Basics of Mental Health and Clinical Psychiatry
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Lecture 07
Synapse & Neurotransmitters-II

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Hello everyone. So, today we shall start our next chapter that is Synapse and Neurotransmitter part 2.

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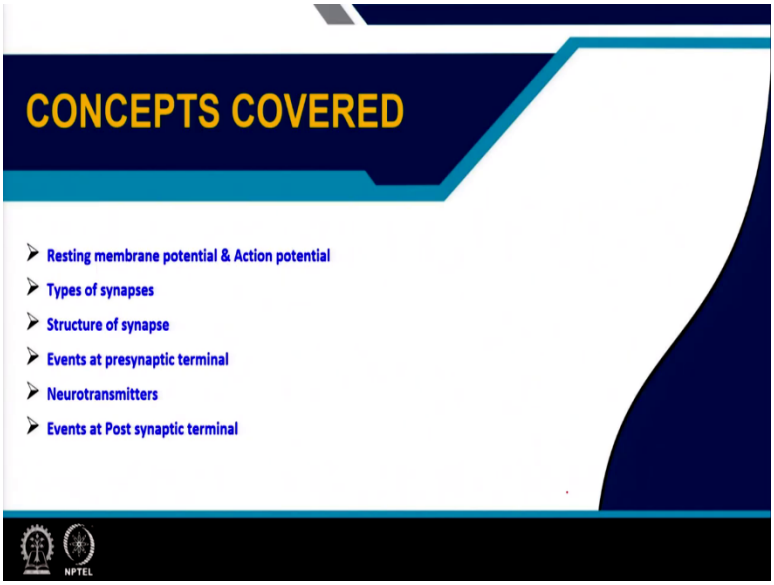

Already the part 1 has been discussed in the previous lectures. So, the concepts already I had covered were resting membrane potential and action potential, the types of synapses, the structure of the synapses, what are the events taking place at presynaptic terminal, the neurotransmitters I had already discussed about glutamate. Today, we will discuss the other neurotransmitters like acetylcholine, GABA, dopamine, serotonin, norepinephrine. And we will see the rest events which take place at postsynaptic terminal.

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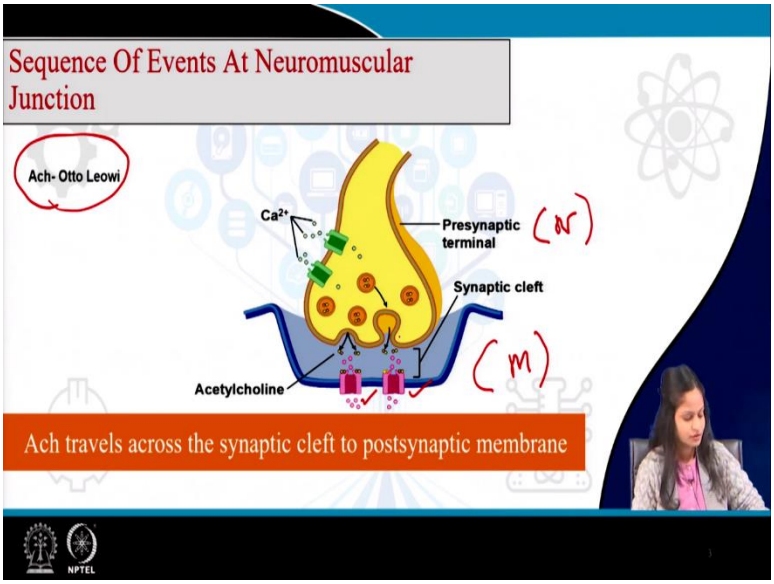

So, when we talk about CNS we also talk about the peripheral nervous system, which is also very important in terms of neuromuscular junction. So, acetylcholine forms a very important neurotransmitter at the level of neuromuscular junction and it is very important to know the sequence of events which take place at the neuromuscular junction. Now, acetylcholine is the neurotransmitter it is the first neurotransmitter which has been discovered by Otto Leowi.

So, you have to remember this the discoverer of acetylcholine at least, even if you do not remember the other discoveries of other neurotransmitters. So, acetylcholine gets secreted from the presynaptic membrane. Here, the presynaptic terminal is obviously in case of neuromuscular junction will be a nerve and it will act on the postsynaptic receptors.

These postsynaptic receptors are present on the postsynaptic membrane, here the postsynaptic membrane obviously, it will be of the muscle and plate or the motor and plate of the muscle. So,

in this way, it forms the neuron and muscular junction. The acetylcholine gets released from the vesicles, which is present in the presynaptic terminal. It travels across the synaptic cleft to the postsynaptic neuron and performs its actions.

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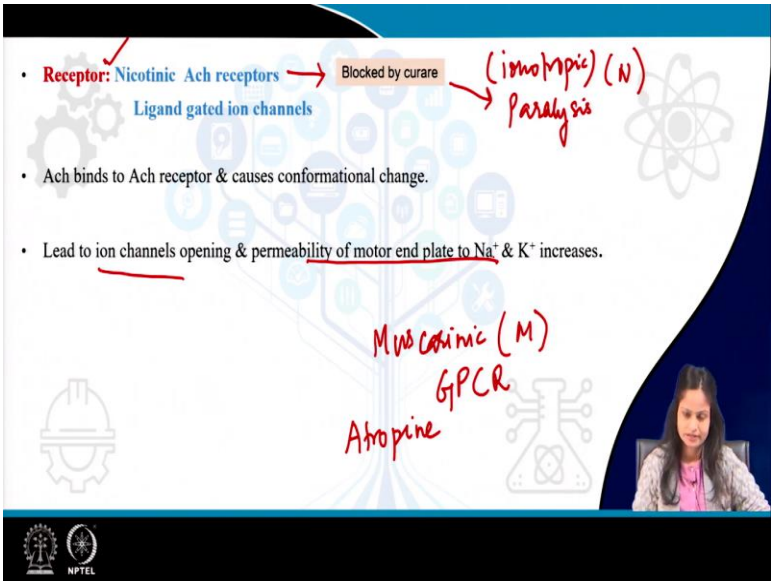

So, what are the receptors of acetylcholine? Now, acetylcholine has got mainly two types of receptors, the first receptor is nicotinic receptors, and the second receptor is the metabotropic receptors, those are known as muscarinic receptors. So, we will talk about the nicotinic receptors. Now, nicotinic receptors are also known as ionotropic receptors, ionotropic metabotropic receptors actions I have already discussed in the previous lecture, like ionotropic receptors are very fast acting it will open rapidly it will close rapidly and whichever ions it will bind to the receptors, the receptors will cause influx or reflux of those ions.

So, nicotinic receptors of the acetylcholine these are the ionotropic receptors, and these receptors are mainly blocked by a drug known as curare. Now, this curare drugs if they blocked the acetylcholine nicotinic receptors, it will lead to paralysis. Whereas, the ligand gated channel receptors or the muscarinic receptors. The other receptors are muscarinic receptors, these are denoted usually by M, whereas, nicotinic receptors are usually denoted by N.

So, the muscarinic receptors are metabotropic receptors that means, these are G protein coupled receptors, these act very slow and the blocker of this receptors are mainly atropine and

scopolamine. So, whenever this atropine blocks these muscarinic receptors, what will happen there will be changes in the cognitive functions there will be drowsiness, there will be blurring of vision, there will be confusion, dizziness.

So, these are the effects of the blocking of the muscarinic receptors by atropine. Now, what will happen when acetylcholine binds to the acetylcholine receptor, whenever a substance binds to its receptor, there will be conformational change in that receptor, that conformational change will lead to the ion channels opening.

Now, since I am talking about the ionotropic receptors, so, which ion channels opening will be there mainly sodium. It also leads to the opening of the potassium channels, but it mainly caused the permeability of the motor endplate to the sodium and potassium channels or the potassium ions. So, the permeability of the sodium and potassium increases.

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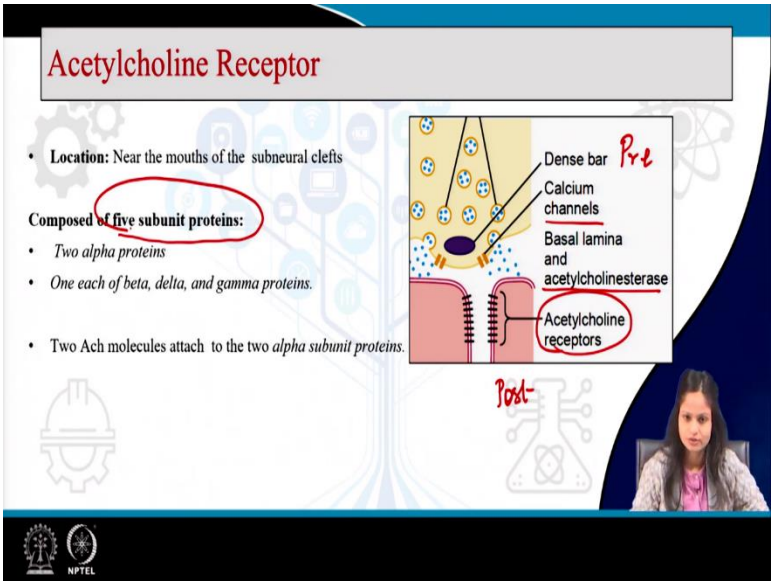

Now, acetylcholine receptors as you can see, these are the acetylcholine receptors. So, receptors mean this is the postsynaptic terminal and here this is the presynaptic terminal. So, whenever there is an influx of the action potential, this action potential will cause opening of the calcium channels which are also very important. Because if the calcium channels do not open, there will not be released of the neurotransmitters.

So, when the calcium channels will open there will be the vesicles fusion to the presynaptic terminal and release of the neurotransmitter, here we are talking about the neurotransmitter acetylcholine. Now, there is a enzyme which is known as acetylcholine esterase enzyme which is present in the synaptic cleft which destroys the acetylcholine after its action of course.

So, the acetylcholine when they will bind to this acetylcholine receptors, these acetylcholine receptors are present on the mouth of the sub neural cleft. So, these receptors are consisting of the five subunit proteins that is two alpha, one beta, one delta and one gamma. So, these two subunit proteins two acetylcholine molecules have to get bind.

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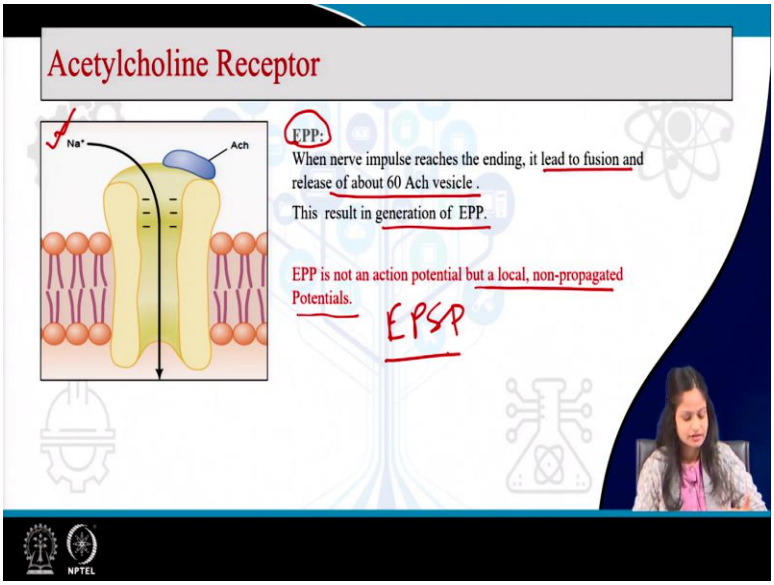

So, whenever there will be binding of this acetylcholine to this receptor, as I told you, there will be in flux of the sodium ions, since it is an ionotropic receptor. So, whenever there will be influx of this sodium ion, there will be generation of end plate potential. Now, here positive ions or the cations are moving inside, so obviously, the inside of the membrane will become more positive, that means, more depolarization will occur.

So, here we are talking about excitatory postsynaptic potential. Here, the excitatory postsynaptic potential has the end plate potential which happens usually leading to the release of 60 acetylcholine vesicles, approximately 60 it has been shown in detected in various experiments. So, generation of EPP occurs because of the 60 acetylcholine vesicles.

Now, end plate potential is not an action potential but it is a local non-propagated potential. Here, we are talking about excitatory postsynaptic potential which is also a local non-propagated potential, it does not, when it will cross the threshold level definitely it will give rise to the action potential otherwise it does not give rise or it does not propagate to the further cells.

So, in this way to make the end plate potential results in action potential there has to be more and more neurotransmitter release so that there could be more and more sodium in flux and hence that will cause depolarization, more depolarizations, and finally, the threshold level will be reached an action potential will be generated.

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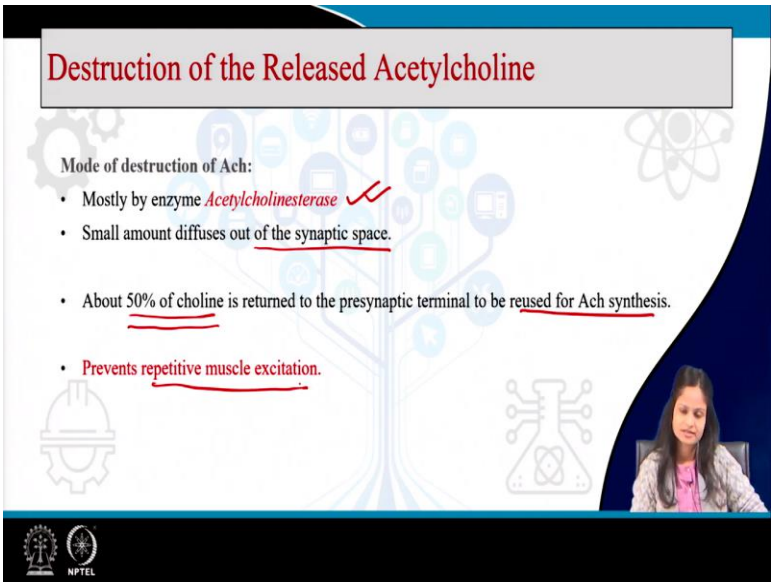

Now, after the function of this acetylcholine, the acetylcholine as I told you it is mostly destroyed by acetylcholine esterase enzyme. Some amount of acetylcholine they also diffuse out of the synaptic space whereas the 50 percent of the choline is taken back. The reuptake is done by the vesicles for refusal of the acetylcholine synthesis. This has been already discussed how the reuptake of the vesicles and neurotransmitter occurs with the help of endocytosis and other phenomenon in the previous lecture.

Now, why there is a need of destruction of acetylcholine. The acetylcholine is the neurotransmitter which is an excitatory neurotransmitter. This excitatory neurotransmitter is

doing what it is causing it is exciting the postsynaptic terminal. Whether that terminals can be a neuron or a muscle. Here, we are talking about the neuromuscular junction.

So, that means we are talking about the muscle. So, when nerve action potential is coming, and it is causing the release of neurotransmitters from the presynaptic terminal, those neurotransmitters will bind to the postsynaptic receptors present on the motor end plate, and finally, with this vicious cycle going on, there will be generation of action potential. So, wherever there will be generation of action potential, this action potential will be traversed and finally our muscle will contract.

So, muscle contraction is a mechanical event following a previous to that preceding that mechanical event the electrical event is being done with the help of action potential. So, if this acetylcholine is not destroyed, there will be repeated generation of action potential and there will be repeated mechanical events that is in the form of muscle contraction. So, that is what happens. Repeated muscle excitation. So, this acetylcholine esterase enzyme prevents repeated muscle excitation or repeated muscle contraction because we do not want unnecessary muscle contraction to happen. So, that is why destruction of the released acetylcholine is required.

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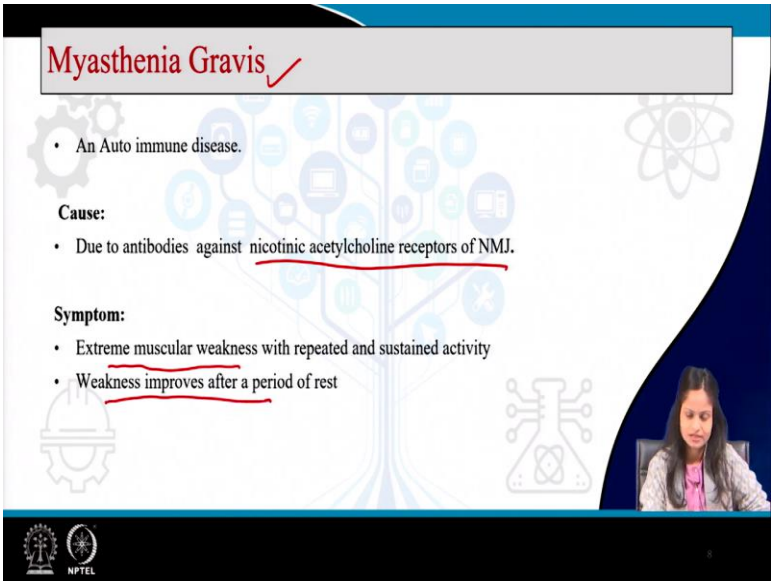

Now, too many important applied aspects related to neuromuscular junctions that is one is the disease known as myasthenia gravis. Myasthenia gravis is an autoimmune disorder. So, what

happens when our antibodies are formed in our body which will destroy our own sense that is autoimmune disorders.

Here, the antibodies are formed against the nicotinic receptors, the nicotinic acetylcholine receptors which are present in the NMJ junction that has neuromuscular junctions, those are being attacked by the body's produced antibodies. So, obviously, when the antibodies will attack the nicotinic receptors, there will be no binding of the acetylcholine to its receptors, the receptors are getting destroyed. So, where the neurotransmitter will bind.

So, when the neurotransmitters are not getting bind, so obviously they will get destroyed by its enzyme. So, the nerve potential is not getting traverse, the nerve potential is not getting conducted. So, what will happen the muscle is not getting excited. So, that is what happens in symptoms, extreme muscular weakness, with repeated and sustained activity, after the person takes some rest that weakness is usually resolved or improves after a period of rest. So, myasthenia gravis occurs due to the, you have to remember, antibodies against the nicotinic receptors of neuromuscular junction.

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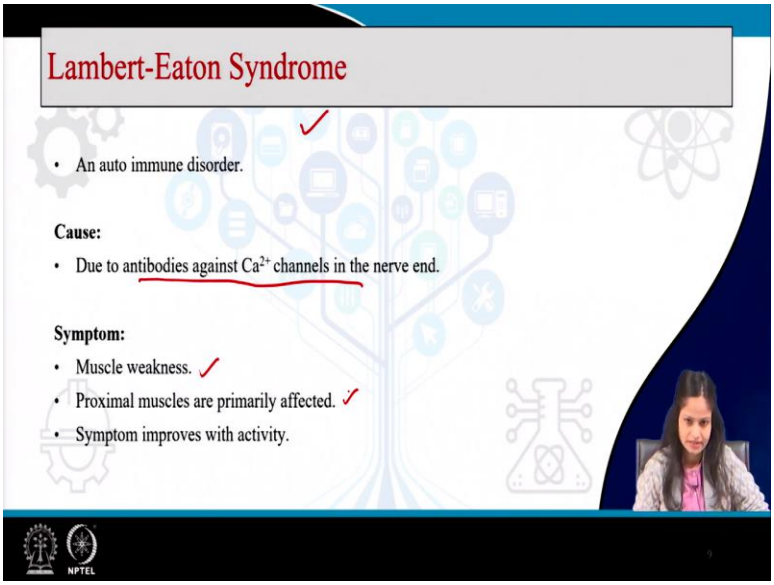

The other similar type of disease is Lambert-Eaton syndrome. Lambert-Eaton syndrome occurs due to, this is also an autoimmune disorder, it also occurs due to the antibodies against calcium channels, I told you that calcium channels are also very important because whenever the action

potential reaches the nerve terminal, mainly the presynaptic terminal, the calcium from the, the calcium voltage gated calcium channels will open, and this calcium entry will lead to the vesicles fusion and then the neurotransmitter release will occur and the further events will take place in the postsynaptic events.

Now, if the calcium channels are not opened, or the antibodies destroy this calcium channels, the further events will not be taking place that will give the similar result that of the previous disease that is myasthenia gravis, that means there will not be any action potential propagation, there will not be any excitation or contraction of the muscle. So, the symptoms are muscle weakness, the proximal muscles are primarily affected the symptoms improves with activity.

Now, in myasthenia gravis, the extraocular muscles are mainly involved. The most common site of involvement that is a weakness of the extraocular muscles. Whereas in Lambert-Eaton syndrome, the proximal muscles are primarily affected and when we do the activity, there will be symptoms improvement.

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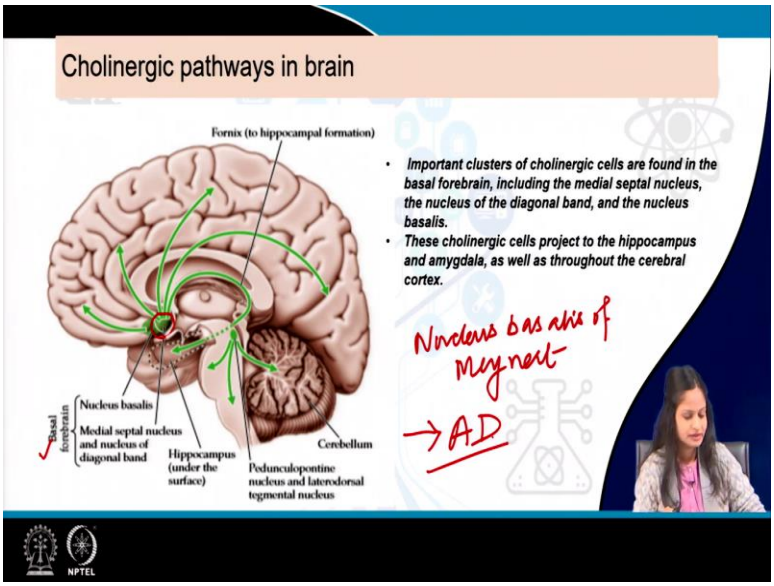

So, what are the cholinergic pathways? This we had discussed about the peripheral nervous system. Now, coming to the brain, where these cholinergic pathways are located. Now, these cholinergic pathways usually arise from the cell bodies, this is shown over here in green. This

cell bodies are present over here. So, from the basal forebrain, the basal forebrain that is basal forebrain of Meynert or we tell it as nucleus basalis of Meynert.

Now, this important clusters of new cholinergic cells are present in mainly in the basal forebrain which is also present in other parts but most important you have to remember is the nucleus basalis of Meynert. From here, the cholinergic pathways are projected, you can see to the various levels to the cerebellum to the limbic cortex to the other part of the hippocampus and the cerebral cortex.

Now, if this cholinergic pathway gets destroyed, that means if the cholinergic cell bodies get destroyed either in the basal forebrain or any of the pathways getting destroyed, that results in the Alzheimer's disease. Also, neurodegenerative diseases are there but most commonly Alzheimer's disease, in Alzheimer's disease this cholinergic pathway gets destroyed. So, this is one of the basic most important parts you have to remember in the cholinergic pathways in brain.

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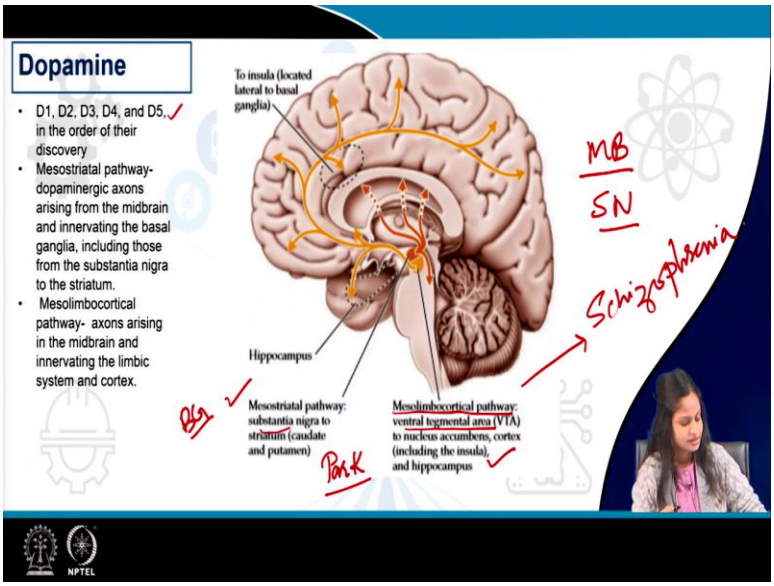

Next, we come to the dopamine. Now, dopamine receptors till now five receptors been discovered that is D1, D2, D3, D4 and D5, the mainly dopamine again, they are these neurotransmitters specifically present in the midbrain. More specifically present in the substantia nigra. So, the dopamine pathways are mainly two types of pathway which we have to remember one is the mesostriatal pathway, another one is the mesolimbocortical pathway.

Now, mesostriatal pathway as the name suggests, the striatum it mainly supplies this pathway, supplies the neurons dopaminergic neurons to the dopaminergic transmitters to the striatum. That means and substantia nigra to striatum, this I am talking about basal ganglia mainly. I had already discussed this pathway in basal ganglia and hence you must be remembering that this is very important pathway where if the dopaminergic neurons get destroyed, that is the nigrostriatal pathway that results in the loss of motor control and hence the Parkinsonism.

The disease Parkinsonism mainly occurs because of the destruction of the mesostriatal pathway. Now, the other pathway which is also important that is mesolimbocortical pathway, it gets started from the ventral tegmental area to nucleus accumbens and further cortex and hippocampus. Since, it is supplying the other areas of the cortex, the neocortex and the hippocampus, so this pathway is mainly responsible for various symptoms of Schizophrenia.

So, psychotic disorders, and it is this pathway is mainly related with the mood and emotional behavior, affective behavior. So, this pathway gets affected in Schizophrenia. So, the two pathways dopaminergic pathway, mainly you have to remember one is the mesostriatal pathway, the other one is the mesolimbocortical pathway. Mesostriatal pathway Parkinsonism, mesolimbocortical pathway Schizophrenia.

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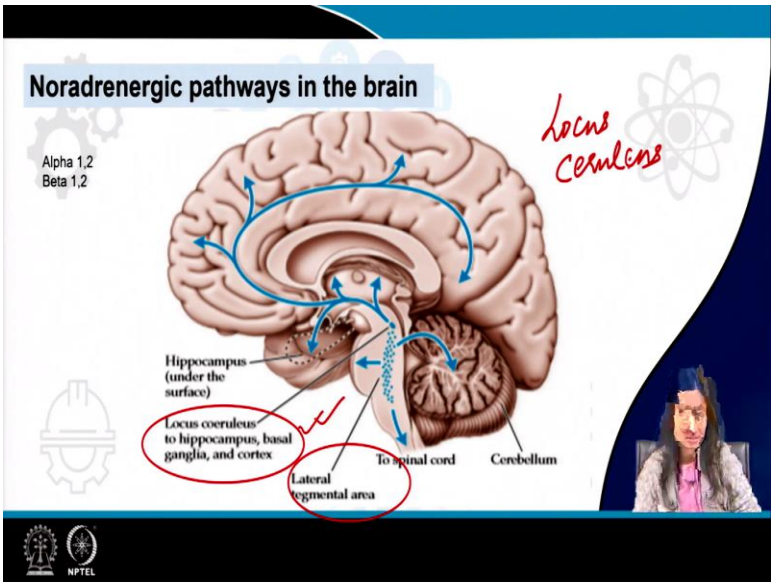

Now, the noradrenergic pathways, noradrenergic pathways means norepinephrine, so norepinephrine has got many poor receptors like it is present in other parts of the body, alpha 1 and alpha 2 receptors, beta 1 and beta 2 receptors. So, this no non-adrenaline or non-adrenergic pathways mainly arise from the locus coeruleus.

So, this is the main structure even if you do not remember the literal tegmental area, you have to remember locus coeruleus, which is mainly important and this plays a very important role in secretion of this neurotransmitter. From here it gets traversed to the other parts like cerebellum, hippocampus and to the spinal cord. So, locus coeruleus is the main portion for the generation of this neurotransmitter on noradrenergic pathways in the brain.

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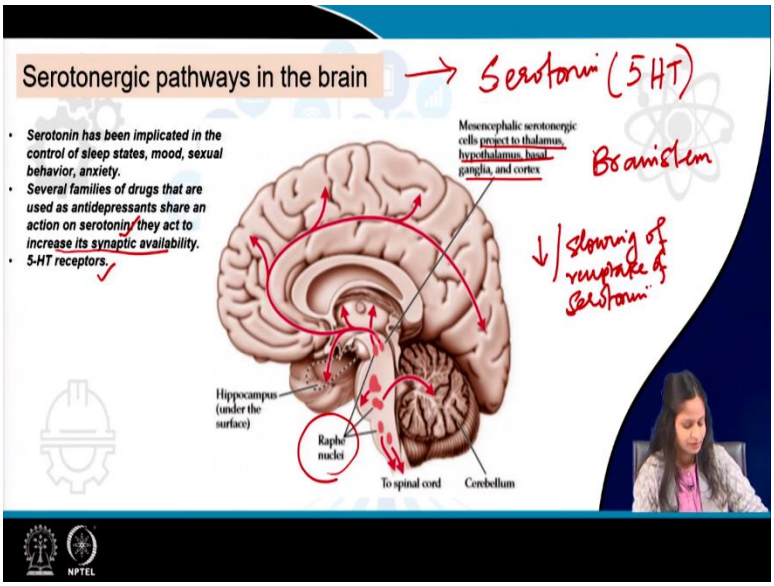

Then the next pathway is the serotonergic pathway. When we talk about serotonergic pathway that means we are talking about serotonin. Serotonin the other name of serotonin is 5HT or 5 hydroxy tryptamine. So, this serotonin has been implicated in control of sleep states, the sleep wake cycle, the mood behavior, the sexual behavior and also anxiety.

So, this serotonin is also important because the main nucleus or the nuclei which are present in the brainstem, the serotonin main secretion occurs in the brain stem. So, the raphe nuclei is mainly the organ which secretes the serotonin and further it gets traversed to the cerebellum and hippocampus and the other areas of the cortex.

So, the serotonergic cells projections occurs to the thalamus, hypothalamus, basal ganglia and the neocortex. So, here we have to remember that raphe nuclei. Now, this raphe nucleus is mainly important, as already been told, it plays an important role in arousal, attention, mood behaviors, sexual behavior, and also in the analgesic system that is in the pain pathway.

Now, several families of drugs, the main drugs, antidepressants, which we use in case of depression, they act on this serotonin or 5 hydroxy tryptamine receptors, the receptors there are various receptors, the receptors are very much specific. So, these antidepressants act or the share mechanism that acts on the serotonin, is usually causes increase in the synaptic availability of the serotonin.

Increase in the synaptic availability means there will be decreased destruction of the serotonin in the synaptic cleft, or there will be slowing down of the reuptake of serotonin by the axon terminal so serotonin will not be reuptake will not be taken back the serotonin should be present more in the synapses, so that the action could be generated. So, this is the serotonergic pathways and this is mainly done by the raphe nucleus.

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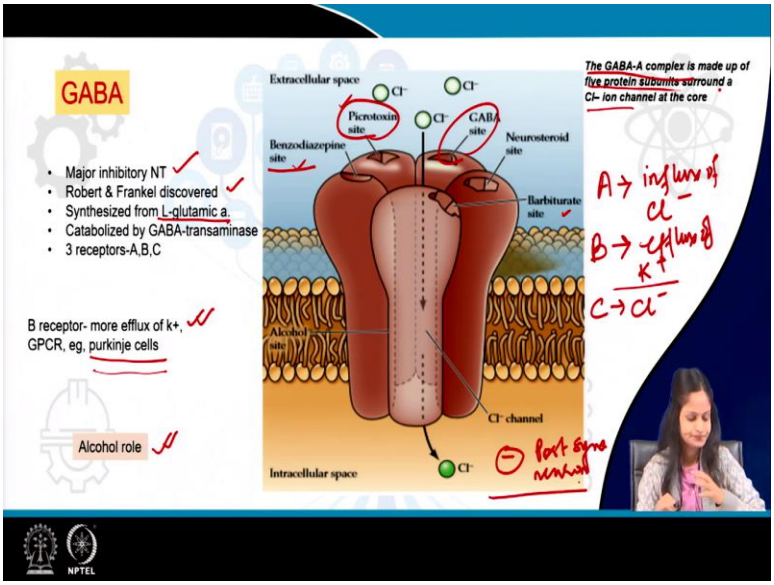

Now, coming to, till now we have discussed about the excitatory postsynaptic potential, the inhibitory postsynaptic potential is mainly done by the GABA. GABA is the major inhibitory neurotransmitter in our brain. Now, besides glycine, the major inhibitory neurotransmitter is

GABA, Robert and Frankel they have discovered this GABA neurotransmitter, this GABA is synthesized from the ail glutamic acid and it is catalyzed by GABA translaminar enzyme present in various synaptic neurons and glial cells.

Now, GABA has got three receptors, A receptors, B receptors and C receptors. The diagram has been shown mainly of the A receptors. Now, these three receptors they have different modes of actions, mainly if we talk about GABA A receptors which is shown in the diagram, you can see it is made up of five protein subunits surrounding a chloride ion. So, A receptors will cause influx of chloride ion, A receptors going to cause influx of chloride ion, B receptor will cause efflux of potassium positive ions going out.

And again, C receptors again of the fluoride chloride ions influx. So, this you have to remember. Now, the five sites present in the GABA A receptor one is the barbiturates site. The other one important is the picrotoxin. And the third is the benzodiazepine site you have to remember. Now, what are these sites?

These are the sites known as allosteric modulators, allosteric modulators means any substance which is binding on the receptors other than the GABA original binding site, like GABA is binding in this site but these are the regions which are binding not on the original GABA site, but on the other sides of the receptor they perform either inhibition of this GABA or excitation of the GABA means they can cause either enhancing the GABA action or they can decrease the GABA action.

For example, benzodiazepines, many benzodiazepines, many antidepressants or anti-anxiety drugs, these mainly constitutes the benzodiazepines. So, benzodiazepines what it will do it is a positive allosteric modulator of GABA. Now, GABA causes inhibition of the postsynaptic neuron. So, any positive allosteric modulator means it will further inhibit whenever the substance will bind to its receptor.

Suppose benzodiazepine is binding to the receptor, it will further cause again inhibition more inhibition of the neuron, postsynaptic neuron. So, that is what is done by the benzodiazepines. The reverse is done by the picrotoxin. What is picrotoxin? It is a negative allosteric modulator of GABA that means picrotoxin in brief inhibits the GABA action that means there will be excitatory reactions of the postsynaptic neuron it will no more inhibit the postsynaptic neuron.

So, another important is the alcohol, the role of alcohol, alcohol causes increase or upregulation of the GABA receptors. The other one is the betta receptor, which is causing, which is a G protein coupled receptors. Now, G protein coupled receptors means it is a metabotropic receptors. And it causes as I already told, that is efflux of the potassium ions.

It is mainly present in the granule cells and the Purkinje cells. So, GABA three receptors are there receptor 1, receptor B, receptors C, A B C receptor, A and C act via influx of the chloride ions and B receptor is mainly causing efflux of the potassium ions. All the GABA receptors will finally cause inhibition of the postsynaptic neuron.

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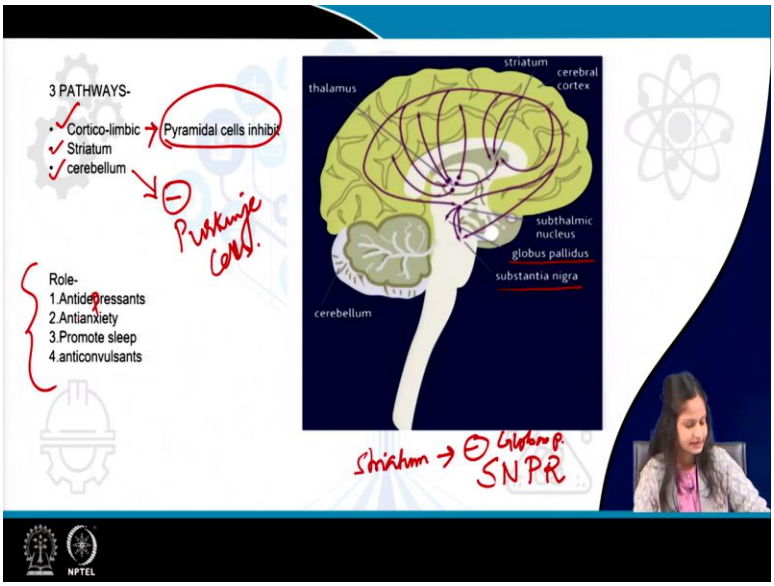

So, what are the GABA energy pathways present in our brain we will see the GABA energy pathway presents that is mainly the cortico-limbic pathway, the striatal pathway, striatum and the cerebellum pathway. Now, cerebellum pathway as I already told you they mainly inhibit the Purkinje cells. In the cerebellum circuits, the major output of the cerebellum that is to the Purkinje cells. So, this GABA usually inhibit the Purkinje cells.

And the other pathways like cortico-limbic pathway, in the cortico-limbic pathway, they mainly inhibit the pyramidal cells. As you can see, the pyramidal cells are mainly inhibited. When we talk about striatum, the striatum is mainly I am talking about the substantia nigra pars reticulata and globus pallidus.

So, striatum here means the GABA will inhibit globus pallidus and substantia nigra, we have two substantia nigra pars compacta and pars reticulata but here, it is pars reticulata. If you could remember the basal ganglia pathways, then you could easily see it is substantia nigra pars reticulata. So, what are the role presented by this GABA? As I told you it acts as antidepressants. It plays an important role by antidepressants, anti-anxiety, it promotes sleep and anticonvulsants.

Now, whenever the postsynaptic neuron is getting inhibited, that means I am depressing my CNS, I am inhibiting my CNS functions, the brain functions I am inhibiting that is why what it is causing, it is reducing the anxiety, reducing the tension, it is promoting the sleep. And anticonvulsants means it is preventing the epileptic fits, epilepsy or seizures occurs because of the over activation of the brain regions over activation of the neurons. So, it will inhibit the seizures or the fits like activity.

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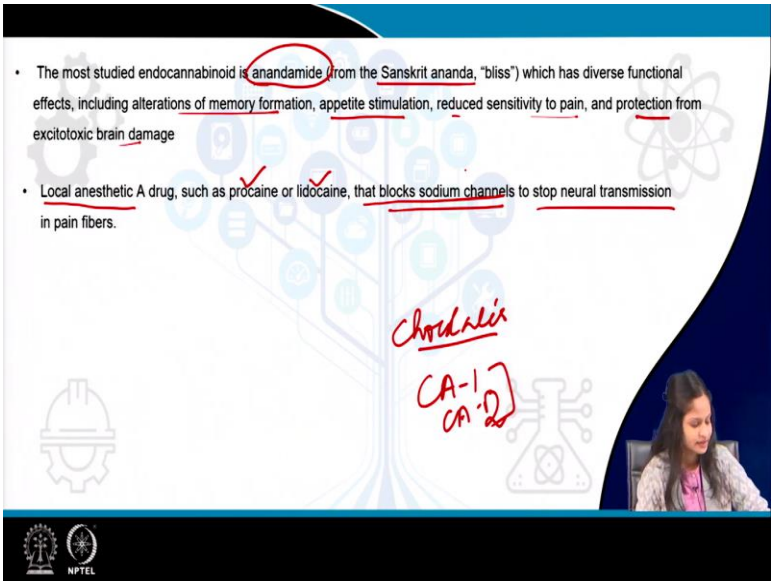

So, these are the functions of GABA. Besides this, what you have to remember is the most studied cannabinoid is anandamide. Anandamide, you can say, or you can say as anandamide because it is discovered from the Sanskrit word ananda which is mean which means bliss. Now, cannabinoids whenever we take it gives a blissful feeling. Like as if aesthetic feeling euphoric feeling. So, this anandamide neurotransmitter is seen to be present more in chocolates.

So, whenever we take chocolates, we feel very happy. So, this is present and it has diverse functional effects like alterations of the memory formation, appetite stimulations, reduced sensitivity to pain, analgesic system and protection from the excitotoxic brain damage. Besides this and also it acts on the cannabinoid receptors, cannabinoid receptors are there and it can act on any of these receptors. So, two receptors are there, any of the receptors that can act.

Besides this, the anesthetic drugs, the local anesthetics which we give, how do they act, the whether it is procaine or lidocaine, they usually block the sodium channels. The sodium channels are the important channels which if the sodium transmission does not occur, what will happen the nerve impulse transmission will not occur, so the neural transmission will get affected.

So, that is what we want to do by giving anesthesia. So, local anesthetics what it does, it blocks the sodium channels and there will be no transmission in the pain fibers that is why we do not get any sensation in our body and we do not get any sensation of pain also. So, in this way local anesthetic acts.

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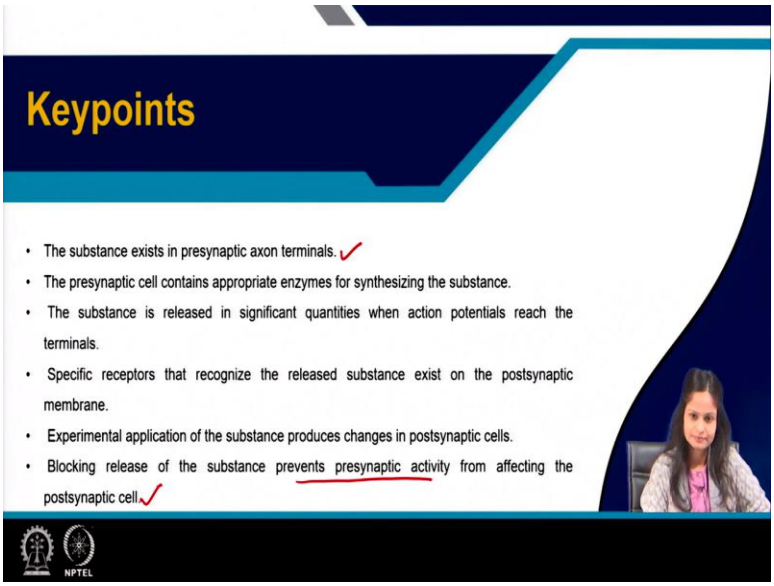

And the key points, the substance neurotransmitter exist in the presynaptic axon terminals you have to remember besides it contains appropriate enzymes for synthesizing that substance. The substance is released in significant quantities when action potentials reach the terminals as I already told the 60 acetylcholine vesicles are released from the terminal to generate end plate

potential. Specific receptors are there which will recognize the release substance exist on the postsynaptic membrane.

And applications of this substances produce different types of changes in the postsynaptic cells that can be inhibitory that can be excitatory depends on which neurotransmitter is getting released. Blocking of the release of the substances prevents presynaptic activity, and hence, that affects the postsynaptic neural transmission also. So, this much you have to remember in synapse. So, in this way I want to conclude today's topic.

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These are the references. Thank you.