Basics of Mental Health & Clinical Psychiatry
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Lecture 23
Learning & Memory - 2

Hello, everyone. So, today we will start the next part of our learning and memory.

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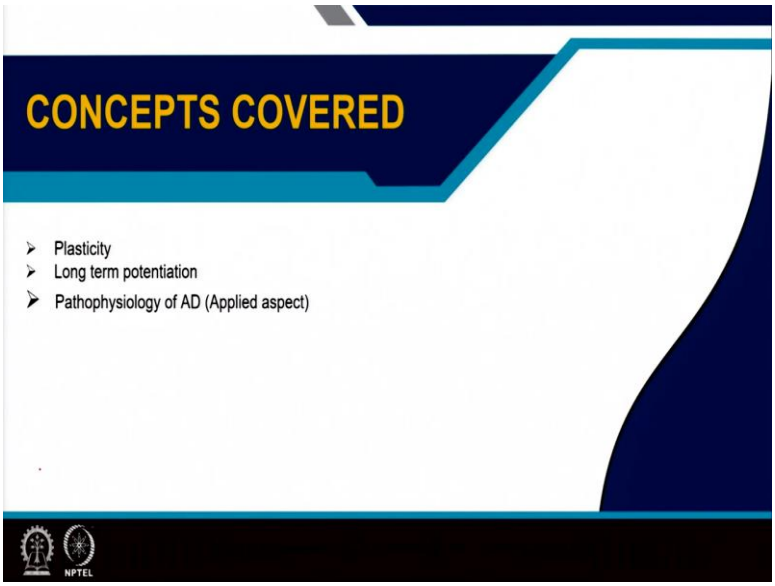

So, far we had seen what are the cellular basis of short term and long term memory. So, today we will discuss about the plasticity, the long term potentiation. And mainly what is the pathophysiology in brief of Alzheimer's disease that is a neurodegenerative condition.

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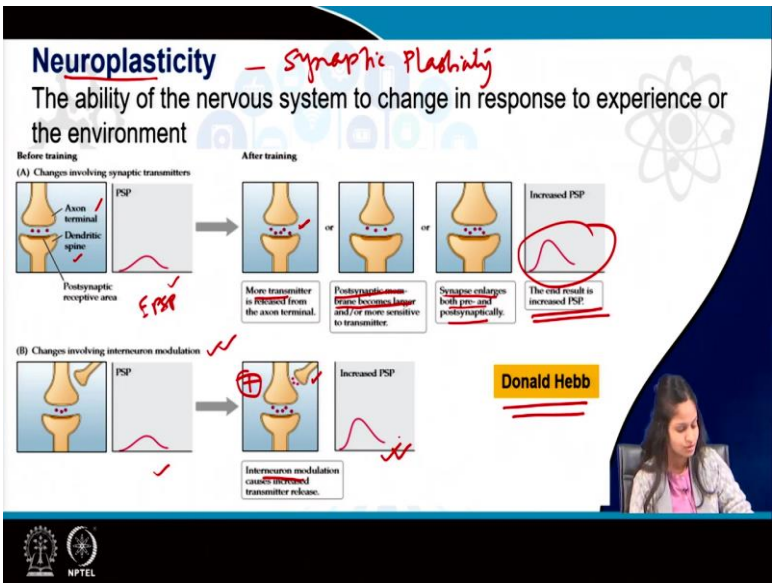

So, neuroplasticity is defined by the ability of the nervous system to change in response to experience or environment. This neuroplasticity is also known as synaptic plasticity. So, the strength of the stimulus based on the strength of the stimulus, in response to experience or environment, how the neurons change in our system in our central nervous system, in our nervous system, so that is neuro plasticity.

So, this is mainly described this neuroplasticity phenomenon by Donald Hebb, and we call it as heavy and synapses. So, we will see before training, what happens, the changes involving in the synaptic transmitters. So, this is an axon terminal, this is the dendritic spine, of the post synaptic area and there is release of neurotransmitter which gives rise to post synaptic potential. Here the potential is obviously excitatory post synaptic potential.

Now, after you train a person, there can happen various things like three changes can happen what you can see, when you train a person, there can be released of more neurotransmitters, more neurotransmitters can get released from the axon terminal or there can be change in the structure of the post synaptic membrane, the post synaptic membrane becomes larger so, they are more receptive for the neurotransmitters and there can be changes both at the level of presynaptic level, more presynaptic level size increases so, more neurotransmitters there will be more synthesis of receptors and more release of neurotransmitters.

So, finally the end result will be released of more neurotransmitters and increased post synaptic potential, excitatory post synaptic potential. This is one. The second thing is there can be change involving the modulation. The modulation is done by inter neuron. So, this is the same diagram whenever there is an inter neuron is coming, if this inter neuron is secreting excitatory neurotransmitter, it will stimulate this initial synapse or it will stimulate the presynaptic terminal to secrete more neurotransmitters.

So, this is inter neuron modulation, which causes increased neurotransmitter to release and again there will be increased or synaptic potential. The reverse can also happen this inter neuron can be inhibitory in nature and they can inhibit this signups, they can inhibit the presynaptic terminal and there will be less release of signup neurotransmitters. So, there will be less modulation of the transmitter release and less generation of synaptic potentials. So, this way the synaptic changes occur based on the strength of the stimulus.

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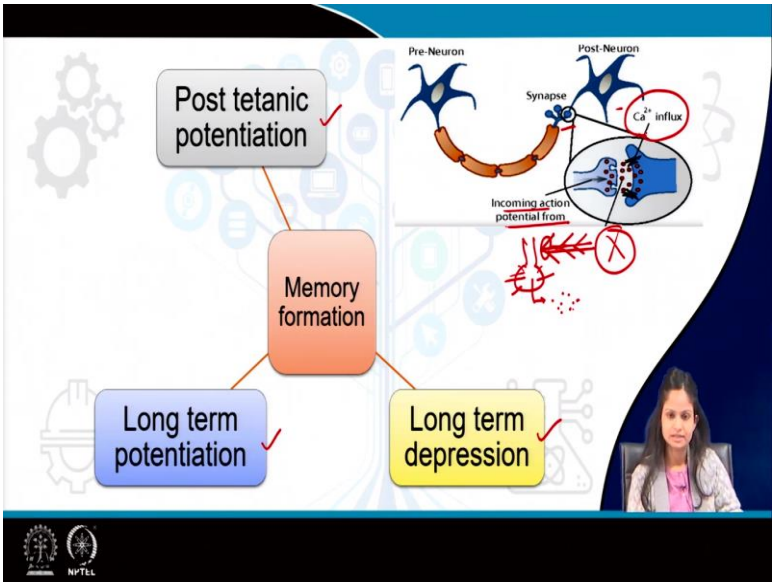

So, this is mainly done with the help of three mechanisms, the memory formation is nothing but activation of your neurons, when you activate neurons several times that results in synaptic plasticity, so, that can be post tetanic potentiation, there can be long term potentiation, there can be long term depression.

What happens in post tetanic potentiation? Say this is a pre-neuron, this is the synaptic end and this is the post neuron. Now, when there is a incoming action potential from the presynaptic terminal, there is presynaptic terminal. This is if I show in the diagram of posted on a potential. This is a neuron and there is another stimulus, you are giving repeated stimulus to this neuron.

What will happen? Whenever you give repeated constant stimulus with high frequency, there will be constant opening of calcium channels. And this calcium channels will cause release of neurotransmitters. So, this release of neurotransmitters will be more and there will be further impulse transduction.

Now, this calcium channels or this calcium influx will be even more or it will remain more even you when you stop this giving the stimulus. That is the basis of post tetanic potential that means, in the presynaptic terminal you have increased the calcium level to certain level that even if you stop giving the stimulus, there will be constant release of neurotransmitter. So, that is posted on a potentiation. Further we have long term potentiation and then we have long term depression.

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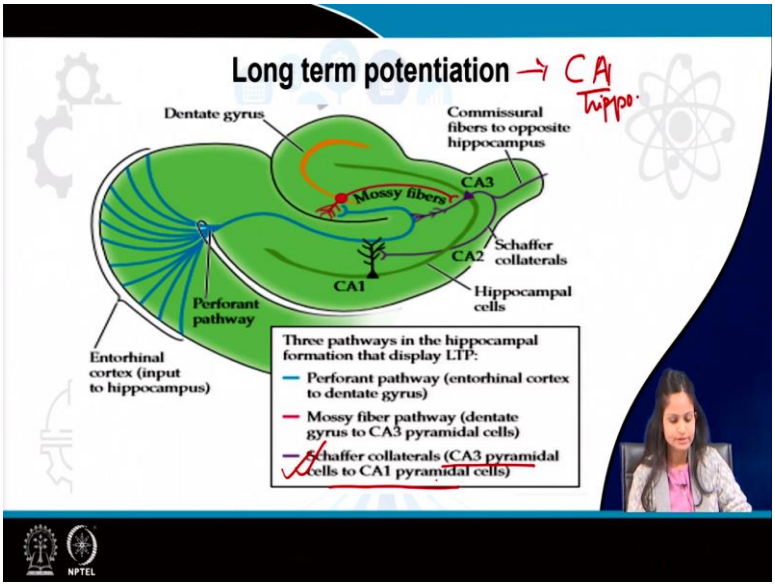

Now, when we talk about long term potentiation, the pathway I had already discussed previously, long term potentiation occurs in the hippocampus. Mainly the CA 1 region of the hippocampus. This you have to remember. It occurs hippocampal potentiation occurs can in may various pathway but most important pathway is the Schaffer collateral pathway that is CA 3 to CA 1 region that is CA 1 region on the hippocampus. Now, how it will occur.

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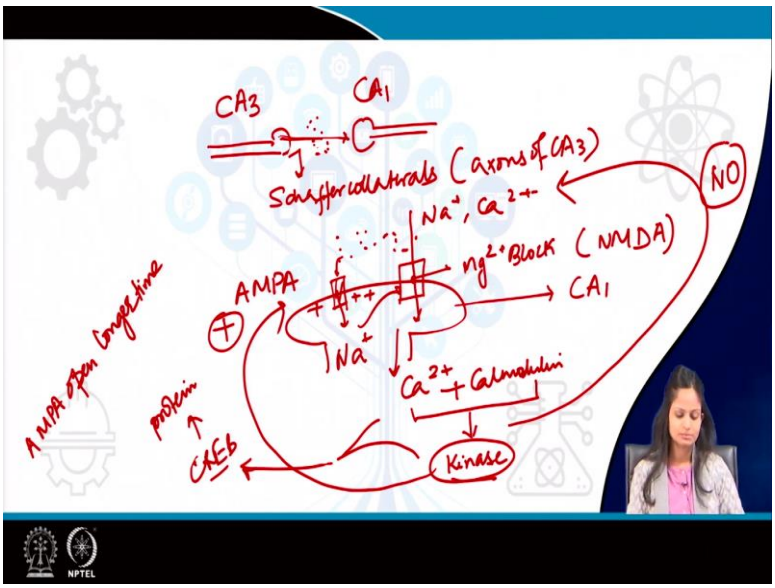

Now, suppose the you have this is the CA 3 neuron this is a CA 3 region of the hippocampus. This is the exon end these are the exons which will stimulate this CA 1 region. Now, this is a CA 1 region of the hippocampus is CA 3 region of the hippocampus. Now, this exons of this

CA 1 region is known as Schaffer collaterals. So, Schaffer collaterals are nothing but the exons of CA 3 regions, CA 3 pyramidal cells to CA 1 pyramidal cells, this axons are known as scrapper collaterals.

Now, this will release the neurotransmitters which are glutamatergic. This will release glutamate neurotransmitters, which is of course, excitatory in nature, and this will cause the post synaptic event. So, let us see what post synaptic event it does, suppose, the glutamate are released and this is the neurotransmitters glutamate which is released, so, it will bind and this is the post synaptic membrane of what CA 1 region of the hippocampus. So, there will be receptors known as AMPA receptors.

When this neurotransmitter will bind to this AMPA receptors, there will be influx of sodium. The basics of this glutamate receptors has already been discussed in the glutamate the neurotransmitters chapter. So, though I shall be repeating in brief while drawing this. So, when this AMPA receptors are activated with the help of neurotransmitters binding to the dutamax neurotransmitters binding to the receptors, there will be influx of sodium ions.

So, whenever there is influx of sodium ions, what happens, there will be depolarization of the membrane inside the membrane, this depolarization causes what, it will remove the magnesium block here is the magnesium block present in the which receptor, this is NMDA receptor, this is the other receptor of the glutamate.

So, it will remove the magnesium block of the NMDA receptor and this NMDA receptor will become active. Remember this magnesium block is only removed with the help of depolarization done by AMPA receptors. Now, when this magnesium block is removed, there will be further entry of sodium and calcium.

So, when this entry of sodium and calcium will occur, what will happen? There will be more and more depolarization. Now, after this entry of calcium, this calcium will get entered there will be influx of calcium, this calcium will bind with calmodulin complex and form calcium calmodulin complex. This calcium calmodulin complex will stimulate various kinase enzymes, kinases are meant for phosphorylation.

So, this kinase enzyme what it will do? It will phosphorylate or it will stimulate the phosphorylation of AMPA receptors. And when there will be stimulation of this AMPA receptors, this AMPA receptors will remain open for longer time. The first thing is the

AMPA receptors will open longer time. So, you can see the sodium ion is binding sorry the neurotransmitter is binding to the AMPA receptor that is a glutamate. So, when this glutamate is binding to the AMPA receptor, there will be sodium influx because of the sodium influx there is depolarization. This depolarization is causing to remove the magnesium block of the NMDA receptor.

When this block will get removed, this NMDA receptor will get active and it will cause further influx of sodium and calcium. Now, this calcium will bind to the calmodulin and complex and this complex will activate the various kinases, this kinases will cause further phosphorylation of more AMPA receptors and in this way AMPA receptors will remain open for longer time. Again, another important thing is also this kinases and this calcium calmodulin complex will cause various synthesis of gene, the most important gene over here is CREB.

So, this gene synthesis will cause various protein synthesis and this protein synthesis will cause various permanent changes, structural changes of the neurons or in the signups there will be structural changes. The third thing is this kinases will also send a retrograde signal, retrograde signal means it will send a signal to the presynaptic neuron with the help of nitric oxide NO, what this retrograde signal nitric oxide it will do? It will stimulate the presynaptic terminal to secrete more and more glutamate.

So, more glutamate will synthesized or more glutamate will secreted and this pathway will occur again and again I mean, this will be AMPA will get activated again that will indirectly activate the NMDA receptors, there will be binding of more calcium there will be binding of calcium calmodulin complex kinases will be formed, receptors will form more, various proteins will form and which will cause permanent structural changes.

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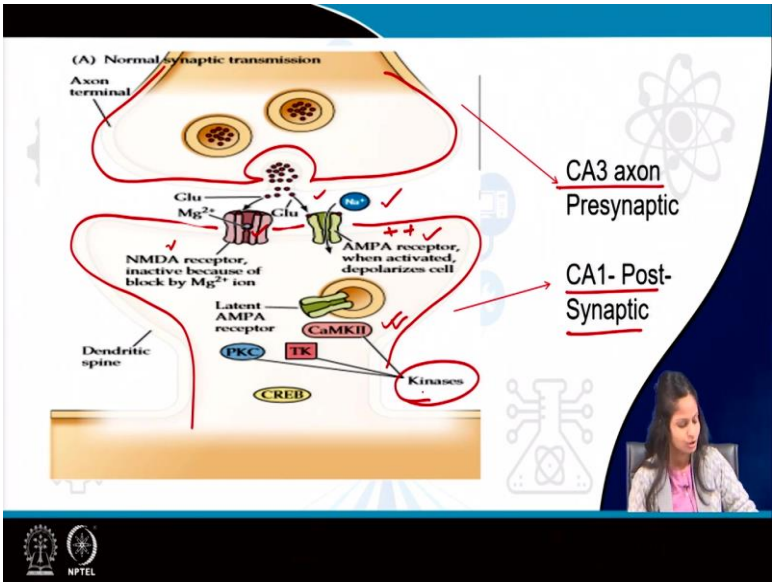

So, with this understanding, I will move on to the diagram of the normal synaptic transmission. So, this is all I had already discussed is a CA 3 axon, the Scraffer collateral of the that is a presynaptic neuron and CA 1 is the post synaptic neuron. So, this is the post synaptic neuron and this is the presynaptic neuron.

So, as you can see there is synaptic transmission the glutamate release is occurring, this glutamate is binding to the AMPA receptors which activated and sodium entry occurs, it depolarizes the membrane because of depolarization the magnesium block is removed and this NMDA receptors becomes active. And this NMDA receptors will cause entry of calcium and sodium. Now, this calcium and sodium what it will do? It will bind to this calmodulin complex and this calmodulin complex will further cause activation of various kinases.

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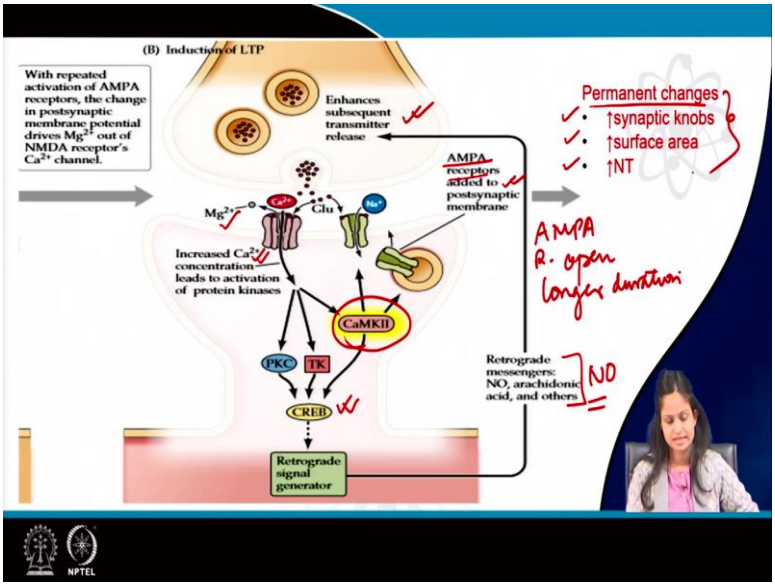

So, if you see this diagram, where there is induction of long term potentiation, enhanced release of neurotransmitter, magnesium is removed, increased calcium concentration is there, this calcium will bind to the calcium calmodulin complex, which will cause more kinases formation that will cause AMPA receptors added to the post synaptic membrane and this will cause more AMPA receptors to remain open for longer duration. And also there is synthesis of gene that is CREB gene, which will cause permanent and structural changes, these are permanent changes are increased synaptic norms, increased surface area, increased neurotransmitter.

Obviously, if the surface area of the zones are increased, there will be more release of neurotransmitter. So, these are the permanent changes which lead to the synaptic plasticity on neuroplasticity along with the retrograde signal that is done by nitric oxide to secrete enhance subsequent neurotransmitter release. Here the neurotransmitters glutamate, so, there will be more glutamate release.

So, what is the long term potentiation? I mean this long term potentiation is actually causing finally causing this permanent changes and this long term potentiation is when you are repeatedly activating this AMPA receptors then only we are getting this long term potentiation or the permanent changes, and that is what actually happens when you read anything once you do not remember. So, what do you do? You activate your synapses, how, by revision.

So, number of times you revise, you are actually creating this long term potentiation in your brain, which will cause the structural changes in the synapses. And that forms the basis of your long term memory and you remember the things. So, this is the molecular basis of long term memory.

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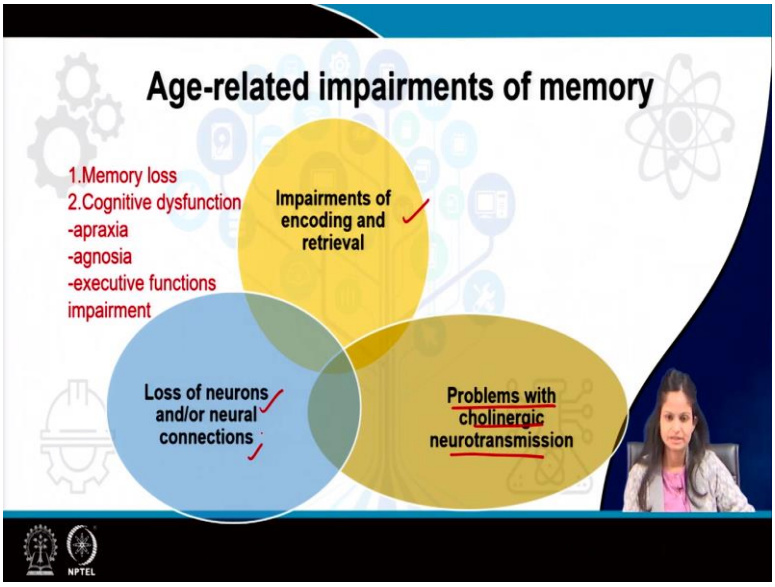

Now, what happens the impairments of memory can occur either due to the coding or a tribal impairment, there can be problems with cholinergic neurotransmission. As I told you the destruction of cholinergic pathway, there can be loss of neurons or loss of neural connections. So, any of this can result in memory loss, or cognitive dysfunctions. Cognitive dysfunctions can be apraxia, agnosia, executive functions impairments, the person is not a person knows the thing, but the person is not able to execute the performance. The person is seeing something the person is not able to recognize. The person is recognizing something but the person is not able to execute.

So, this sort of cognitive dysfunction occurs along with memory loss in the memory impairment or neurodegenerative disease.

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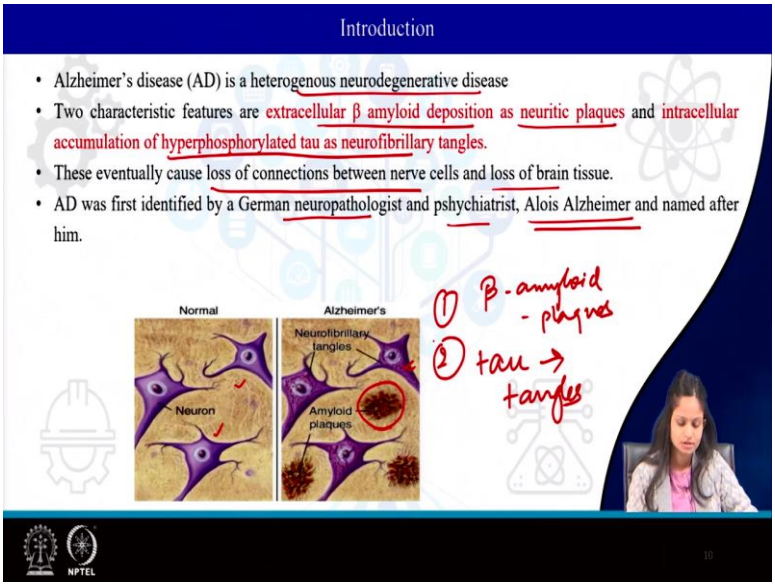

So, we will talk about Alzheimer's disease in brief. Alzheimer's disease is a heterogeneous neurodegenerative disease, the mainly pathology which occurs and the Alzheimer's disease is the extracellular beta amyloid deposition, there is a beta amyloid deposition as neuritic plaques, the beta amyloid deposition as plaque and also there is hyperphosphorylated I mean, there is accumulation of tau proteins that is hyper phosphorylated tau proteins, this form neurofibrillary tangles, this is very actually dangerous, (()) (17:12) protein.

So, there is accumulation of top proteins, hyperphosphorylated tau proteins as neurofibrillary tangles, there is deposition of beta amyloid plaques. So, these will eventually cause loss of connections between the nerve cells and the loss of brain tissue. And this was coincidentally identified by a German neuro pathologist and psychiatrist that is Alois Alzheimer's and the disease is named after him.

So, you can see this is the normal brain which is consisting of neurons, and you can see the neurofibrillary tangles and these are the amyloid plaques deposition, then these are the neurofibrillary tangles inside the neurons. So, these are the histological features of the Alzheimer's disease neuron.

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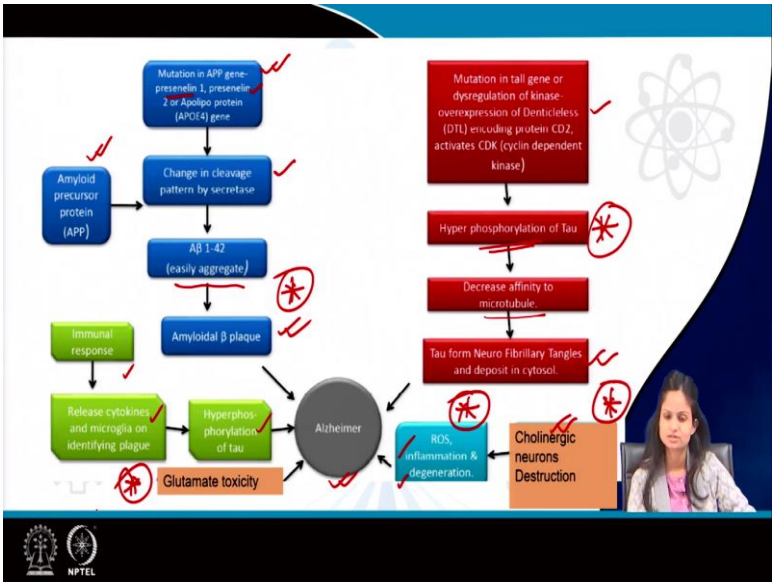

So, general pathology of the pathogenesis of Alzheimer's disease, there is various factors but the main I told you is the deposition of myeloid body and top protein formations. Now, a myeloid body deposition occurs because of generally mutation. There are mutation changes which can occur in a myeloid precursor protein APP. There can be mutation of the amyloid precursor protein gene that the presenelin 1 and presenelin 2, these are the genes which usually code for a myeloid precursor protein.

So, whatever happens, whether it is mutation of the gene or mutation of the proteins, that results in whenever anything is forming in our body which is not required or unnecessary. So, that will immediately get degraded and it will be considered as waste products and if those waste products are accumulated in our body that will cause further symptoms and destroy the normal functioning of the cells.

So, that is what happening. There is change in cleavage pattern by Securitas enzyme and this will form aggregation of this amyloid proteins, because these are amyloid proteins are all not helpful in our body because it has already the structure has changed there is a mutation. So, that will result in aggregation or accumulation of this amyloid proteins or amyloid plaques. Besides this, whenever anything, like any inflammation is occurring in our body because of the foreign particle because this amyloid is a foreign particle for us.

So, there will be immune response, release of cytokines and hence there will be hyper phosphorylation of tau. Now this hyper phosphorylation of tau also occurs because of another mutation in another gene. The mutation or dysregulation of kindness, over expressions so that

is cyclin dependent kinase. So, these genes also cause hyper phosphorylation of tau. So, one is hyper phosphorylation of tau and the other one is a myeloid betta flux.

Now, what happens, this hyper phosphorylation of tau will cause decreased affinity of the microtubules. Now, this microtubules arrangement will get disturbed because of this tau and they will form tangles and they get deposited in the cytoplasm of the neuron. So, this results in Alzheimer's disease.

Besides there are glutamate toxicity, if more and more glutamate is secreted and if the glutamate is not degraded, then there is cholinergic neurons destructions. All these factors will cause oxidative stress in the neurons in the brain that will lead to reactive oxygen species, reactive oxygen species, the oxidants and the antioxidants in our body usually prevent the oxidative stress.

So, when this reactive oxygen species are done, there will be inflammation and finally, neuro degeneration. So, this is the in brief the pathophysiology of Alzheimer's disease, which is concerned with amyloid plaque formation, hyperphosphorylation of tau, cholinergic neuron disruption, reactive oxygen species oxidative stress and glutamate toxicity. These are the five main mechanisms by which Alzheimer's disease or neuro degeneration occurs.

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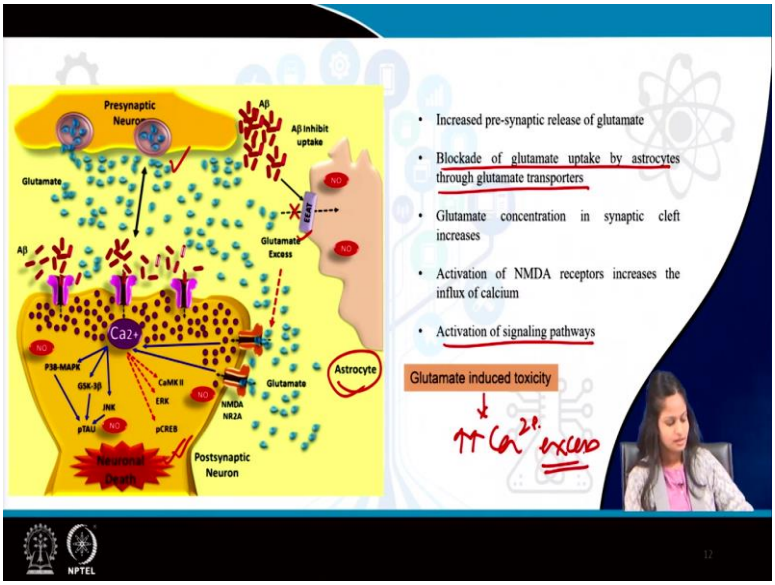

Now, glutamate induced toxicity usually occurs because of the failure of reuptake of glutamate. Now, there is increased glutamate synthesis from the presynaptic neuron. This is taken by the receptors and what will happen, the receptors will do signaling, there will be

calcium influx there will be long term potentiation. Everything is good when there is which occurs if it occurs under a limit. But if the glutamate synthesis occurs in excess, and if it is not degraded, degraded means glutamate is usually when the function is over the glutamate is usually reuptake is done, or this reuptake is done mainly at the level of astrocytes.

And through glutamate like receptors, so, blockade of glutamate reuptake by astrocytes through glutamate transporters, if the glutamate transporters are blocked by any mechanisms, the astrocytes will not be able to take the glutamate. So, what will happen this glutamate will get accumulated in the synapse, so, there is the more glutamate accumulation, the more calcium influx will be there.

So, calcium influx in excess causes toxicity in our body. So, there will be more calcium, there will be activation of more signaling pathways and there will be more calcium induced toxicity and that will cause neuronal death. So, glutamate induced toxicity is mainly because of increased calcium excess.

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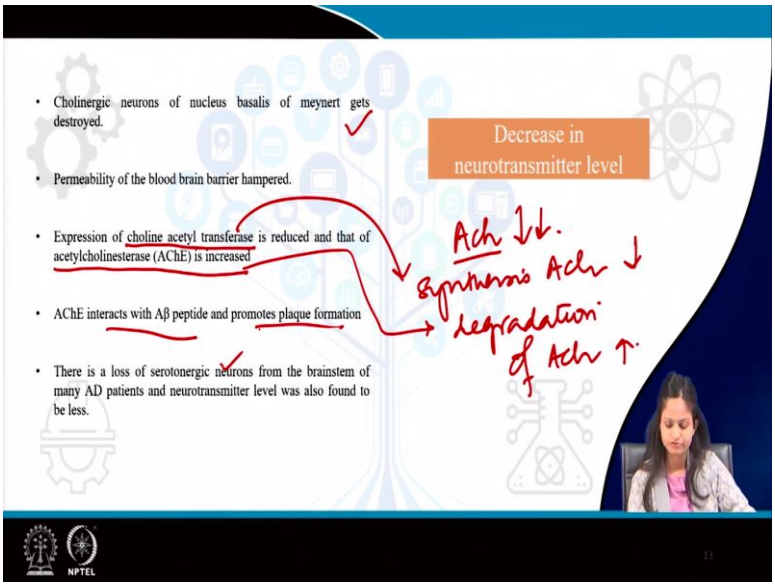

Then there is decrease in the neurotransmitter level. Neurotransmitter level means the acetylcholine and since the cholinergic neurons of the nucleus basalis of meynert gets destroyed that is a basal forebrain. So, there is the decrease in the acetylcholine level. So, acetylcholine level is decreased. Now, whenever there is decrease in the acetylcholine level, what will happen there is expression of choline acetyltransferase which is reduced and acetylcholine esterase is increased.

Choline acetyl transferase causes synthesis of acetylcholine that means acetylcholine formation, so, this is reduced and acetylcholine esterase causes degradation of acetylcholine which is increased. So, in our body the synthesis and degradation needs to be balanced. Now, if there is an disbalance, if the synthesis is decreased and degradation is or destruction is happening more than obviously, it will lead to neuro degeneration and that again forms flux with amyloid beta peptide and promotes plaque formation.

There is also loss of serotonergic neurons from the brainstem which has already been found where the neurotransmitter level also been found to be less but most importantly you have to remember the acetylcholine which is less which becomes less and the neurotransmitter level because of synthesis of the choline, acetylcholine transporters and acetylcholine esterase enzyme activity which is more which leads to degradation of more acetylcholine.

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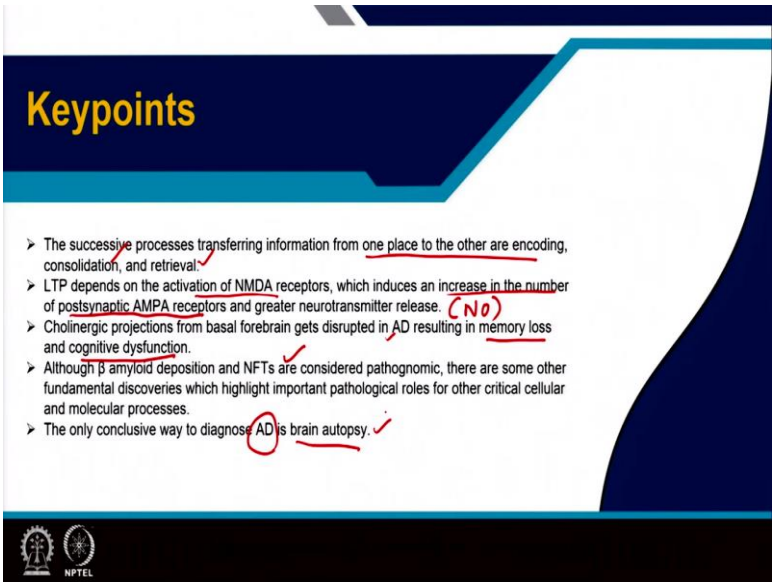

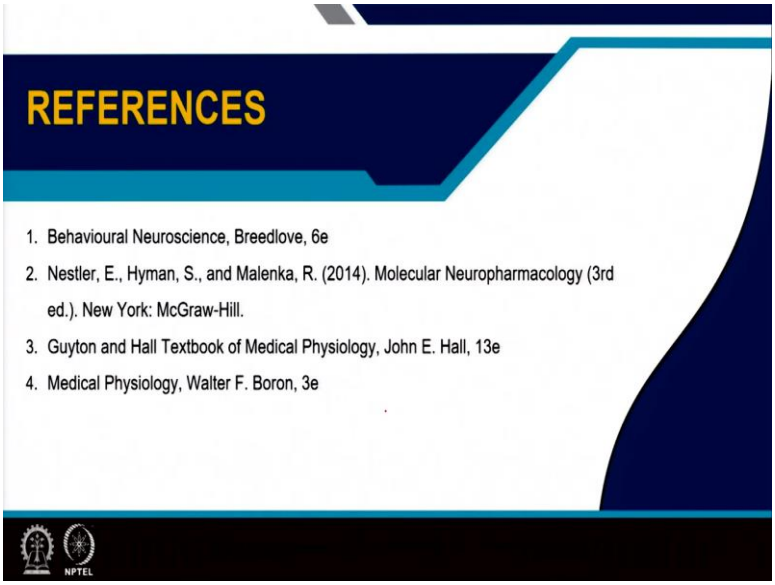

So, the key points you have to remember in case of learning and memory, the successive process transferring information from one place to the other, that is encoding, consolidation and retrieval. Any hindrance in encoding, consolidation or retrieval leads to loss of memory functions or dementia. Long term potentiation depends upon the activation of NMDA receptors.

Now this activation of NMDA receptors also happens because of the activation of AMPA receptors. And further activation of NMDA receptors also causes increase in the or upregulation of the post synaptic AMPA receptors and hence greater neurotransmitter release with the help of nitric oxide or retrograde signal.

Cholinergic projections from basal forebrain gets disrupted in Alzheimer's disease results in memory loss and cognitive dysfunctions. So, mainly the cognitive dysfunctions, which is seen in apraxia or executive dysfunction that is usually mainly because of the cholinergic projections which gets disrupted.

Further amyloid depositions and neurofibrillary tangles are considered the most pathognomic besides various pathological roles, played by glutamate toxicity and reactive oxygen species. The only conclusive way to diagnose Alzheimer's disease is brain autopsy. Now, for this the person needs to be dead. That does not mean that we do not diagnose Alzheimer's disease when the person is leaving, the person is when the person is living, we get the diagnosis, the clinical diagnosis based on the MRI, CT scan, PET scan.

So, all the scannings are done based on that we get the diagnosis, but the confirmatory diagnosis of Alzheimer's disease is seen when we do the histopathological examinations. So, that histopathological examinations is only done with the help of brain autopsy. So, the confirmatory diagnosis or conclusive way of diagnosis is brain autopsy. So, in this way, I want to conclude today's topic, finally, of learning and memory. Thank you.