Basics of Mental Health and Clinical Psychiatry
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Lecture 06
Synapse & Neurotransmitters-I

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Hello everyone. Today, we will discuss our next topic that is Synapses and Neurotransmitters.

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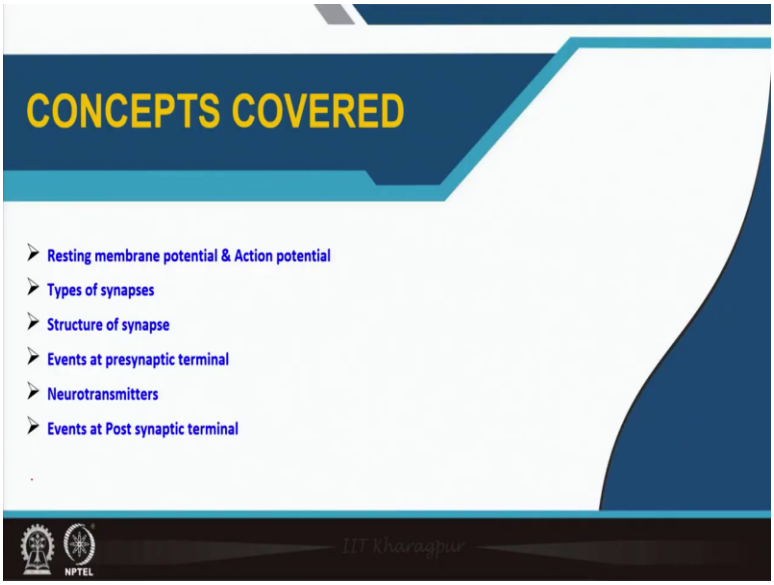

So, till now we had discussed more of neuro anatomy. So, today we will discuss more of neuro physiology. So, the concepts will cover the resting membrane potential and the action potential, the types of synapses, the structure of a synapse, what are the events taking place at presynaptic terminal, the neurotransmitters and how they are released, what events take place at postsynaptic terminal.

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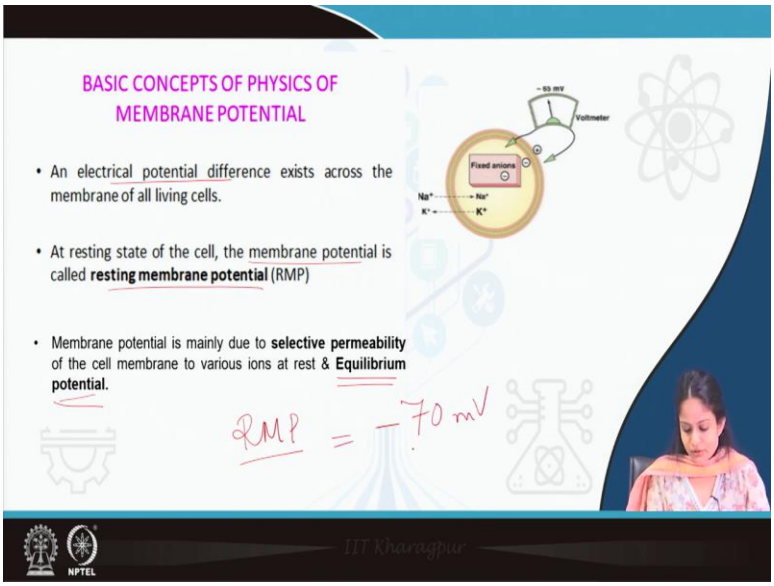

So, first and foremost, let us talk about the resting membrane potential. What do you mean by resting membrane potential? Now, whenever the cell is at rest, if I connect a voltmeter, voltmeter does what, it obviously detects the potential difference, so at that time across the cell membrane, what is the potential difference measured using a voltmeter when the cell is at rest, that is known as resting membrane potential.

So, at rest the membrane potential is called as resting membrane potential which is nothing but the electrical potential difference which exists across the cell membrane, this resting membrane potential depends mainly on the selective permeability of the ions of that cell membrane, like the cell membrane is more permeable to potassium ions, then it also depends on the equilibrium potential. What is the equilibrium potential?

Equilibrium potential is the potential at which there will be no net flow of ions across the or between the either side of the cell membrane, so there will not be any inflow or outflow of any

ions. So, at that potential, that is known as the equilibrium potential. So, usually, these two main factors govern the membrane potential in a cell. For example, the resting membrane potential in case of a neuron is minus 70 millivolts. It differs from cell to cell. So, since we are talking about more of neurons, so the resting membrane potential of a neuron is minus 70 millivolts.

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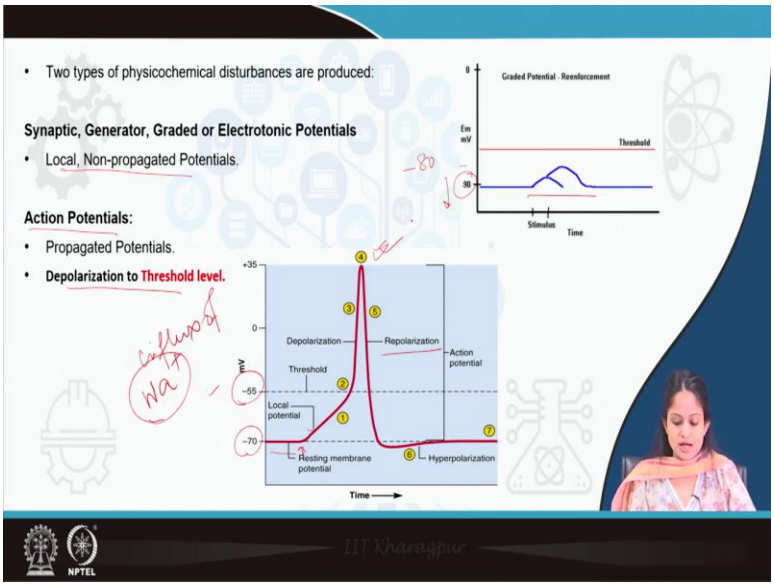

Now, this is when the cell is at rest, if I stimulate a cell, what I already told you that neurons are excitable, that means it responds to the stimuli. So, whenever we give stimuli there can be two types of responses, there will be either local potential generated or there can be action potential. Now, local potential is known as graded potential or non-propagated.

That means, it will be generated for a brief amount of time, it is not propagated from one neuron to the other neuron. And action potential means it is a propagated potential which is of great strength, it is of such strength that it gets propagated along the neurons or to one neuron from the other neuron to the other cell other cell in this way. So, how this action potential is generated from a local potential?

So, initially the local potential which is generated if the strength of the stimulus you can see from the diagram if this strength, this is the resting membrane potential of a neuron which is at minus 70 millivolts. Now, this is the local potential, local potential means, I have given a stimulus over here. So, this local potential you can see it is rising towards the positive from minus towards the positive. That means, minus 70, suppose this is minus 65, this is minus 60.

And when it reaches minus 55 millivolts it causes a shoot or overshoot, it causes a spike, a sharp spike with the downfall with a sharp downfall. And then finally, it reaches back to the resting membrane potential even lower than the resting membrane potential and tries to cover up the changes and becomes equal to the resting membrane potential. So, these events occur. So, whenever you stimulate a cell whenever an action potential is generated, so action potential is generated whenever the depolarization occurs to the threshold level.

Now, depolarization means whenever the mind potential is towards the positive level, as you can see, this is minus 90 and this is an upward stroke. Upward stroke means this is around suppose minus 80. So, it is actually towards the positive it is towards the 0, so that is depolarization. If it is more negative it is hyperpolarization or when it is coming towards the negative side then it is repolarization.

So, when this depolarization reaches a threshold level, that means, here the threshold level is minus 55 millivolts there gives a rise of action potential you can see the spike potential. Now, this action potential will rise to how, will rise how much, to what level it will get rised, it will get raised to normally the equilibrium potential of that ion which has generated that action potential. Now, for example, if this depolarization is occurring, because of influx of sodium ions.

Obviously, cations are getting influx, so that is why the membrane potential from negative it is becoming towards positive. Now, when more and more number of sodium are getting influxed, so it is more the slope is rising, rising, rising, rising and it is not rising slowly also it is rising there is a sharp rise. It will rise till there is it reaches the equilibrium potential of sodium ion.

Generally, it does not happen, so it does not reach till the equilibrium potential before that only there is exit of other cations, which causes this repolarization curve, but what you have to remember is the action potential usually gets tried to reach the equilibrium potential of the ion which has caused that action potential. So, there is two types of potential local potential which is graded potential which does not propagate which usually occurs for a brief amount of time.

This is the local potential because it does not reach the threshold level. Action potential is when there is local potential or if you give a back good strength stimulus, if you give the maximum strength stimulus and it will reach the threshold stimuli, it will reach a threshold level it will give

rise to the action potential and this impulse will be conducted. So, having said these two potentials that is resting membrane potentials and the action potential we will talk about synapse.

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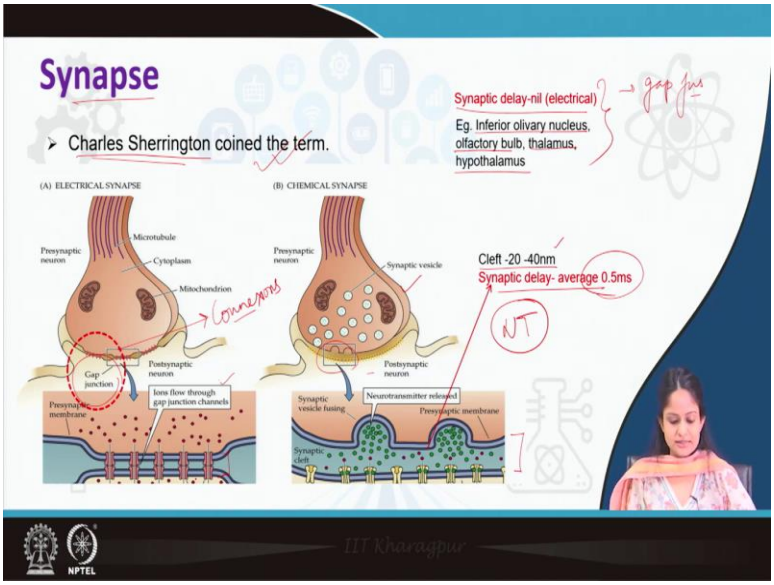

The synapse term has been coined by Charles Sherrington, this you have to remember. The Charles Sherrington has coined this synapse There are mainly two types of synapse which are present in our body electrical synapse and the chemical synapse we will mainly talk about the chemical synapse because electrical synapse are present specifically in certain areas, the rest of the synapses, all our chemical synapse.

So, what is the main difference between electrical synapse and chemical synapse. As the name suggests, the electrical synapses mainly because of the presence of gap junctions. What is this gap junctions? You can see these are nothing these are present in the postsynaptic between the postsynaptic membrane and the presynaptic membrane you can see this gap junctions are present.

This gap junctions are made of certain proteins known as connexons proteins, this will cause transmit of ions, the ion channels say sodium channels, calcium channels, potassium channels whatever ions are there, these ions will rapidly enter and it will enter very fast through this gap junctions, ions flow through this gap junctions occur very fast.

So, when ions flow is occurring very fast, there will not be any delay in the transmission. The transmission is very fast through these electrical synapses. Whereas, in the chemical synapses if you see this is the synaptic cleft. Chemical synapses as the name suggests, it is not because of any gap junctions it is mainly because of a chemical. Chemical means here the chemical is the neurotransmitter, a neurotransmitter which is released from the vesicles.

Now, as you can understand from the vesicles the neurotransmitter will get released in the presynaptic level, it will travel through the synaptic cleft, it will then attach to the receptors of this postsynaptic neuron and then it will act. So, obviously it will take some time. So, there is always a delay which is known as synaptic delay in case of chemical transmission or chemical synapses which is usually 0.5 milliseconds whereas in electrical synapse there is no delay.

Since it is present, electrical synapses present in very few areas so it becomes a very important topic. It is present in the inferior olivary nucleus, olfactory bulb, thalamus and hypothalamus this you have to remember where electrical synapses are present and these electrical synapses are mainly because of the gap junctions. Whereas, you can see the synaptic cleft which is present in the chemical synapse, this is the synaptic cleft you can see it is the cleft is 20 to 40 nanometer.

Whereas, if you see this this synaptic cleft it is hardly 4-nanometer. So, which means or which says that obviously the electrical synapses transmission is very fast, which happens in this thalamus and hypothalamus and olfactory bulb. The other part of the body is made responsible for the chemical transmission or the chemical synapse transmission. So, these two you have to remember types of synapses which is coined by Charles Sherrington.

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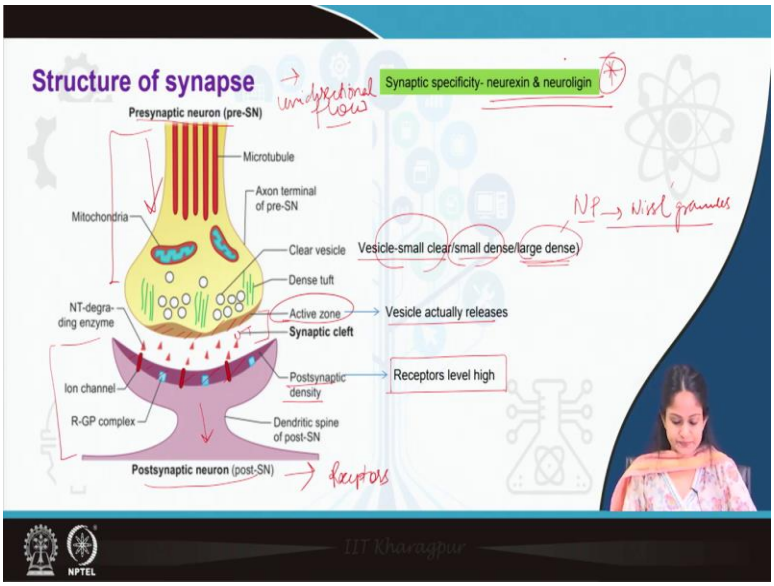

Now, coming to the structure of the synapse. This is the presynaptic neuron. This yellow one is the presynaptic neuron and this pink one is the postsynaptic neuron in between this white portion is the synaptic cleft. So, as I told in the previous lecture in the first lecture, the neurotransmitter will always flow unidirectionally So, the neuro transmission will occur over here in the chemical transmission unidirectionally, unidirectional flow of neuro transmitter or the impulse in a chemical synapse.

So, from the presynaptic neuron, there will be flow and from the presynaptic neuron, whenever the action potential reaches the presynaptic neuron, you can see there are various vesicles. There are various types of vesicles, there can be small clear vesicles, there can be small dense vesicles, there can be large dense vesicles. So, there are various vesicles, which secretes neurotransmitter, whenever these vesicles will get activated they will secrete neurotransmitter in the synaptic cleft and this neurotransmitter will get bind to the receptors which are present in the postsynaptic neuron. The postsynaptic neuron receptors are present.

After the binding of this receptors, there will be some changes occurring in the postsynaptic terminal and the impulse will travel based on which neurotransmitter is released. Now, here vesicles coming to these vesicles, as you can see, the large dense vesicles are usually neuro peptides. And if you could remember this neuro peptides are large dense vesicles. Peptides

means they consist of ribonucleoprotein and this are synthesized from the cell body specifically Nissl's granules, Nissl's granules in the cell body or the soma of the neuron.

So, Nissl's granule secretes these vesicles. The other vesicles which will present that is small clear or small dense vesicles, these are initially synthesized in the cell body, but later on recycling takes place even at the nerve terminals, but you have to remember these neuropeptides large dense neuropeptides which are only and only synthesized in the cell body that two Nissl's granules. Now, whenever these clear vesicles are reaching the end of this presynaptic membrane you can see this is the end of the presynaptic membrane here the vesicles density is very very high, this is known as active zone.

From this zone, the vesicle will actually release the neuro transmitter. Then there is a postsynaptic neuron where you have very high density of receptors, this is known as postsynaptic density here the receptors level are very high. Now, there is a receptor and the neurotransmitter will get released. Now, after the release of the neurotransmitter the neurotransmitter and receptors are very much specific.

So, when neurotransmitters get released, they will not go into the synaptic cleft and search for its receptors. So, for releasing of the neurotransmitter there has to be some specificity which is maintained. So, that neurotransmitter are released close to its own receptors. This specificity is maintained by these two proteins that is neurexin and neuroligin this you have to remember very new concepts neurexin and neuroligin will cause the specificity of the receptors the neurotransmitter will release gets released close to its receptors. So, this is all about structure of the synapse.

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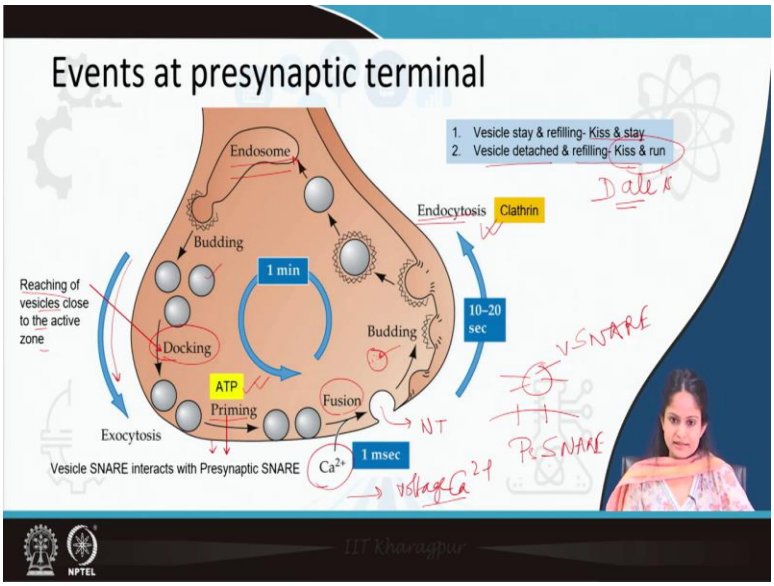

Now, we will see what happens in the presynaptic terminal how vesicles get released. Now, this is the vesicles are coming. This is you can see the vesicles are coming they are reaching towards the active zone, I mean towards the presynaptic cell membrane, they have not yet reached but they are reaching. This reaching of vesicles towards the active zone is known as docking, this docking is mainly the reaching of the vesicles towards the active zone.

Here, there is no interaction between the vesicles and the presynaptic membrane, this is the presynaptic membrane and these are the vesicles. Now, after that with the help of ATP molecule, there will be interaction between the vesicles and the presynaptic membrane. There will be certain interactions between the vesicles and the presynaptic membrane of what of some proteins those proteins are known as SNARE proteins.

The vesicle, this is the vesicle and this is the suppose presynaptic membrane, there are certain proteins present in the vesicles, there are certain proteins present in the presynaptic membrane, the proteins which are present in the vesicles, they are known as vesicle SNARE proteins and the proteins which are present in the presynaptic membrane they are known as presynaptic membrane SNARE proteins.

Now, this interaction does not take place till docking, it will only take place whenever there is a ATP molecule is intervening. So, this is known as priming. After this, calcium will enter, this

calcium usually comes from the voltage gated calcium channels. The voltage gated calcium channel will cause entry of the calcium and this calcium will cause fusion of the vesicle to the membrane.

The vesicles will get fused and there will be release of neurotransmitter to the synaptic cleft. Now, after this release of this neurotransmitter what is the fate of the vesicle? There can be three fate. The first fate is the vesicle can stay in the presynaptic membrane it can attach it can stay attached, the empty vesicle obviously, it can stay attached in the presynaptic membrane and new neurotransmitter filling can occurs.

This is known as kiss and stay, it is just staying in the presynaptic membrane and there is spilling of the neurotransmitter. The second one is the vesicle can get detached. And then, refilling can occur of the neurotransmitter this is known as kiss and run phenomenon also known as Dale's phenomenon. So, vesicles are getting detached from the neurotransmitter and there is neurotransmitter filling occurs and then this will enter the vesicle pool.

And the third one is the vesicle can go complete recycling with the help of endosome endocytosis and they will enter endosomes will be formed and from the other end you can see the new vesicles will be formed. So, there is complete vesicle. So, this complete vesicle for this complete vesicle endocytosis occurs for that we have to remember one protein that is clathrin which is responsible for this endosome formation. So, vesicle, what is the fate of vesicle?

First, it can go full recycling, the second it can stay in the membrane and neuro transmitter filling can occur that is kiss and stay. The third is vesicles can get detached and then neurotransmitter filling can occur that is kiss and run and then it can move to the vesicle pool. So, these are the events which takes place in the presynaptic terminal.

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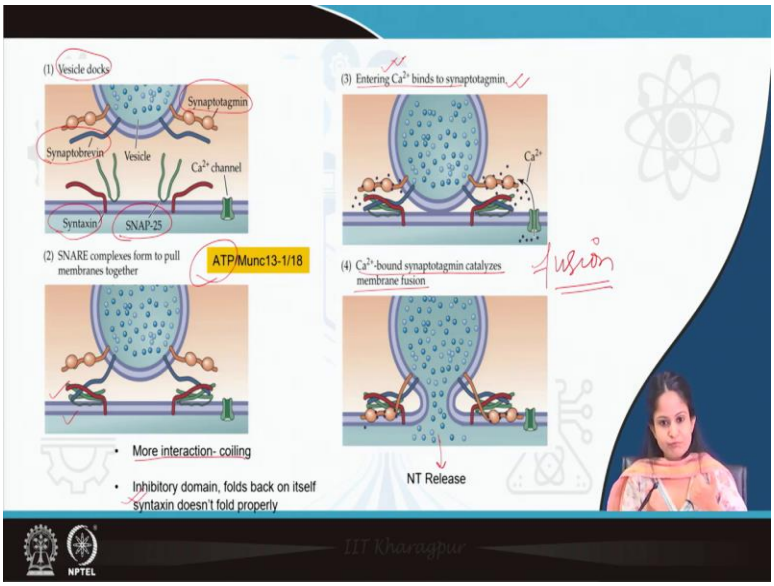

Now, I told you the docking, priming, fusion these mechanisms, how this mechanism takes place, because based on these mechanisms, we have certain toxins so that is why we will talk about this mechanism. Now, docking is the stage I told you where the vesicles are approaching towards the membrane. Now, this is a presynaptic cell membrane the vesicles are approaching but it is not yet touching the cell membrane, so that is docking.

You have two SNARE proteins you can see in the vesicle that is Synaptotagmin and Synaptobrevin these are the vesicle SNARE proteins. And in the synaptic membrane, you have Syntaxin and SNAP-25 these two SNARE proteins are present in the presynaptic membrane. After that, what happens this docking there will be ATP molecule which will help in the fusion or it will help in the interaction of these two SNARE proteins the vesicle SNARE proteins and the presynaptic SNARE proteins.

Also, there are some other protein molecules there. As you can see, there is interaction of this synaptic, you can see there is interaction of the Synaptobrevin and the Syntaxin. Interaction means that the Synaptobrevin and Syntaxin will interact bind and do coiling. The more coiling is there the more the membrane will pull the vesicle towards the membrane. So, there is more interaction there is more coiling, but what happens there is one inhibitory domain which is present in the Syntaxin molecule itself which folds back so that prevents the coiling.

So, the Syntaxin is not able to coil or fold properly because of this inhibitory domain. So, this priming process is further enhanced by calcium, this calcium will enter and interact with this Synaptotagmin this molecule and it will remove that inhibitory domain. So, there will be what there will be more coiling the inhibitory domain will be removed there will be more pulling off the vesicle towards the presynaptic neuron and you can see the membrane fusion which occurs this calcium is actually causing the complete fusion of the vesicle to the membrane and there will be neurotransmitter finally release.

So, this SNARE proteins vesicle SNARE proteins and the presynaptic SNARE proteins these two sets of SNARE proteins, they do not interact initially, they interact that is priming occurs with the help of ATP and some other molecules which causes coiling, but this coiling is again interrupted because of an inhibitory domain which is present in the Syntaxin which is further enhanced by calcium entry. When this calcium will enter and bind with the Synaptotagmin there will be fusion of this vesicle to the presynaptic membrane there will be extensive pulling and neurotransmitter release will take place.

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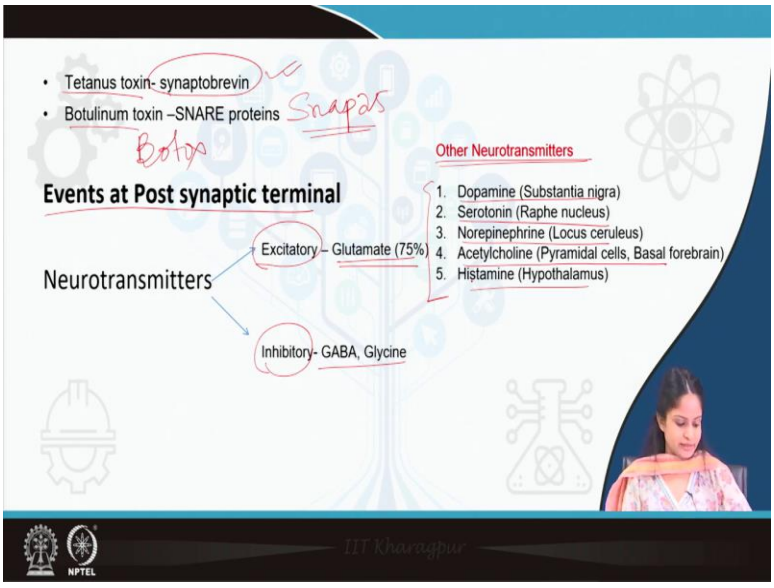

So, this phenomenon you have to remember because there are two toxins which are very common, which affects this transmission, the first one is tetanus, the tetanus toxin, all of you must be aware of tetanus toxin we take tetanus shots to avoid this infection. So, it is caused by the bacteria Clostridium tetani. What this bacteria cause is this tetani bacteria secretes tetanus

toxin, this tetanus toxin will affect this Synaptobrevin, Synaptobrevin is the vesicular SNARE protein. Now, this vesicular SNARE protein if it is affected any SNARE proteins if it gets affected what will happen.

Finally, there will not be neurotransmitter release, the whole phenomenon will get disrupted there will be no release of neurotransmitter. Now, what is the purpose of taking this lecture? Neurotransmitter release is occurring. What it will do? It is actually transmitting the impulse from one cell to the other cell. So, obviously, the impulse will not get transmitted. So, that what occurs in the tetanus infection.

The impulse transmission or impulse conduction the neurons are not able to conduct the impulse. So, how because the tetanus toxin binds to this Synaptobrevin molecule. The other toxin is known as botulinum or very commercially known as Botox, you know cosmetically it is used very much. Botox is used to prevent the wrinkles. So, this Botox toxin can affect any of this SNARE proteins, but specifically if it is asked it will affect the SNAP-25.

Now, if you ask me that if it is a toxin then how it is affecting how it has been used commercially, it has been commercially used to prevent the wrinkles. Now, how wrinkles? Wrinkles and nothing but your muscle contractions like I am closing my eyes my forehead is getting with old age with aging there will be wrinkles on my forehead that means there will be muscles contraction which occurs. So, this toxin will prevent this contraction.

Now, how a muscle contract? The muscle contracts this is a mechanical phenomenon before that mechanical phenomenon or electrical phenomenon occurs in our body that is the impulse conduction. So, the toxin actually affects that electrical phenomenon. So, if the electrical phenomenon does not occur, the mechanical phenomenon will also not occur. So, I am hampering the electrical phenomenon by giving Botox so that is why the muscle is not finally getting contracted. So, you are not seeing any wrinkles.

So, that is a function of botulinum toxin. So, these are the events which are seen in the presynaptic level. So, now what are the events seen at the postsynaptic level? Postsynaptic terminal events whatever we see depends on which neurotransmitter is released, whether it is excitatory or inhibitory and what are the receptors. Now, mainly the neurotransmitter which are

present in our brain, it is mainly divided into classified into excitatory neurotransmitter and inhibitory.

Maximum neurotransmitter which are present glutamate and aspartate. So, 75 percent of the neurotransmitter is present in our brain glutamate. Inhibitory neurotransmitter, gamma aminobutyric acid that is GABA and glycine this two are the inhibitory neurotransmitter. Other neurotransmitters are these five neurotransmitters, I have written other because they are located in the specific regions.

So, this dopamine is mainly located in the substantia nigra and also in the mesolimbic region. This is mainly responsible for the behavioral disorders like schizophrenia and dopamine is also responsible for the Parkinsonism disease has already been discussed. Serotonin, this is present in the raphe nucleus. Norepinephrine, this is present in the locus coeruleus. Acetylcholine, it is mainly located in the pyramidal cells and basal forebrain.

And histamine as I already discussed, it is the weight promoting neurotransmitters present in the hypothalamus. So, this neurotransmitter have their specific roles and disorders of any of these neurotransmitters mainly, this will cause various symptoms and signs in the patients. And these are mainly modulated by giving drugs which will control or which will modulate this neurotransmitters. So, that is why this neurotransmitters role of actions are very important.

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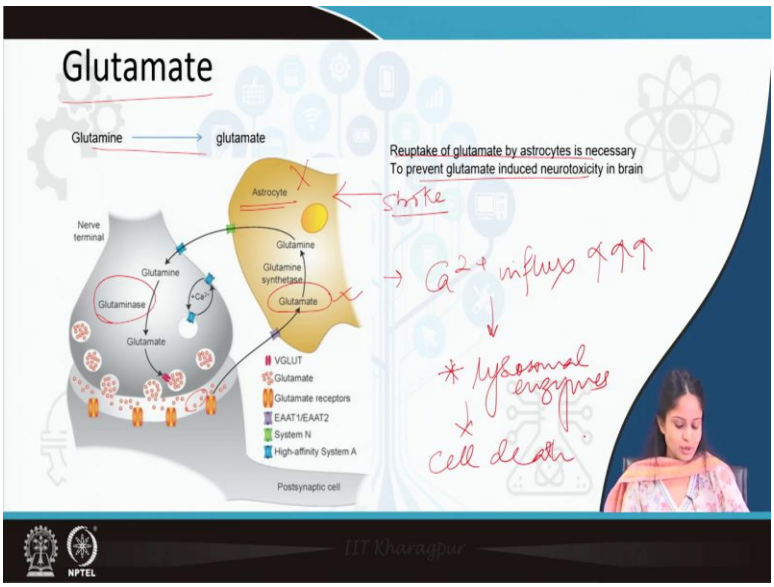

So, today we will see the excitatory neurotransmitter that is glutamate. Glutamate is synthesized from glutamine with the help of glutamines enzyme in the neuron. Now, before moving on to the receptors the very, very important thing is after a neurotransmitter action is over, it should either get recycled or it should either get or it should get degraded, because we do not want neurotransmitter to accumulate in the synaptic cleft.

So, it has to get recycled or it should get degraded. Now, what happens in case of glutamate, there are the glial cells, which I had talked, which I had told you, in my first lecture, present in our brain, mainly astrocyte. These astrocytes take up the glutamate, they take up this excess glutamate and the convert back into the glutamine. So, reuptake of glutamate is very necessary by the astrocytes because it will prevent glutamate induced neurotoxicity in the brain.

Now, suppose this glutamate is not been taken up, which happens in case of death of these astrocytes. So, whenever there is stroke, there is death of this astrocytes and they will not be able to take up this glutamate. So, if this glutamate is not taken, then there will be accumulation of glutamate in the synaptic cleft. So, more glutamate will get accumulated, more excitation will be there, when it will bind to the receptors.

Now, when glutamate bind to the receptors, there will be more and more calcium influx. And when more calcium influx occurs, this will cause activation of some lysosomal enzymes. This will cause activation of some lysosomal enzymes, and this will cause cell death. So, you are actually hampering your own brain cell by causing more glutamate release. So, since there is no reuptake of this glutamate by the astrocytes, so that is why this reuptake is very important.

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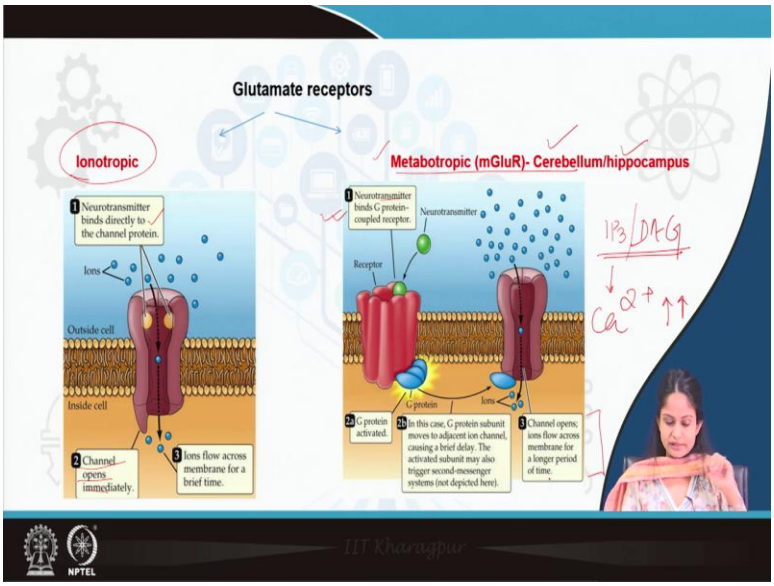

Now, coming to the glutamate receptors, the glutamate receptors are mainly of two types one is ionotropic glutamate receptors, the other one is metabotropic glutamate receptors. Normally ionotropic glutamate receptors are present everywhere in the brain except this metabotropic glutamate receptors, which are present mainly in the cerebellum region and the hippocampus region.

Now, as the name suggests, ionotropic glutamate receptors, the neurotransmitter will directly bind to the channel protein, whichever channel protein it will bind, that will the, that particular iron will get influx, so if it is binding to the sodium channel protein sodium ions will get influx, if it is binding to the calcium channel protein the calcium ions will get influx. So, the main feature of this ionotropic glutamate, ionotropic receptors are these channels are very fast acting they open immediately and they remain open for a brief amount of time it will again get closed, but metabotropic glutamate receptors, these are the G protein coupled receptors.

So, the neurotransmitter binds to the G protein coupled receptors, this G protein coupled receptors when they get activated, they will cause activation of second messenger system. In this case, the second messenger system is IP3 inositol phosphate or diacyl glycerol, this IP3 and diacylglycerol when the second messengers will get activated, this will cause influx of calcium.

So, there will be influx of calcium and this channel will remain open for a longer period of time. So, the ionotropic is mainly for the ions which rapidly opens and gets rapidly closed, but

metabotropic glutamate receptors, these are G protein coupled receptors, which remain open for a longer period of time.

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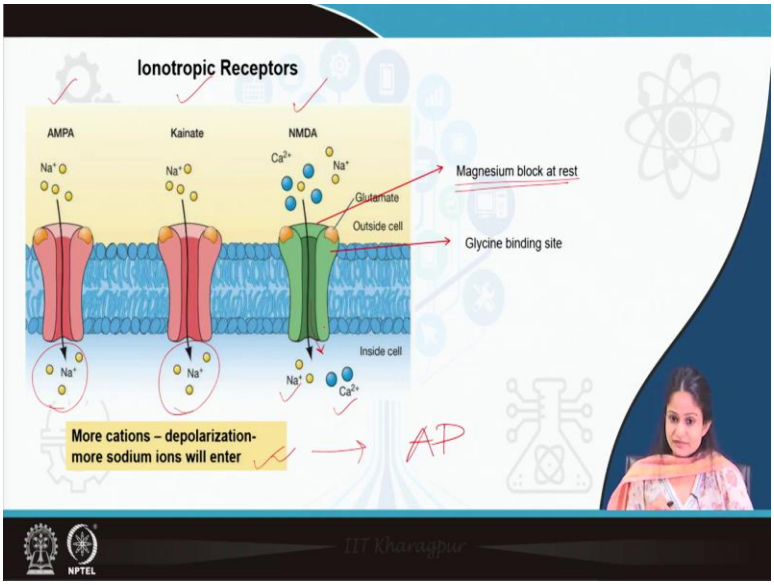

So, Ionotropic receptors, whichever receptors they are AMPA, Kainate or NMDA receptors mainly three types of receptors are there. You can see AMPA receptors are causing sodium influx, Kainate is also causing sodium influx. NMDA receptor is causing sodium as well as calcium influx, they are causing positive ions or the cations influx. So, the more cations influx will be there, there will be more depolarization which will finally lead to what action potential which I had already discussed in the previous slide.

So, this NMDA receptor has a particular phenomenon, it has got a magnesium block, it has got a magnesium ion which usually blocks the transmission. So, this magnesium block is usually removed with the help of depolarization and then there can be influx of sodium and calcium. So, whichever ions whichever cation ions are getting influx that will cause depolarization.

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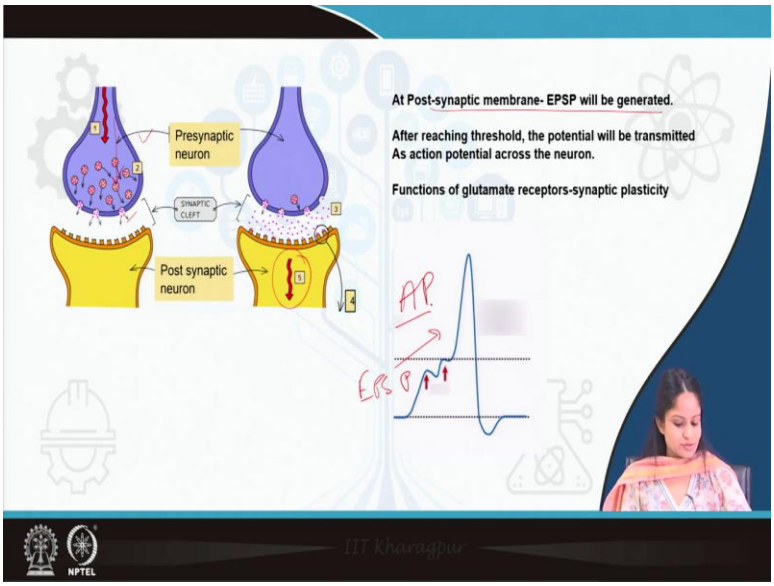

And you can see the presynaptic neuron action potential is coming. There is release of neurotransmitter. In the postsynaptic neuron, you can see there is binding of the receptors. And finally, in this case glutamate, there is generation of excitatory postsynaptic potential. Excitatory postsynaptic potential is a local potential which is developed due to depolarization. The more depolarization will occur, this excitatory postsynaptic potential will give rise to action potential when it will reach the threshold.

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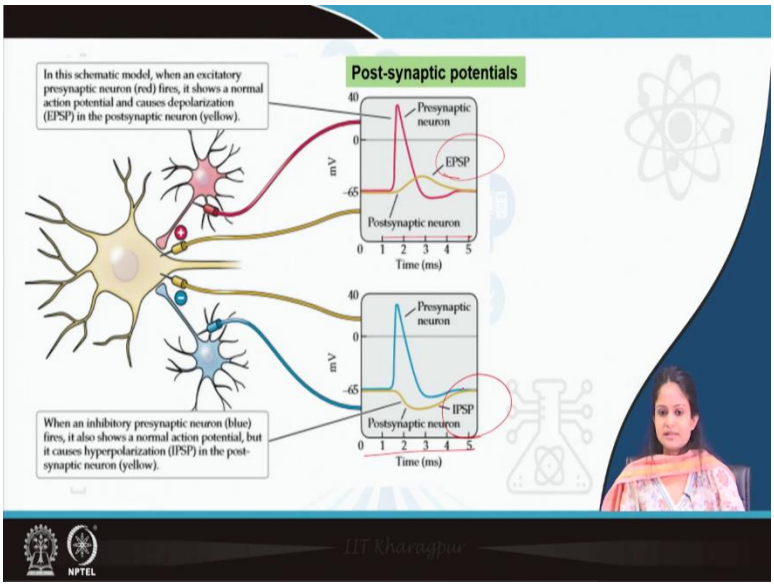

So, depend on the neurotransmitter which is excitatory or inhibitory that gives rise to the, that type of potential. For example, here in this postsynaptic neuron, because of the excitatory neurotransmitter release, it is giving rise to excitatory postsynaptic potential, but here in this postsynaptic neuron, because of the inhibitory neurotransmitter, it is giving rise to inhibitory postsynaptic neuron.

You can see the curve is more towards the negative. So, we will talk more about the inhibitory neurotransmitters and then mechanism of actions in the further lectures. So, till now, this much you have to remember about the glutamate receptors which will give rise to the excitatory postsynaptic potentials as well as the action potential.

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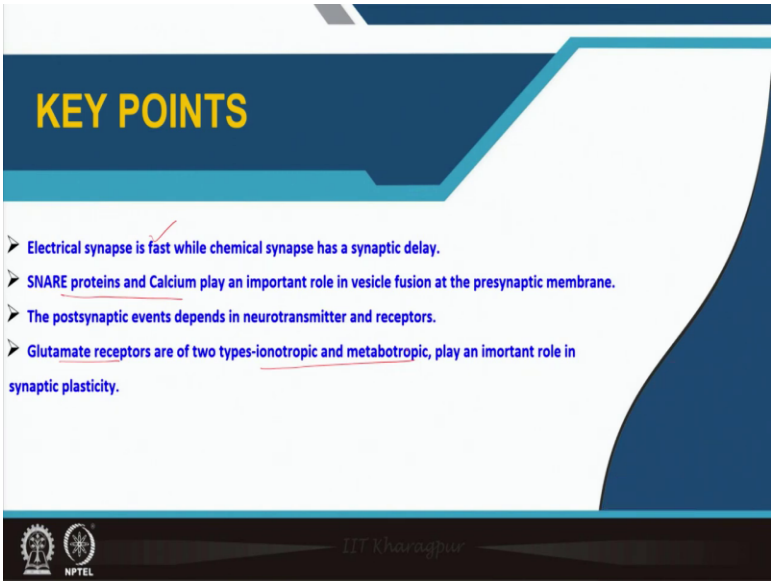

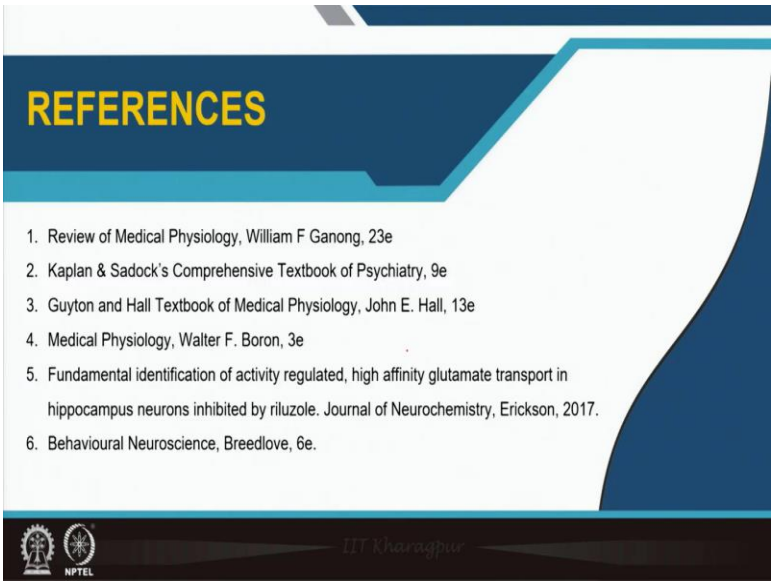

So, these are the key points you should remember. And electrical synapses fast whereas the chemical synapse has got the synaptic delay. The SNARE proteins and calcium play an important role for the fusion of the vesicles. And the postsynaptic events depend on the type of neurotransmitter and its receptors. And glutamate receptors are mainly of two types ionotropic and metabotropic, which plays a very important role for the synaptic plasticity. So, this is all about your synapse. The other part of the lecture will be taken on other day. So, this much you have to remember. Thank you.