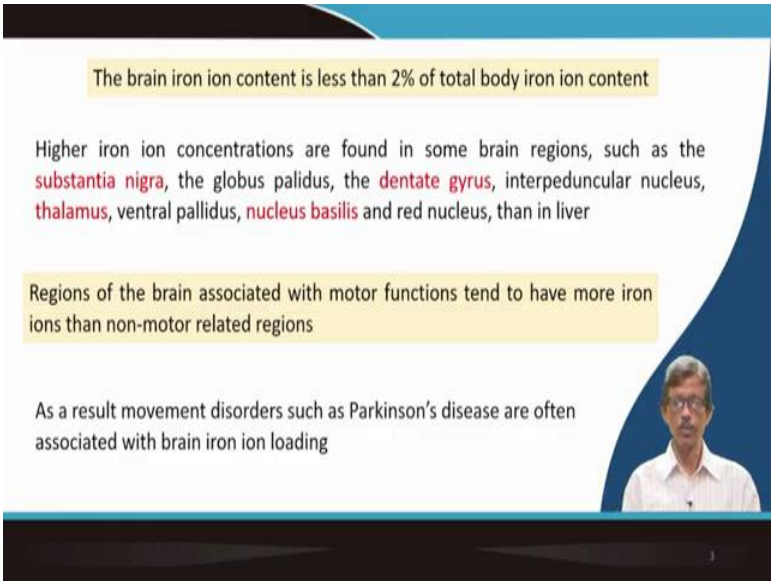

So, how much iron we have in our body we know compared to any other metal ions like zinc and copper and we know that a person having a body weight of 75 kg how much iron you can have for your blood content, cytochrome content and all these things, but we never discussed about the corresponding amount what we can have in our brain. So, the iron ions present in brain is only 2% of the total amount of iron what we have in our body particularly for our blood circulation, for the cytochromes and many other important molecules, the metalloenzymes and metalloproteins. So, only 2% of this basically gives some very important role to play.

And always we know that is there should be some optimum concentration of these ions. The way we do in our analytical chemistry classes, when some unknown sample is given to you and we go for the quantitative analysis of that particular concentration, so you can go for your quantitative estimation of iron ions in the given sample. So, either you can go for the volumetric exhibition, that means the titrimetric method or we can go for the gravimetric estimation or any other instrumental methods of technique.

So, there we find the actual amount of iron what is given in the sample and what is present in the sample. But while reporting we always have some care about whether we are reporting the positive error or we are reporting the negative error. Both these two things are bad. So, you must have a particular optimum concentration which is required for our proper functioning of the brain which is dependent on the metal ions like, any important metal ion is the ferric ion. So, in some cases, we can have some regions or the compartments where the metal ions are stored.

So, concentrations what he found maximum in these particular areas so is basically the biological terms of those bare brain areas, such as substantia nigra, globus palidus, dentate gyrus and interpretpeduncular nucleus, thalamus, hypothalamus we all know and the ventral palidus, nucleus basalis, all I told you, and the red nucleus. So, which is there, that means then, these regions basically the iron will be deposited or concentrated and can be useful in solution also for your regular activity of the brain.

So, the concentration what is stored we always compare that particular concentration with regard to our liver concentration, because we know the liver and the bone marrow is the region where we go for the synthesis of the erythrocytes. So, many such regions or compartments in the brain associated with we all know that the our motor neuron functions or motor neuron activities or our

motor nerves are there for our movement, the finger movement, the hand movement and the way we talk also for that also we require the motor movement.

So, the motor functions tend to have more iron ions than non-motor related regions. So, you see that brain having that optimum concentration of iron is important. If we have higher concentration of that iron will be there, then we can have some malfunctioning of that particular motor nerves or some other very useful or the vital region of our brain. Because it is typically associated with the motor nerves and that is why it is required for your motor functions and the motor activity. So, the dependence of these ion is important for our neuronal activity and for our motor activity also.

So, when we go for the result of the movement disorder, particularly the aged persons, a person having an age of 67 or 65 or 70, above 70 or sometimes 75 we know that there is some disturbance in the movement of the hands, legs and all these things. People cannot run the way we run in our younger ages. Sometimes we take the support of thumb stick for our walking also. So, walking is also a motor movement thing.

But sometimes we say that we can have many other problems like that of your knee joint, your bone related thing and all these things, but most important thing is the signals what we are receiving from our brain to do some work. First we get the signal from the brain then only I will be able to talk, otherwise I will not be able to take this class also. So, these movement disorders we call in a particular type of diseases, the Parkinson's disease which is very much deadly also for the elderly people like Alzheimer's are often associated with the brain iron loading.

That means you have some positive amount of that means that whatever you have you have determined something so is basically the positive error of the analytical chemistry class for your determination of iron ion in some experiment. So, the loading of the iron, so the maximum loading or the overloading is bad and under loading or the minimum concentration of that iron is also will be bad. So, that will go for your Parkinson's disease as well as the corresponding movement related to your Parkinson's disease.

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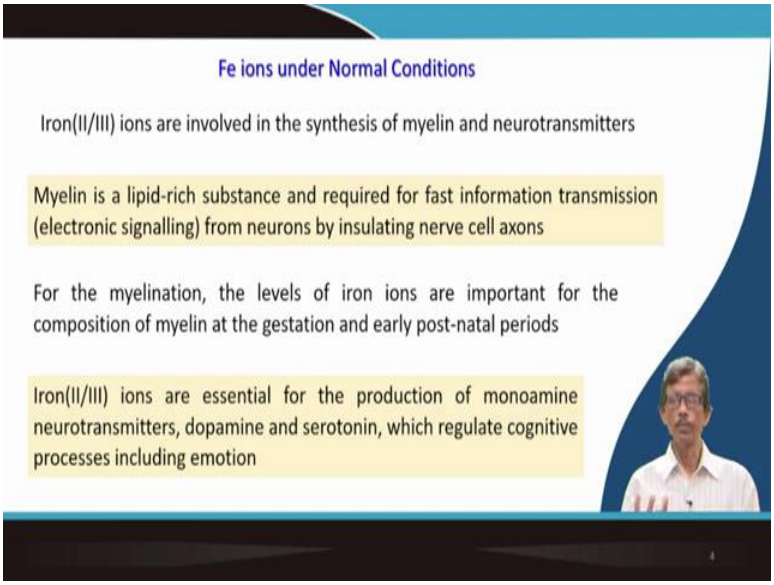

So, we can have two different conditions. One is your normal conditions and another is your diseased conditions or abnormal conditions. So, how the presence of iron ions, the optimum concentration of iron ions are important for have your typical function. And sometimes it is not only the iron ion, but the other metal ions, what we have discussed earlier in our previous classes, that we have seen that we can have the zinc ions, we can have the copper ions, and now we are talking about the irons ions. But they are not independent, they are interdependent.

So, the function of the zinc ions can sometime be dependent on the corresponding activity of the iron ions. So, these things are there. So, many enzymes and many protons can have some abnormal activity if we do not get the right amount of iron concentration in our system or in our brain. So, as we all know that there will be redox since iron is present. So, you have the corresponding conversion of the ferric ferrous ions and during the synthesis of myelin as well as different neurotransmitters.

So, these are basically the biosynthetic routes for myelination of neuron or axon or the synthesis of the neurotransmitter like very vital and very important biomolecules. We require the presence of iron as a catalyst or a cofactor or a co-catalyst. What is myelin? Myelin is nothing but your lipid. So, lipid layering on your neuron, on axon is required. So, is a lipid rich substance and required for fast information transmission, because it is required for your information

transmission, for your signaling process, which is not electrical signaling, but is electronic signaling.

We all know that we can have sometimes the electrical signaling and sometimes we can have also the electronic signaling from the neurons by covering the nerve cell axons. So, you have the insulation and insulation is required for your signal processing and signal transmission also and that is required for your myelin formation. And the myelin, if the myelin formation is disturbed, we have the disease condition. And that disturbance can come from the involvement of this particular metal iron.

So, what we can have for the myelination, the levels of iron ions, that means optimum level of iron concentration, not above and not below, for the composition of the myelin at the gestation period that when people conceive and as the postnatal period that means after birth. We call that we have, must have some good amount of all these things for our brain growth or brain development. When baby is in mother's womb also the brain development is important and after the birth also your brain development is important, because within the mother's own the complete maturation of the brain is not taking place.

So, that means the right amount of supply of iron what the baby is getting from the mother's blood is important such that you can have the proper or the regular development of the brain, otherwise you will have the problem, not immediately, but you can have problem in future time also. During your older period also you can have some problem. So, it is required for requiring that is the other thing is your neurotransmitter formation and these neurotransmitters always we know these are amine compound mostly.

So, the production of monoamine neurotransmitters that means one amine presence is there, presence of one amine is there. Then other two important neurotransmitter, sometime we call them as the hormones or dopamine, so the dopamine as well as serotonin, which basically control or is required, the right level of dopamine and serotonin in our brain is required for your good amount of neurotransmission for our cognitive behavior, we call how we behave it. A person is behaving abnormally that means this cognitive behavior is wrong.

So, basically all these can regulate your cognitive process including your emotion, your depression, your wellness, all these things, and finally, the happiness also. So, the cognitive

disorder, your emotional control all these things we all know is controlled by the neurotransmitter and these synthesis as well as the right concentration of these corresponding neurotransmitters is required and that is dependent on the typical chemistry of this metal ion, that means the iron ion chemistry. So, is the iron dependent all these activities.

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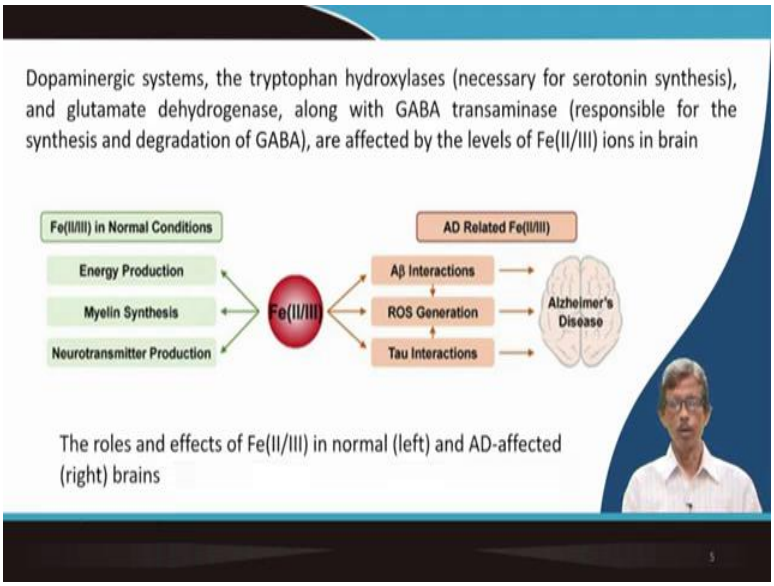

So, since we have the dopamine and the dopamine can give us some activity or some system which is responsible for some useful actions. So, dopaminergic systems, so that means which is dopamine dependent, dopamine concentration dependent, not only the nature of the dopamine is important, but also the concentration, the right concentration of the dopamine is also important. Sometimes these are required for your hydroxylase reaction based on the substrate tryptophan. When you go for the hydroxylase reaction on the tryptophan we produce serotonin, because these are some redox conversion or oxidation reactions sometimes or sometimes the hydroxylation reactions.

Then glutamate dehydrogenase so it is dehydrogenation reaction but the substrate is glutamate. So, you see the right amount of your amino acids, essential amino acids, whether you have tryptophan or you have the glutamate. Then you can see that the iron dependent reactions are important. Then gamma aminobutyric acid, which we all know popularly known as GABA, then GABA transaminase, that means responsible for the movement of the amine function from one carbon to the other or the movement of the amine function of the GABA to some other molecule.

So, which is required for our synthesis of GABA molecule as well as its breaking product of the GABA molecule and are also affected, therefore, all these activities, all these actions, whether you have the biosynthetic route or the biodegradation route for all these molecules are dependent on the availability of these ferrous ion as well as ferric ion in our brain.

So, like copper, everything is same, just we remove the copper center and put the iron center. But all are basically responsible for our iron II, iron III normal condition behavior as well as the Alzheimer disease related condition where you have some abnormal amount of iron, either a low concentration or a higher concentration of iron, but you can have a diseased conditions that is why we have the Alzheimer's disease. So, same drawing, same figure, but we put now iron instead of copper. Why it is so, because the activity of the copper what we have seen for all these general reactions or the activities like your energy production to the synthesis or biosynthesis of neurotransmitters are dependent on electron transfer reactions, oxidation reduction reactions and the presence of copper.

Now, we are seeing that the same reactions or the same activities or same properties or functions we can see for the availability of ferric ions. So, ferric ion can give rise to a thermodynamic electron transfer potential the E0 value, which is different for your copper potential that means cuprous, cupric potential. That is why at a different potential, we get different neurotransmitters, we go for the different level of energy production as well as the myelin synthesis. So, your A beta plaque, ROS generation and the tau interactions are all will be different depending on the different metal ion. So, you have the normal condition and you have the corresponding abnormal conditions.

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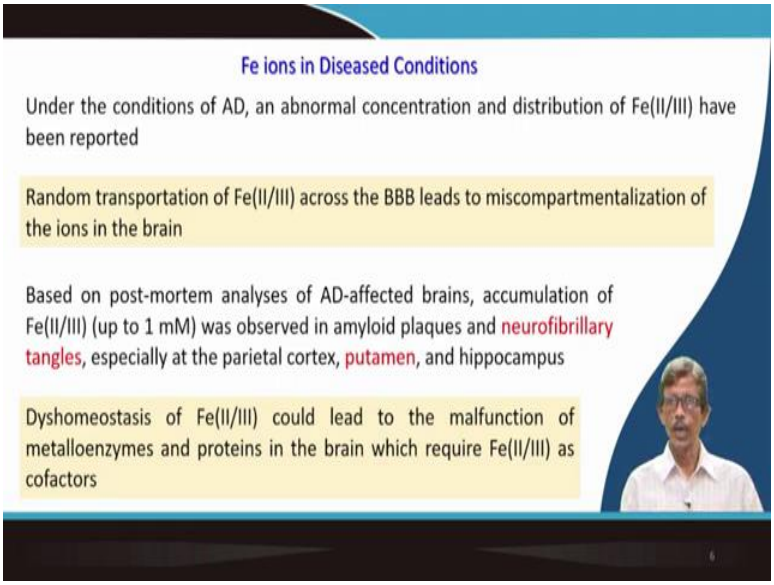

So, when you have the abnormal conditions from the proper level or the regular level or the optimum level, either you can have the over concentration or the decreased concentration of iron to your hand. So, that condition we call as the diseased conditions. You are suffering from some abnormality and you are having some condition which we can consider as your Alzheimer's disease also. So, when you have the condition of Alzheimer's disease so abnormal concentration and not only the concentration, abnormal means it can evolve or it can below, but also the distribution of these iron in different pockets or different compartments.

As we have seen earlier just now that there are some pockets or some positions or some areas or some regions where you can have iron concentrations, so the biomolecules which are reacting to produce your neurotransmitter or the myelin synthesis will come to that particular region and expect that your iron ions will be available for that particular conversion A and B is reacting giving you C or D.

So, it can happen in such a way that you can have the transportation to go for those particular pockets. So, transportation of ferrous and the ferric ion across the blood brain barrier leads to miscompartmentalization, that means the abnormal compartmentalization, that means where we required the right amount of iron, storage is not taking place, it is stored somewhere else.

So, that is why within the brain that movement of these ions are important and that is why how we can analyze a person suffering from Alzheimer disease, died also due to that Alzheimer

disease, so you have your brain, which is Alzheimer affected brain, Alzheimer disease affected brain, so if some person died out of that, then we can go for the postmortem. And the postmortem for only the iron accumulation within the brain is very simple like that of your taking the sample from the earth surface like the geologist take, we also have different samples, chemical samples, we go for the analysis of the iron.

So, the tissues and the brain matters basically for analyzing the amount of iron presenting it. So, the accumulation of iron up to 1 millimolar concentration is a very high concentration. We are talking about micromolar concentration for brain function or sometimes only the low concentration as the nanomolar concentration is also fine. But this millimolar concentration are our concentration which we use for our spectrophotometric measurements 10 to the power minus 3 molar concentration which is a visible spectroscopy we use it.

So, when you have the plaque formation we call is the amyloid plaque formation or amyloid beta plaque formation and neurofibrillary tangles so one particular thing also is known as the triangles formation, tangles formation especially where it is parietal cortex, putamen and hippocampus. So, these are the brain areas if we can collect it, so taking the help of the doctor, a postmortem is can be done and taking the regions basically of that brain, the diseased brain, and then you analyze for only the iron concentration that gives some valuable information to us.

So, that tells us not only the homeostasis in your body, that means the proper distribution of the iron, location of the iron, that means proper matching of the iron concentration compartmentalization, not miscompartmentalization of those iron ions is required. But if you go for the dyshomeostasis, you will go for the malfunction, not the function, of what, of the iron metalloenzymes, iron proteins in the brain which basically dependent on its activity for iron as your cofactor and the electron transfer between these ferrous and the ferric ions.

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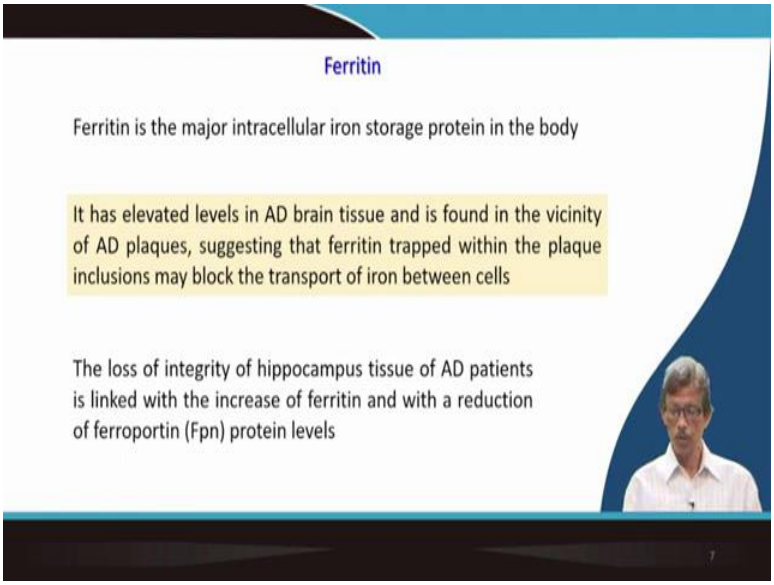

So, long back we read about ferritin. We know that the ferritin is our storage molecules, where we can store the excess amount of iron when we take our food material, our duodenum is basically absorbing the food and it goes from that particular bloodstream. And while going to that bloodstream through the help of the transferrin molecules, at some point it goes inside the cell also, but it can be released also from that cell and it can be stored within the transferrin molecule, sorry, ferritin molecule for its future use. We all know that is why is a major intracellular iron storage, iron ion storage protein in our body.

Not only the concentration of hemoglobin and myoglobin we should know, we also should go for your analysis or analytical clinical biochemistry for the content of your ferritin in your body. But whether we can have ferritin in our brain or not, so that is there. We can have also ferritin in our brain. Earlier we are talking about ferritin in our body. We never focus our attention for the corresponding concentration in the brain. So, if we have higher level of concentration of that particular ferritin not iron now is the protein which has covered with that particular thing and you have the corresponding biomineralized iron clusters.

So, in AD brain tissues it is found in the vicinity of at plaque formation. So, if you have the Alzheimer diseased person, you have the corresponding brain tissues what you can collect, you can have the corresponding AD plaques also, but what you can determine, whether like us like a typical analytical chemist, analytical inorganic chemist, whether we go for only the analysis of

iron, whether we go for the analysis of ferritin or hematin or we can go for the corresponding ferritin determination. So, the determination of ferritin we have to take the help of a clinical biochemist, a doctor or to go for the analysis of iron only we can take the help of an analytical chemist only.

So, basically, during that determination that means, the total amount of iron in the millimolar concentration and the amount of ferritin in some other concentration range, what we can find that it is trapped basically, it is encased within the plaque inclusions and may block the transport of iron between the cells. Because if you have one cell here and another cell over here and we require the transport of iron from one cell to the other and that is required for the movement of these irons without plaque formation, without deposition, without mineralization, but ferritin we all know it is not only in the mineralized form it is storing, but as and when required, it can also liberate the solubilized iron for our right function or proper functioning.

So, the hippocampus tissues will be affected. So, that will go for the loss of integrity for the AD patients and that is basically the NPs of ferritin with the reduction of ferroportin Fpn abbreviated as Fpn protein levels. Another protein levels is a marker protein levels. You have to mark it. Ferritin is a marker protein, ferropotin is another marker protein where you can have the reduction of these things, where you can have the corresponding increase in ferritin. So, the iron is taking up for the ferritin deposition. At the same time what do you require for your ferroportin protein level that means the concentration of iron bound ferroportin is not without iron is with iron level will be decreasing.

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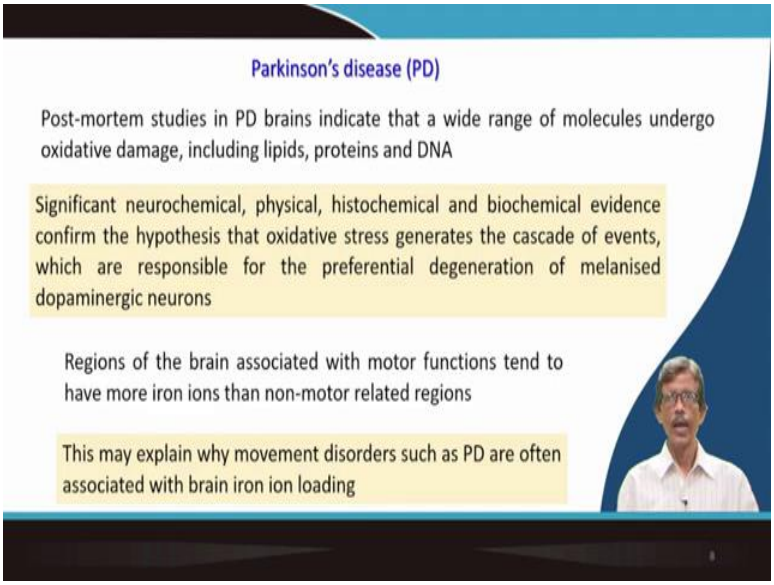

So, we can have also how the Parkinson's disease can take place. Again, the postmortem analysis can help us. And in that particular case, wide range of molecules undergo oxidative damage that means ROS is there and ROS can damage with the help of iron based Fenton chemistry. So, we damage the protein, we damage the proteins as well as the DNA molecules. So, all these evidences whether you follow the neurochemistry, physical chemistry, histochemistry or biochemistry, so many molecules are informed. How you determine them.

And they basically tells us that the hypothesis is that you have oxidative stress. As you are older and older you are getting oxidized and oxidized. So, many consecutive events are taking place which we call as the cascade of events which are responsible for preferential degradation of melanized dopaminergic neurons. So, you are basically destroying the neurons, which basically tells us also the regions of the brain associated with the motor function, so the motor functions will be destroyed or damaging. So, that is why we have the problem in the movement disorders. And often associated again I am telling is that already I told you that you have the malfunctioning of iron loading in the brain.

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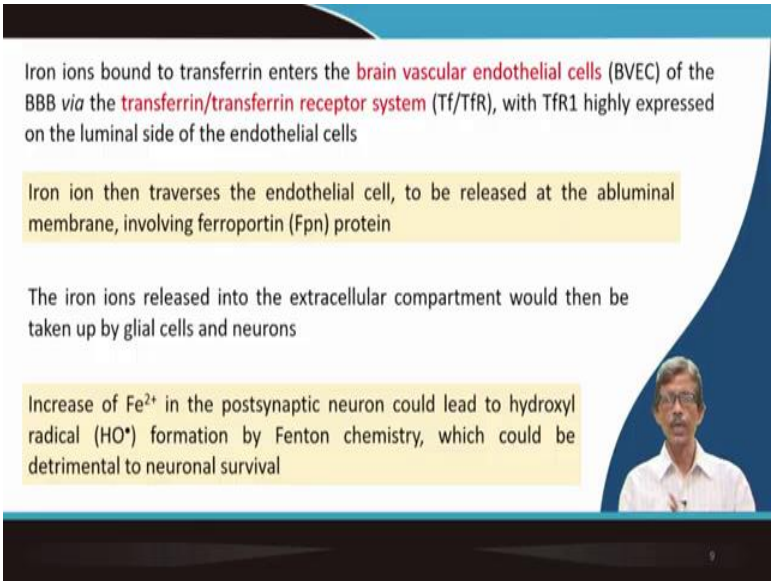

So, bound to the transferrin also when it is released from the ferritin and in the brain vascular endothelial cells and that way it basically goes for the transferrin and the transferrin receptor molecules. So, these iron ions which are released from these ferritin molecule can be taken up by the transferrin and when it is released, the abluminal membrane basically can have the ferroportin protein and that can accept that iron for their survival or for their synthesis.

Then finally, it can be released to the extracellular compartment and then can be taken up by the glial cells or the neurons. So, slowly one after another basically the basic definitions of these, what is your glial cell, what is your neuron cell, because the Fenton chemistry will be operative producing hydroxyl radicals and many other oxidized species. So, the reactive oxygen species can be there and which can oxidize it.

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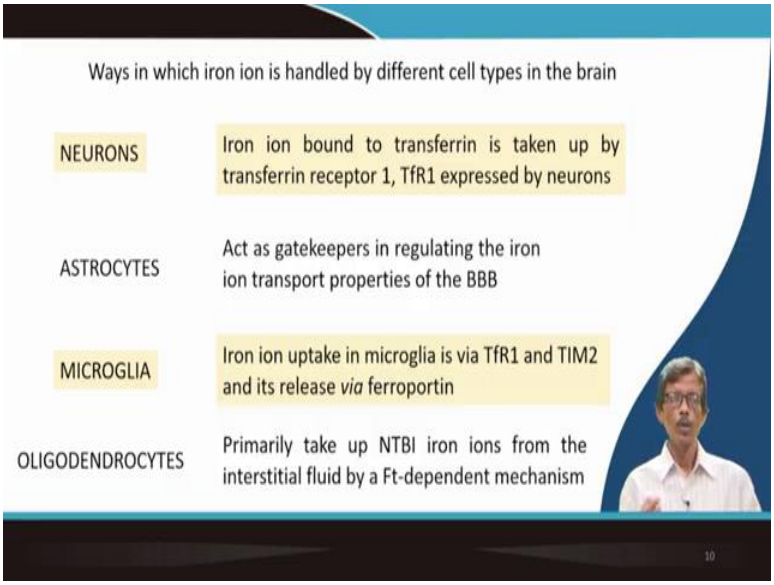

So, the different paths basically the different ways what you can have which can be handled by different cell types in the brain, the neurons we have, which can have the transferrin receptors and the transferrin receptors can take up iron in transfer. Then astrocytes we have. Astrocytes are gatekeepers basically when it is moving from cell to the other side and regulating the iron ion transport in your blood brain barrier. Then microglia, microglia is basically a very important thing, uptake of microglia via again TfR1 that mean transferrin receptor 1, TIM2 and is released via ferroportin. So, these all are interconnected up to that oligodendrocytes.

That oligodendrocytes are primarily taken up by some other important biomolecule, but they are all ferroportin dependent mechanism and these are also some time dependent on your ferritin concentration.

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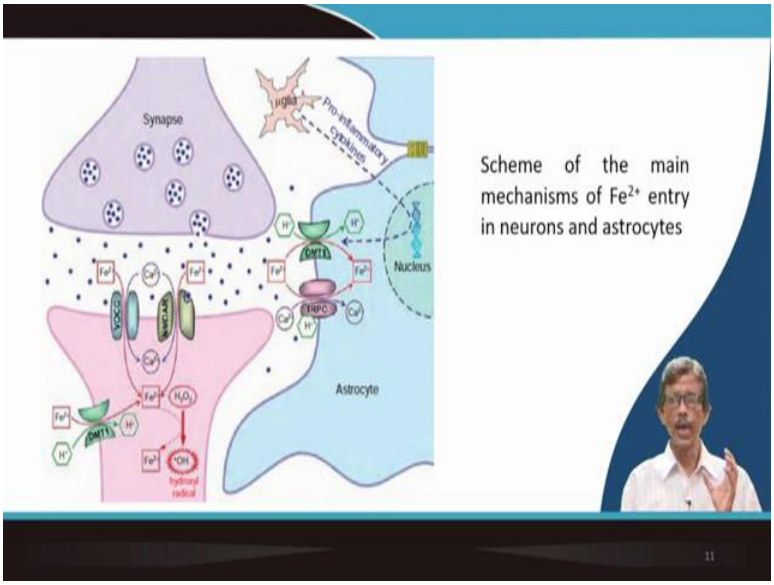

So, pictorially what we can see, we already know that synaps, the neurons are there, the synaps are there, then DMT we all know the divalent metal transporter proteins are there which can transport iron and as well as the protons, then you can have the astrocytes on the right. So, astrocytes are there, so these astrocytes. So, these three basically parts, so considered is at some corresponding geographical thing that you can have one geographical location and you can have the corresponding mapping, so geography based mapping is there, and you have, you see at the top you have the microglia.

So, the microglia is there which is required for your pre-inflammatory cytokines. So, cytokines all we know during our COVID days also we know about the cytokine storm. So, there also the cytokine signaling is there, which is ultimately reaching to the nucleus and all these things are dependent on the movement of the iron. So, how in a map, we can map the movement of these iron starting from your ferritin iron to the released iron and then how the signaling process is taking place up to your hydroxyl radical formation. So, the entry in the neurons and in the astrocytes are important.

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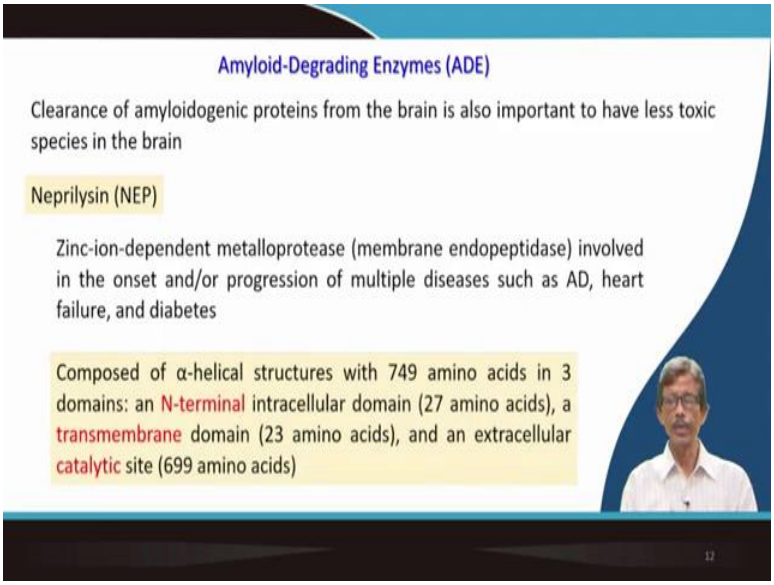

Then we can quickly see, these already we discussed but a missed it, but with regard to that of your iron, we can also have some good understanding about your amyloid degrading enzyme, which is basically helping our amyloid formation by degrading it, which is neprilysin and this neprilysin is not iron independent enzyme or metalloprotease which is responsible for the hydrolysis of the protein chain, but is zinc dependent. So, there are many terminal terms and all these things are there, different amount is inside there, which can take care of this iron dependent metalloproteases.

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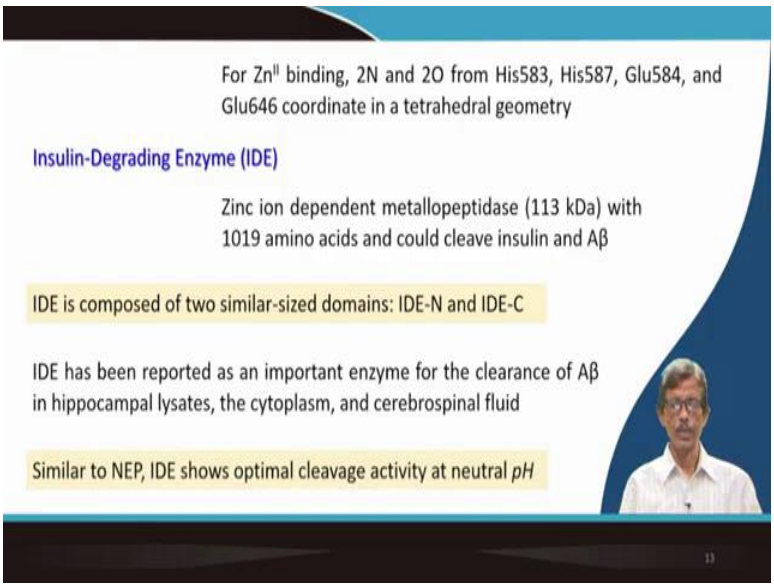

So, zinc binding site is there and it is in tetrahedral geometry, and finally, the insulin degrading enzyme which is also important for their functioning and the hormonal degradation, which is again zinc dependent. So, what I am saying this zinc with that of your iron, because not only these but the function of the zinc and the proper thing is that you have the A beta for hippocampal lysates, cytoplasm and cerebrospinal fluid. So, brain is connected to your cerebellum and the cerebellum is connected to your spinal cord and all these are interdependent. So, you have the corresponding optimal cleavage activity and neutral pH medium for their actions.

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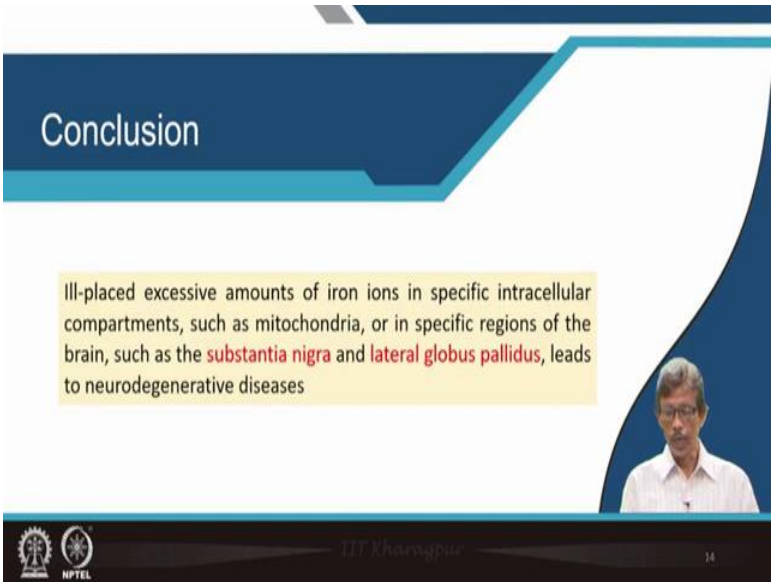

So, if these are all hampered, if they are not functioning in a proper way, what we can have, we have ill-placed, is not properly, ill-placed excessive amounts of iron ions in particular region, particular pockets or particular zones which we call as the compartments, such as mitochondria. Mitochondria we all know is the main functioning material or main functioning body within our cell or some other specific regions of the brain, where we can have all these irons, which is your substantia nigra or lateral globus pallidus. Do not worry about the names, because these are related to all typical biological terms. These are medical terms basically. So, they are responsible for your neurodegenerative diseases, which are dependent on malfunctioning of your iron concentration.

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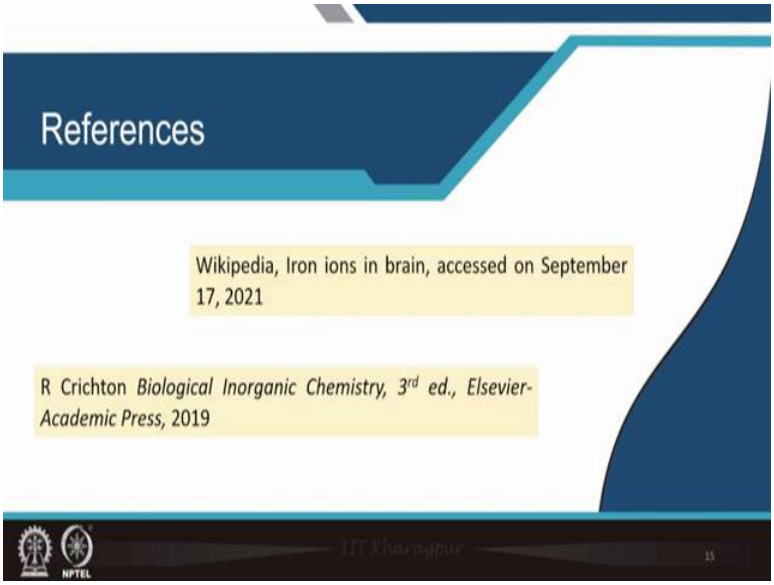

So, we can have iron ions not in your body, but we can study for your brain, how much iron we can have, and why do we require iron for our proper functioning and proper movement and the diseased condition of our brain and the book of Crichton definitely. Thank you very much for your kind attention.