Biological Inorganic Chemistry
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Lecture 57
Zinc and copper ions

Hello, students. So, good morning, everybody.

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So, we have reached to lecture number 57, where today we will be talking about specifically two metal ions in brain, which are zinc and copper ions.

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So, basically, one after another what we can see that how the supply of d metal ions, not only these two, we will also, in our next class we will be talking about the availability of iron in our brain. So, how these are required, basically, whether they require a optimum concentration of these metal ions for proper brain functioning. And during our birth and also in the neonatal stage, the presence of zinc ions in the brain is also important for our development and particularly the brain development also.

So, the opposite of homeostasis that means the regular environment, the proper environment of these metal ions we call is the homeostasis. But when that is disrupted, we will see how it can affect for you dyshomeostasis process. Then if we go to the copper we all know the copper is redox active metal and so what happens with, if you have not only the zinc if you have also the copper in the brain and many such related things which are your neurological diseases.

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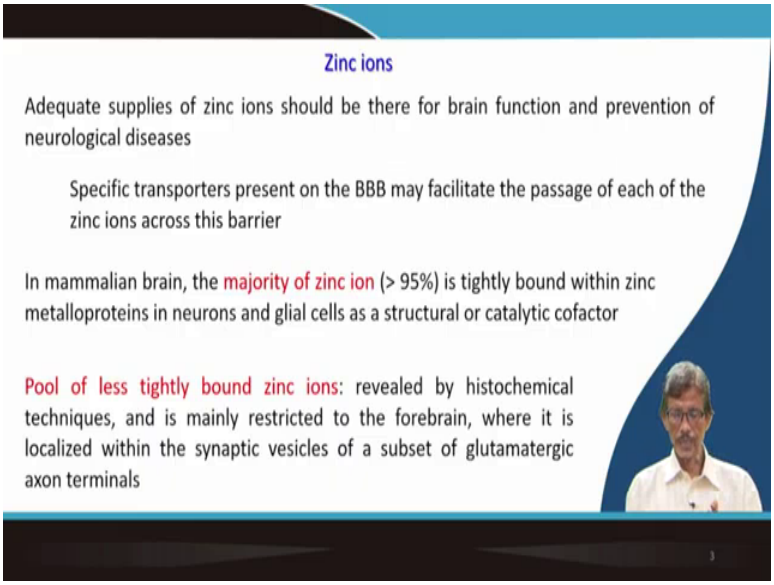

So, we talked about the zinc ions the way we talked earlier about our presence of zinc ions in our body, but now we are confined our attention in your brain only. So, we need some adequate supply, the proper supply of zinc ions for our proper or the right brain functioning and the prevention of many neurological diseases, because there are many neurological diseases or neural problem is basically originating from the brain and then it is traveling towards your central nervous system. So, the neurons are getting affected also due to the shortage or the excess of metal ions.

So, we can have different types of transporters. We all know that the transport proteins we can have. So, several such transporters, we call them the transport proteins for the different metal ions, so the transporters are nothing but a beautiful type of the ligand system which can bind or trap the metal ion and move from one point to the other. That is why they are following the mechanism of transportation.

So, when we talk about the corresponding blood brain barrier, so whether that can pass that particular barrier or not, so it can basically facilitate the passage of each of these zinc ions across these barriers. So, if the transporters are there and it is just going at the point of your BBB or B3 what we call, then if it is not going along with that transporters to cause that particular membrane it can deliver over there and the receptor molecules if it is there so receptors can bind in a new form so attach that particular metal ion.

So, in our brain, what we can have that whatever amount of zinc ion is available greater than 95% is in the form of tightly bound form. That means is that not, in the cytosol like thing, or not in very loosely bound form. So, zinc ion bound metalloproteins are important in neurons and glial cells. So, two places that we can have zinc ions, where people can detect it, like your identification of your iron in the ferritin breakdown molecule like hemosiderin, we can also find the corresponding detection which is definitely a difficult task, because the zinc ion like your sodium, potassium, magnesium, and calcium is spectroscopically silent.

So, if we try to establish the presence of these zinc ions in neurons and glial cells, we have to go for some other technique where we can find out the corresponding interaction and the corresponding effect of the presence of these metal ions. And as you all know from our previous knowledge what we have gathered so far, the zinc is present in your superoxide dismutases in our body. But that zinc when we talk about some activity related to electron transfer, like that of your breakdown of your superoxide dismutase or the dismutation reaction of the superoxide anion, we need the help of copper ions.

So, that is why in this particular class we are talking these two metal ions first. Then our next class we will be talking about iron separately. Though the amount of these particular metal ions are in the same line that we can have in our body, iron has the maximum, then zinc and then copper. So, like superoxide dismutase what we have seen earlier that you require the presence of zinc as a structural role. It gives the definite structure of the other active site which is redox active site which is your copper site to take care of the superoxide anion. So, similarly, here also for the two types of cells, the neuron cells and the glial cells, in one case it is functioning as a structure load like that of your SOD and in other case it can function as your catalytic cofactor like that of your carbonic anhydrase.

We know that is the zinc centered reaction and that will only be achieved through the presence of only zinc ions. So, if we can have the next category of zinc ions, the majority of zinc ions is the 95% of the previous type. Now, if we consider the other type which is your less tightly bound or loosely bound zinc ions and we can have a pool, that means you can have a corresponding equilibrium process where sometime it is in the bound form and sometimes it is in the AcO ions only, the zinc AcO is only.

So, how we can detect the presence of those rare zinc ions compared to the other type we can go for the histochemical analysis and is mainly restricted to our forebrain, so is the front side of the brain, where it is localized within the synaptic vesicles, because the synaps are required basically for transferring the signals and all these things. So, in the bound form and in the closed form or in the released form, these zinc ions can be very important for, going for the signal transduction or other reactions.

So, it is basically another subset of glutamatergic axon terminal. So, we know that the axon terminals are there. The neuron structure you can recall a little bit, because we know from our, again from our school and college days, the structure of the neuron. So, at the end basically we have some terminals which is basically sensing so many things like our sensing on the skin and all these things. So, the axon terminals basically you have the glutamate residue and the glutamatergic. That glutamatergic thing can be activated through the interaction with these ions that means the zinc ions.

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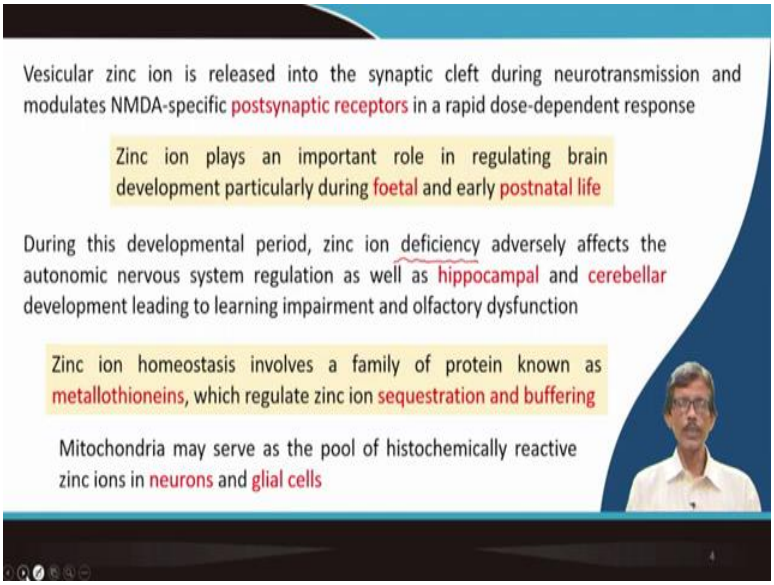

So, you have the vesicles. We all know the vesicles we can form the lipid layers and all this and where you can have the zinc ions inside. So, what we call the physical formation like your mycel formation. So, vesicle formation, the vesicular zinc then, if it is trapped inside those vesicles we call them as the vesicular zinc is released into the synaptic cleft during neurotransmission. So, what does it mean basically? If I ask you a very simple question that what do you mean or what

do you think and what do you believe about a process which is known as the neurotransmission or the signal transmission due to the presence of zinc, due to the absence of zinc and due to the transmission that means the movement of zinc from one side to the other.

And basically it can modulate some postsynaptic receptors also, so one other system that is NMDA type which is specific type of that molecule. But the basic thing is that your postsynaptic receptor in a rapid dose dependent response. That means if we have some neurotransmission that means signal is coming from other side, suppose it can be activated by your sodium or potassium ion or calcium or magnesium ion, but that can be passed through this particular process also.

So, it can regulate basically during the brain development also, because all these things are slowly crystallizing in that particular form particularly after our birth. That means the brain of the fetal then when did you use it in your mother's womb and when the post natal alive that means after the birth also. So, during that time also the development of all these things are very important, because the baby is getting that particular zinc ion from the blood of his or her mother. And after that after the birth also the development also whatever food material and whatever thing we can get that is through that of the corresponding micronutrient which is your zinc ion.

So, at this particular point is typically the development of the brain. If we have a problem of zinc deficiency, it can affect the autonomic nervous system. So, your knob system or the nervous system can be affected very much because of this and what is find that your cerebellum we know the cerebellar development also our hippocampal development also, these are the two, they are the particular region of the brain basically we have seen earlier that the huge brain structure and the other locations what you can have. So, the different locations and their developments are important, because at some point your zinc concentration is higher, but at some other point your zinc concentration can be less.

So, the leading to a learning impairment and olfactory dysfunction it is related to that of your zinc. So, how it is related basically that zinc that hippocampal, cerebellar thing that what we can have that is this thing basically is important, the deficiency, that means the lower concentration. So, this optimal concentration, the maintenance of the optimal concentration of the zinc ions in the brain is important and it is very difficult to maintain also, because we know all are having

some problem or we can have some overactive enzymes and all these. So, either you can go up or you can go down. That means either you have overload of zinc ion or the deficiency of the zinc ion.

Particularly we can separately talk about these things. That means if you have less amount of zinc ions you can have the corresponding development poor for the corresponding learning impairment that means your learning process, your, and the olfactory dysfunction can happen if you have the less amount of zinc ion in your body or your brain. So, the homeostasis is definitely important for our zinc ion and the protein which is taking care of all these things is the metallothioneins, thio means is immediately tells us the protein parts which is providing the sulfur ends that means the thiol ends S minus groups to the metal ions.

So, the zinc definitely can have, the zinc ion can have a very good affinity for the binding to that particular corresponding thiolate anions. And is basically going for sequestration and buffering. That means the buffer system we know all that the proton, in terms of the proton, that means you cannot change much of the proton concentration if you add some amount of base or if you can add some amount of base. That means you can have the stable pH range for that buffered medium. Similarly, for zinc ion system if you have the metallothioneins, zinc bound metallothioneins that can basically inhibit the corresponding very quick change in the zinc concentration either in the upper direction or in the lower direction.

Similarly, in the mitochondria also basically it can serve as a pool of histochemically reactive zinc ions which cash show the histochemical activity. We know the histological thing, the medical things what we do in neurons and the glial cells. The two types of cells we are talking about, we are thinking about and which are affected mostly by the zinc ions.

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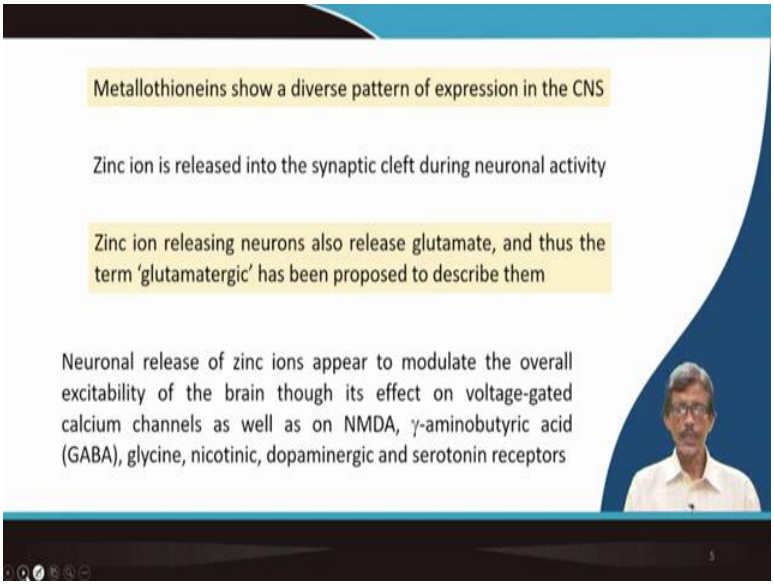

So, if we have these metallothioneins a diverse pattern of expression in the central nervous system. So, zinc ion, metallothioneins and then it is basically ultimately affecting your central nervous system. It can be released into the synaptic cleft during neuronal activity. So, neuron is basically sending signals. Why it is sending signals. Either the zinc is bound or the zinc is released. So, when zinc is in the bound form, in the released form, there is many signals we are just basically following and with that particular thing your neural activity is dependent.

And glutamate basically, the amino acid glutamate is also there so not only the metal ion, but also the ligand. You consider the glutamate 8 basically is the anionic form. So, the ligand is your glutamate anion and thus the term glutamatergic thing is there. That means if you have the glutamate, then only you can think of the controlling of the zinc ions in all these things. So, you want to have the release of zinc ions and the neurons are there for the release of these to the overall excitability of the brain, because the brain excitation is always important.

When I am taking the class I am speaking, I am seeing and I am listening also. So, these all are related to your corresponding excitation and those excitations are coming from your signals, the nervous signals. So, what can happen that you can have the corresponding voltage gated calcium channels so they are not interdependent, because separately we have studied the calcium channels along with your sodium and potassium channels as on NMDA, another biological

molecule as well as the GABA gamma aminobutyric acid, glycine, nicotinic acid and the dopaminergic or serotonin receptor. So, these are basically the receptors.

Is not that you have the receptor which is basically holding the glutamate anion, but you can have the zinc. So, how these two, that means the metal ion as well as the ligand play all these complicated functions when you talk only in terms of the zinc ion, because we are only interested to know about the binding and the release, the way the ligands are binding to your metal ions.

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So, if you have the big structure of all these things. So, you have the glutaminergic neuron terminal. So, then you can have the post synaptic terminal. But you see that this particular part your zinc ions are loaded which are your metallothionein part. So, what we see basically is basically is a big structure so like your bone and all these, our knee structure like this, but is the neural structures where you have the zinc ion.

And the movement of the zinc ion, the zinc ion trafficking at the glutamatergic synaps, sometimes they also call it as the glutaminergic also, another name is a different name, but it will be remembered nicely if we consider that is also similar is also you have the glutamate and the glutamatergic synapses you can have and this is also your glial cell, so another part basically.

So, these things are postsynaptic thing, the neuron terminal. Now, what happens that if we have the metallothionein, metallothionein the zinc ions are coming and binding to that particular way, the way you have all the thiol groups are there. So, if you have many thiol functions are coming like this, all fives from the fingertips basically, if you think that all are thiolate anions and if you have many zinc ions in the pool, so they can come and bind this particular part. So, if you have the protein part from the other side also, two of them are coming and they basically going for the different types of moments and they can bridge the different types.

So, you see here you have the four zinc ions and here you have the three zinc ions all together. A Zn7 system you can tackle from this particular part, Zn7. So, this metallothionein thing is important and another important thing GABA and all these things are there, zinc receptor site is there. The glutamate molecules as I told you the ligands are important. Then if you have to have the corresponding movement from this side to the upper side, that means if we talk about the movement from this side to this side or you can talk about the movement from this side to this side, you have the corresponding receptors over here or the zinc transporters are there. So, the zinc transporters are there which can carry those things, so not only the binding, but also the transport is important for all these cases.

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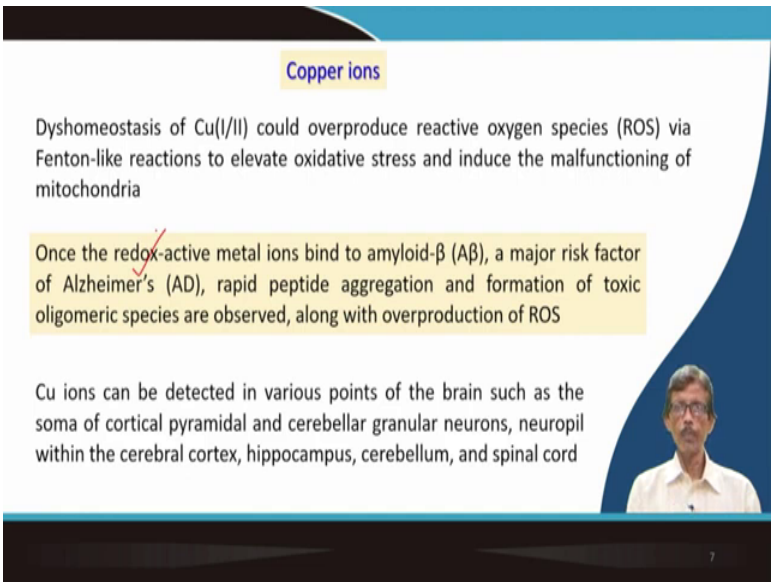

Now, we move to the copper ions. So, let us see how the copper ions will be important compared to your understanding about the zinc ions. We are not talking many thing, many great things, but

we are talking about the availability such that we can have a very good idea about that okay not only we need the zinc for carbonic anhydrase, carboxypeptidase starting from your stomach and everywhere, where our foods are degraded, the amylase activity type of thing, but also it goes to our brain.

So, what is the difference, because already we know that the basic coordination chemistry or the basic inorganic chemistry in terms of the zinc ion and the copper ion. When you bring the copper why you need copper compared to your zinc and how to detect the copper ion nicely compared to your zinc ions that is important. So, think nicely with regard to that. And one most important thing that you can have more complicated metal ion because you can have the electron transfer at biogenic potential.

In biological system, in your brain even, you have many oxidizing agent or many reducing agent. So, if your copper is present like that of your copper sulfate in your test tube, if you have the corresponding bioreductant available over there NADPH type of molecules or FADH type of molecules are there, they immediately can reduce the copper to copper I. So, what we can do basically. Already we are having some problem in tangling about the corresponding concentration of zinc ion as well as the copper ion, now the corresponding concentration between these two oxidation states. Which oxidation state will be useful for us and which is not.

So, during that electron transfer reaction also that the concentration of the cuprous copper as well as the cupric copper is important, and we always have, like your water molecule, we always have the O2 molecule. So, if that electron transfer is mediated by O2 as your oxidizing agent, not other biological molecule, big molecule, biological big molecule for your oxidation reaction, but your O2 can go for the oxidation. So, O2 molecule can accept that electron, taking that electron to its anti-bonding level. So, you can have like iron Fenton chemistry. Here also we will talk as the Fenton-like. When we have the iron as the metal ion, we talk it as a typical Fenton chemistry. But when it is copper, but the same type of electron transport reaction is taking place but at a different potential.

The E0 value for the electron transfer reaction in case of copper is different compared to your ferrous ferric conversion. So, Fenton like reaction we can have and it can increase the our basically stress, the oxidative stress, if we have more and more amount of your superoxide or

peroxide even the radicals in our body, we can have some many problems and also it can trigger basically the malfunctioning of our mitochondria in the cell. So, what are those effect what we can think of for the presence of the redox active metal ions.

So, these redox active metal ions we will talk about afterwards in our next class about iron, but right now we think about only the copper. So, at a particular potential if you have the copper and your copper is presented as the cupric copper so that copper we know that it can accept electron to go to the cuprous so that cupric ion can be a very good oxidizing agent. Now, you bring something amyloid beta protein we can have. So, amyloid beta is, you think of is the protein part and we should know about the binding potential of that amyloid beta or AB we call is abbreviate nicely A beta, so this A beta can have a very good affinity either for cupric copper or for cuprous copper. But it can be a major risk factor of Alzheimer's disease in our brain.

So, what can happen basically not only the aggregation or basically aging process, okay, you are that particular amyloid beta or A beta is pretty old basically. If you are not able to produce a new form of or the newly you can synthesize this A beta you have the very old A beta in your brain and with time it is basically degrading, it is oxidizing, and it is getting deposited. So, this rapid peptide aggregation and the formation of toxic other oligomer, oligomer is more number of this species, monomeric species, so like your polymer is the oligomer so same type of all these pieces are attached.

So, this oligomerization is also observed along with the overproduction of your reactive oxygen species that means your O2 can accept those electrons and you have the corresponding ROS, environment is oxidizing not only through oxidation with O2, but also with the different ROS, because sometimes the ROS much more dangerous the way we know that hydrogen peroxide or potassium superoxide can be much more dangerous to your cell, your body your biomolecule compared to your simple dioxygen molecule.

So, these copper ions, therefore, can be detected at various points of the brain, such as some soma of the cortical pyramidal and cerebellar granular neurons, so basically all these positions the naming of these things that you have the different neurons, the neuropil, within the cerebral cortex, we know the cortex area also, the hippocampus, cerebellum and the spinal cord. So, you see, starting from the spinal cord to your cerebral cortex, we know that a patient suffering from a

cerebral attack, we know heart attack, we know the cerebral attack, so the cerebellum or the cerebral cortex is basically getting affected or brain cells are dying there or the blood vessels are rupturing and all these things happen. So, is a very delicate part, basically.

We are talking not your blood or the blood vessel or your hemoglobin and myoglobin, but the metal ions, this is a dangerous metal ion, but only thing is that the concentration is very, very less. So, this particular deadly metal ion can be there and is nearby. But if you are unable to manage the concentration, the right concentration what do you need, will have the problem.

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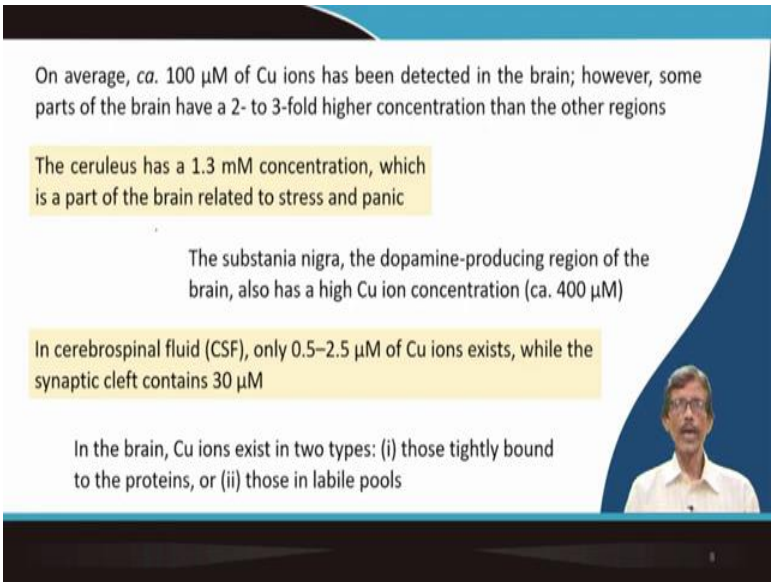

So, on an average what we can have is the micro molar concentration of copper ions can be detected in the brain. So, that is the highest level. But in some parts of the brain 2 to 3 times higher concentration than this particular position you can have. So, if you have the imbalance. Where you require the higher concentration, you should have the higher concentration. Where you require a lower concentration, you must have the lower concentration. Otherwise, you have the problem in its function.

In ceruleus it has 1.3 millimolar concentrations that is higher one, highest one, which is the part of the brain related to the stress and panic. So, you have a higher concentration. So, when we show we call a panic attack or you are under stress, a stressful life you are living. So, depending upon your lifestyle and all these things and you are neurotransmitters are forming, and the dependence of these neurotransmitters with the metal ion concentration is important. So,

substania nigra, which is basically the dopamine producing region we call is basically Latin name sometime we give it, this Latin name is important, where we can have, where you can have the corresponding concentration up to 400 micromolar so the change in all this.

But what about the your CSF, the cerebrospinal fluid, it can only 0.5 to 2.5 micromolar concentration, but in the synaptic cleft it is 30 micromolar. So, you see the range. So, you will consider the lower range and you consider the higher range, you can think of your chemistry related to your copper as well as the copper concentration. So, two types of copper we can have one is like that of your zinc tightly bound one and the labial one. So, if you forget what about copper, you can consider about zinc and you can answer nicely about two types basically. Is a very simplified answer for that.

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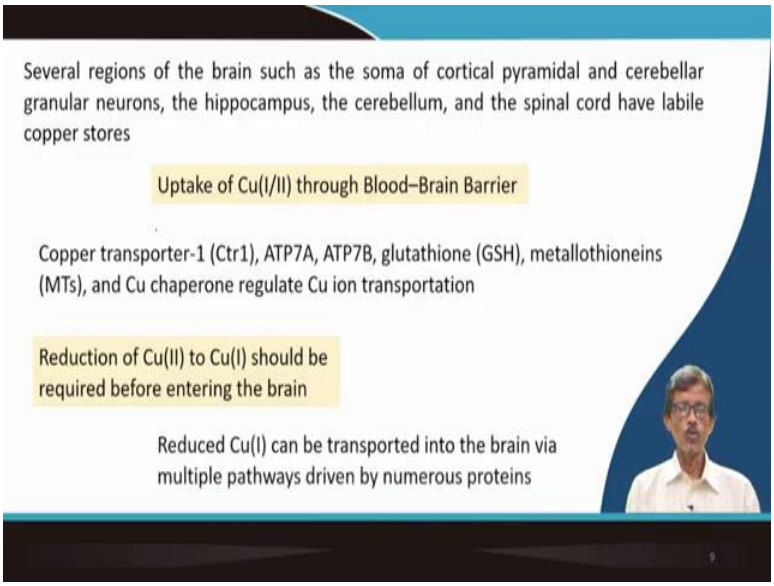

So, several regions we can have the brain such as soma or cerebellar granular regions and hippocampus and the spinal cord so all will have the labile copper ions. So, you have loosely bound copper ions. And these copper ions can be transferred through your B3 barrier, we call as BBB, blood brain barrier. So, blood brain barrier it can go and the transporters you can have. So, Ctr1, the copper, tr is your transporter number 1, ATP7A, ATP7B, glutathione, metallothionein is already we talk and is abbreviated as MTs and copper chaperone which basically regulate the copper transportation reaction.

And during that particular process the reduction of these that means you reduce it to cuprous thing should be required before it is entering to the brain because it is more soluble in the aqueous medium. So, the brain is less amount of aqueous environment. So, it is a little bit of hydrophobic in nature. So, we can move as the cuprous form. So, multiple pathways driven by numerous proteins are required for the transportation of copper I, cuprous copper to your brain.

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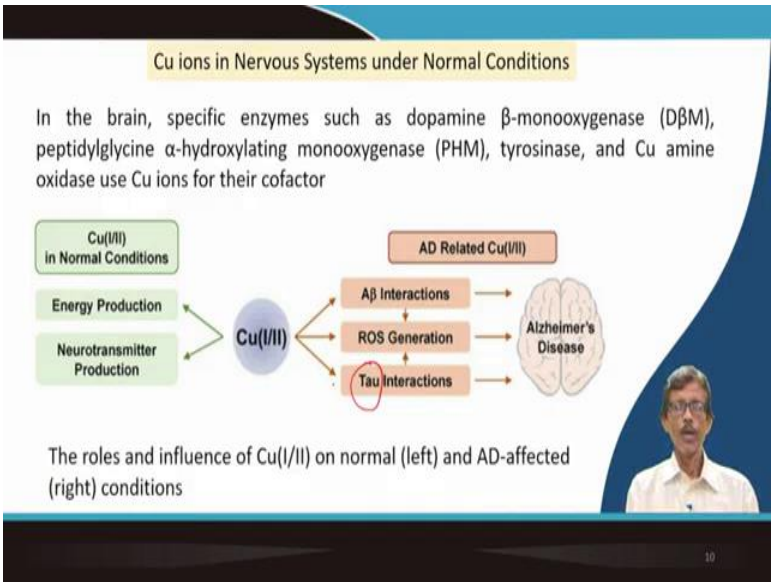

So, in the nervous system under normal conditions what you can have. So, what you can have in the nervous system if it is in the normal condition. Already we know that D beta M, PHM, amine oxidase and other cofactors are there in our brain also, because we produce neurotransmitters. So, neurotransmitters are produced in the brain. So, copper in these two oxidation states in both these two cases left you have the normal part, but right is abnormal part that means you have the disease.

So, is required, copper is required for many right work like your neurotransmitter production to your normal conditions for the normal functioning. But in case of the abnormal situation you have ROS generation and the tau interaction this is one more important definition I am taking the tau proteins are there and your AB interactions thus that you can have the corresponding disease, AD disease or AD we call the Alzheimer's disease. So, the role and influence of copper II ions for the normal and the AD affected condition for our brain.

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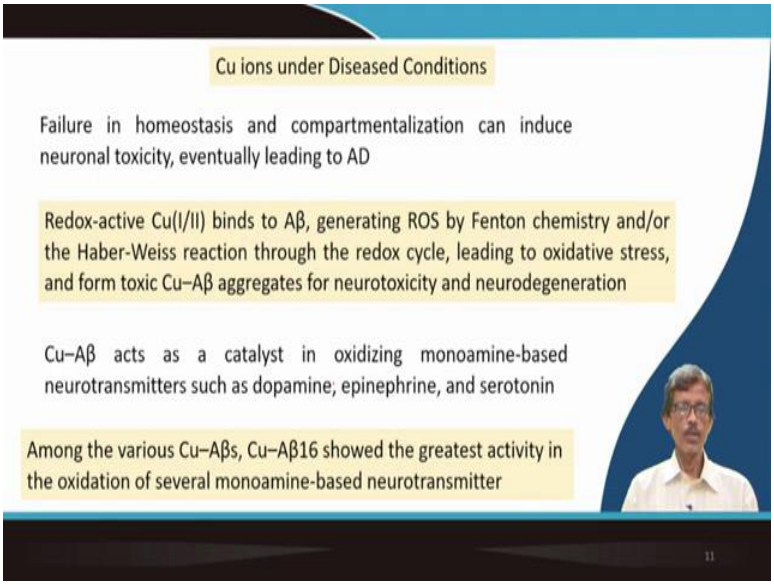

But under diseased conditions what you can have, the failure of the homeostasis, compartmentalization can induce neuronal toxicity and eventually leading to your Alzheimer's disease. So, these redox-active copper II ions can bind to your AB generating ROS and the Fenton like chemistry and the Haber-Weiss reaction through the redox cycle leading to the oxidative stress, form toxic copper A beta aggregation. So, copper is required basically. Is not that AB alone can aggregate. Then it is acting as a catalyst for monoamine-based neurotransmitters such as dopamine, epinephrine and serotonin thing. That means the copper then can function as a very good catalyst for the formation of neurotransmitters there. So, various all these interactions some of them can so greatest activity in oxidation of several monoamine-based neurotransmitters.

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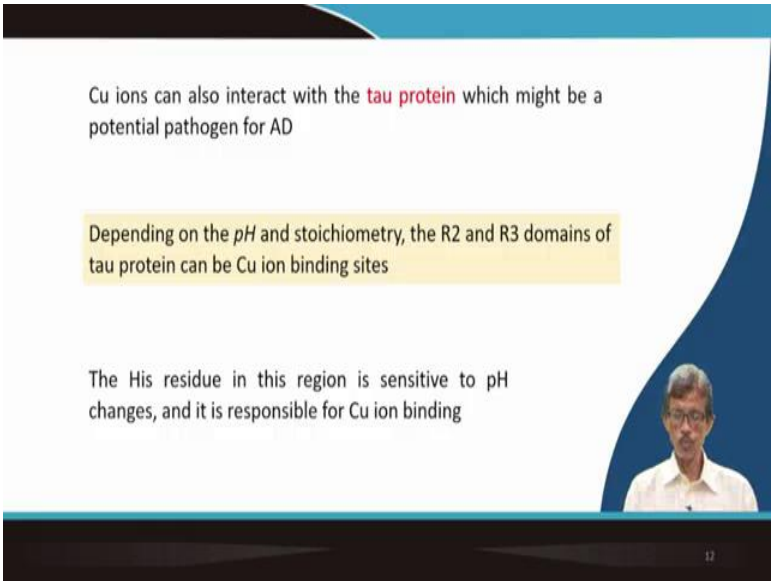

So, can interact with the tau protein, as I told you, can potential pathogen for AD development. Then two regions you can have the domains basically we call R2 and R3 for protein which can bind there with that of your copper. Then histidine residues all we know that the histidine has a very good affinity for the copper and is sensitive to the pH change, because if you protonate the histidine residues, it will no more useful for your copper coordination.

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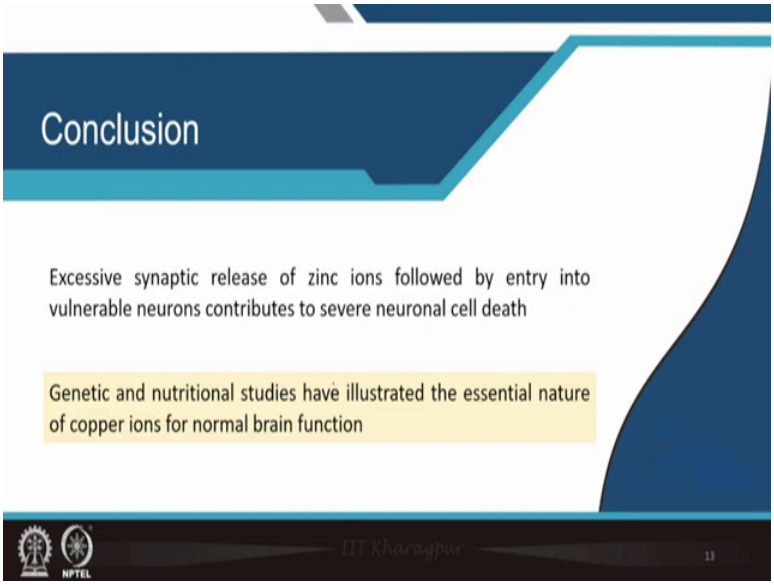

So, what we have seen basically for these two metal ions in your brain that you can have for zinc, when you talk about that gene you can have the synaptic responses and the synaptic,

excessive synaptic release of zinc ions followed by entry into the vulnerable neuron contribute to the severe neuronal cell death. So, first always as we try to understand or try to know about what can happen in the adverse condition, such that what we can avoid. So, we should avoid this particular release of these copper ions in, zinc ions in these particular regions.

What about copper? Copper you can have the control from the genetic region from our birth time also and the nutritional studies also have shown us that it can have a very essential nature for normal brain function. So, we are talking about the effect of the metal ions for their brain functions only.

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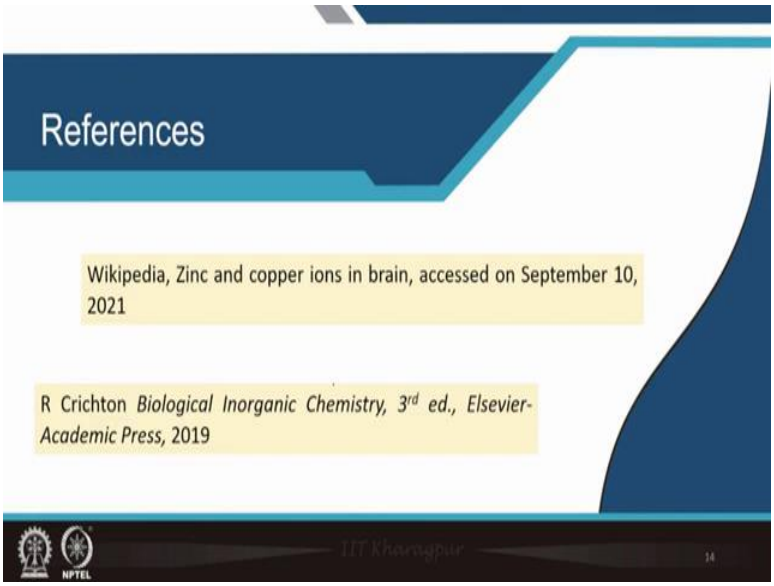

And the references, particularly for the zinc and copper ions in brain and the book also. Thank you very much for your kind attention.