Cognition and its Computation
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Lecture - 13
Synapse and Synaptic Transmission

Welcome. So, we have been discussing about computation in the neurobiology of computation, that is computation in the brain. And, for that we have been discussing the very very basics of how spiking occurs in the neurons and we got introduced to the idea of how a neuron communicates with another neuron via spikes through synapses. So, in the coming lectures coming up, we will have a thorough discussion on how synapses work and how neural plasticity works.

The tremendous capacity of the brain or the neural systems to adapt to very different kinds of situations, to be able to learn different things and during development for a baby to grow up and learn different languages, learn the meaning of things that it observes and so on; what is essentially involved is neural plasticity.

And, in order to understand neural plasticity, we have to delve deeper into what causes this plasticity or what is the mechanism of this plasticity or that is what is the factors that influence this malleability of neural systems or this adaptability of neural systems or overall the tremendous capacity of the brain to adapt for two different kinds of situations and be able to learn. And, in doing so, we will also be able to learn how certain disorders influence at these levels and stop us from learning things or stop us from developing normally or.

I would not say normally or it should, the correct word should be typically and in order to understand cognition which a large aspect of which is plasticity, neural plasticity and attention and memory and language skills and so on. All of these rely on neuronal plasticity. And so, these lectures from now on will be about discussing how a neural system adapts.

And, as I said the very basis of this adaptation are the synapses or synaptic plasticity. So, in order to understand that we have to understand a little more about the synapse. What

we have discussed so far, we have learnt that the synapses are actually producing a current injection into the post synaptic neuron.

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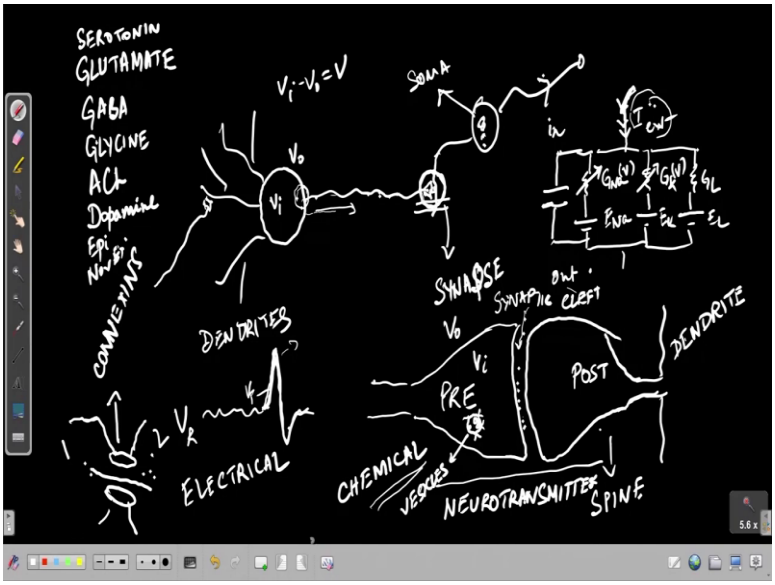

So, if you recollect our earlier discussion, we had a neuron which is receiving inputs through its input side which is the dendrites. And, this neuron is projecting through its axon to another neuron on its dendrites, like this neuron is receiving inputs on its dendrites through other neurons as axons. So, this region which we will call the synapse is of the main interest in the lectures on plasticity or synaptic plasticity. So, this is the dendrite of another neuron which projects forward to another neuron and so on.

So, we saw that we can represent the neuron with a capacitor. This is probably one of the models that is most used. Then, we have the sodium channel which is which has a conductance of GNa. Then, we have the reversal potential ENa, then another parallel branch which is G K and then battery again with the reversal potential of potassium E K. And, then we have the G leak which is passive, it is not variable. These are dependent on voltage that we have discussed earlier.

And, this is the E leak which is the rest of the channels put together. And, here we have the I external and this is the inside of the neuron, this is the outside of the neuron. So, when a current is injected into the neuron from the synapse, essentially what we are talking about is current coming into this kind of a circuit. Of course, it is a model and it is simplified version, but it explains our action potential. So, over time this I external is

varying depending on what input is coming in, how it is getting summed up with other inputs.

And, then the final effect that is reaching this soma here and that will determine whether the neuron will fire action potential or not and forward that information through its axon to the next neuron. So, as you can see, this I external that is produced in the soma is very much dependent on what these synapses are actually doing. So, and what all the other synapses on the neuron are doing and what inputs they are getting.

So, for learning or adaptation, it means if we think of it in this way that given the same situation we behave in a different manner. If that is sort of the basis of learning which means if we now bring it down to the level of a single neuron which means that given the same inputs on the synapses of the neuron, it produces a new output. So, that is what we mean when we say that the system has adapted.

So, it is not that the neuron is itself just getting totally different inputs and now producing totally different outputs. So, in order to achieve this thing that given the same inputs on the neuron, now the neuron produces a different output. If this is what is adaptation, then you can see that the key factor is how an input in the synapse or input from the previous neuron to the synapse impacts the next neuron or how the current injected into the next neuron can change or how the synapse adapts.

That will determine what the final I external is going into the soma of the neuron and that will determine the changed behavior or changed output of the neuron ok. So, now, what is it that is involved in this synaptic transmission? So, we said that spikes action potentials, we remind ourselves V in and V out. So, that is V i minus V o equals our V or the voltage.

And, if you plot the voltage of the previous neuron, it starts at let us say it is at V rest and then there are action potentials or spikes occurring when it crosses the threshold voltage V t. And, it is these that are communicated to the next neuron. So, this action potential initiates in the axon initial segment region in the axon hillock and then it travels along the axon to the presynaptic terminal.

What I mean by travels along the axon means that, at these different locations have this profile of voltage difference in the membrane in the membrane at that point which

resembles the spike. Or, it reaches the synapse means that the synapse is V in minus V or the synaptic terminals V in minus V out reflects an action potential. It will be a filtered version that reaches the synapse.

So, if we blow this up, this synaptic terminal; it may be something like this. And, on the post synaptic site this dendrites usually these synapses form on structures that are mushroom like structures that are called spines. Usually, the excitatory synapses I introduced a new term excitatory synapse, we will talk about it in a little bit. They form on spines, these are mushroom shaped bodies on the dendrites.

This is the dendrites of the next neuron. So, this whole structure is what we mean by a synapse ok. And, this is in our case what is going to be only the chemical synapse. There are another variety of synapses which is called electrical synapses and in that case the there is a direct connection between the two neurons. So, if I have a cell body or neuron soma here and another may be dendrite here or dendrite and dendrite here.

So, they are actually connected through a set of proteins called connexins, proteins called connexins. And, they form a direct connection of the intracellular regions of neuron 1 to neuron 2. And, the flow of ions is totally based on the electrochemical gradient, that is the voltage of the two neurons inside and the ionic concentrations of the different ions on the two sides.

And so, we will not talk much about these synapses, although they are numerous in number and present in many places and actually very much present during development playing a huge role in terms of synchronization of activity. As you can see since these are directly connected, both neurons will behave in a similar manner which synchronizes them.

And, the chemical synapses are the ones that we will talk about which are more involved in terms of the plasticity that we are talking about. And why chemical synapses? Because, these are synapses that have a particular molecule or chemical which will be called the neurotransmitter known as the neurotransmitter. So, in general each neuron produces only one kind of neurotransmitter. There are cases where there can be multiple neurotransmitters or there are cases where a neuron switches its neurotransmitter.

But, for the purposes of this course we will think of a neuron producing only one kind of neurotransmitter. So, what are the neurotransmitters? They are the molecules that actually do the real communication between the two neurons. The molecule that is present in the presynaptic site, this is the presynaptic site, this is the post synaptic site and there is a gap between them, a physical gap and that is called a the synaptic cleft.

So, the presynaptic site contains these molecules that are neurotransmitters that are present usually tightly packed in clathrin coated vesicles. So, this is another kind of protein that they form vesicles that contain the neurotransmitter molecules. So, some of these neurotransmitter molecules are glutamate, GABA or gamma aminobutyric acid, glycine, acetylcholine, dopamine.

You may have heard of dopamine in relation to Parkinson's disease, epinephrine, norepinephrine. Then we can think of I mean there are many others like serotonin, the list is long. There are many many different types of neurotransmitter. The main neurotransmitter that will come up in our discussions throughout the course are glutamate, GABA, acetylcholine, dopamine and serotonin. And, we will actually go through the different neurotransmitters a little bit when we talk about different functions of these neurotransmitters.

So, ultimately these are molecules that are present in the presynaptic site ok. So, and this kind of vesicles. So, we were saying that this action this action potential travels to the presynaptic terminal which means that the V in minus V out at this presynaptic terminal at some point shows this kind of depolarization, where it goes up to very high positive values. And, at that time these vesicles that contain the neurotransmitter actually release the neurotransmitter into the synaptic cleft.

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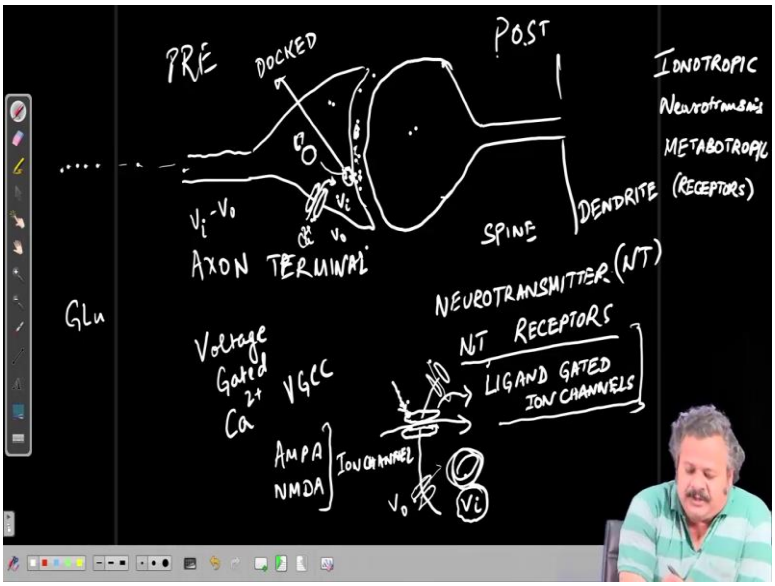

So, let us go into a little more detail about this process. So, as we were saying that we have the presynaptic terminal that is like this and then there is a stereotypical, let us say spine on the dendrites of the postsynaptic neuron. So, this is the axon terminal and this is the spine on the dendrites, this is the dendrites. And, remember these sizes are extremely small nearly about a micron or so, and this these are very tightly coupled with this gap in here.

There are many structural proteins that are involved in maintaining this kind of a structure. And, as we were saying that there is vesicle or rather there are plenty of vesicles here that are actually sitting right near the membrane and are docked there. So, these vesicles are docked at the presynaptic site. So, this is the presynaptic site and this is the postsynaptic site. So, they are docked and there are many complex set of proteins that are involved in this process; that holds the vesicles right at the membrane.

And, the presynaptic site has particular ion channels that are voltage gated, Voltage Gated Calcium Channels. So, they are called VGCCs. So, the voltage gated calcium channels; if you remember from our previous lecture, we talked about voltage gated sodium channels, voltage gated potassium channels, that is the channels opening and closing. The gates of the channels opening and closing depend on the voltage.

Similarly, here also the opening and closing of the ion channels, the voltage gated ion channels present in the presynaptic site that depends on the membrane potential V in

minus V out or the V, V i minus V o. So, at the time the action potential travels and reaches here, it means that the V in minus V out is getting positive large value. So, there is a depolarization here. So, that opens up these voltage gated calcium channels.

So, calcium ions flow in and through a calcium dependent process, the calcium binds to a protein particular protein here that is holding it. And that finally, helps the release of the neurotransmitter molecule into this synaptic cleft. So, if you remove the calcium from here, this kind of transmission is not possible. Actually, I mean there is if there are intracellular calcium stored that are somehow triggered, the calcium is released that still can release the neurotransmitter.

But, outside mostly if the neurotransmitter, if the calcium is gone the neurotransmitter release will not be happening as it should normally, even when the even when the action potential occurs in the presynaptic site. So, now, the second component. So, here this is basically like a transmitter, the presynaptic site is the transmitter. And so, there are there must be a receptor of that information on the postsynaptic site; that will tell the next neuron that there was an event or spike that occurred in the presynaptic site.

Remember, the spikes are the basis of computation and communication in the neurons. So, it is the spikes that are communicated to the next neuron here from the presynaptic site. And, it is these neurotransmitter that go and communicate this information to the postsynaptic site via what is known as neurotransmitter receptors. Neurotransmitter that is the molecule that is being released in the synaptic cleft.

And, on the postsynaptic site we have what is the neurotransmitter; so, if we call this NT, we have the neurotransmitter receptors. So, the different neurotransmitters that we talked about like glutamate which in short we will write with glue, has glutamate receptors on the postsynaptic site and only then can the synapse function. Similarly, GABA would require GABA receptors on the postsynaptic site for the synapse to actually communicate or do the function of communication between the neurons.

And, we have the other kinds of neurotransmitters which also have their own receptors that are that should be present on the postsynaptic site for this communication to happen. So, what essentially happens is that on the postsynaptic site if I draw it like this, the receptor can itself be an ion channel. And, that would mean that we have ion channels on the postsynaptic site and these are special types of ion channels.

So, these are first of all they are neurotransmitter receptors. And, they can be themselves ion channels and they are not really voltage gated anymore. These are what we call ligand gated, ligand meaning a molecule that binds to this receptor. So, these are ligand gated ion channels. So, when we mean receptors, we mean that there is a site on this protein, this neurotransmitter receptor protein where this particular type of neurotransmitter that was released in the synaptic cleft can go and bind here.

And, the energetics of the system when the neurotransmitter binds to the receptor causes the neurotransmitter receptor to gate or open or sometimes even close. And so, this binding actually allows ions to flow in or come out of the neuron depending on the type of ion channel or type of receptor it is. So, for example, type of glutamate receptor is AMPA receptor, another is NMDA receptor. Details of these are will be available in your reading materials and these are themselves ion channels.

And, a particular type of ion channel and that is ligand gated ion channel. And so, when glutamate is released from the presynaptic site, it goes and binds to these transmembrane proteins which are also ion channels. There is a binding site. And so, it opens up the gate and AMPA in this case is non-specific cation channel and actually allows sodium to go in, primarily sodium to go in and potassium can leave.

So, these this is one kind of neurotransmission and that is what we know as a ionotropic transmission, ionotropic neurotransmission. So, that is when the neurotransmitter receptor itself is an ion channel, then we call it an ionotropic receptor and ionotropic neurotransmission happening. And so, as you can imagine this is going to be fast, that is as soon as the ligand is released or the neurotransmitter is released in the synaptic cleft, it will go and bind on the neurotransmitter receptors.

And, since they will immediately open up, the gating time constants are in the scale of lower than milliseconds. And so, it will open up and ions can flow in or out and then cause a depolarization or hyper polarization in the postsynaptic site. So, this is the postsynaptic neurons V in and V out.

And, we will see the effect of the glutamate binding on the multiple ion channels present on the postsynaptic neuron spine at this synapse, that will allow this current to go in; depending on or positive or negative depending on the type. And, that will eventually

change this V in minus V out of the postsynaptic neuron. And, convey the information of the spike occurring in the presynaptic site.

Now, a second type of neurotransmitter can be can happen which is called metabotropic neurotransmission, metabotropic receptor neurotransmitter, neurotransmission or metabotropic. The receptors in this case are also called metabotropic receptors. And, what happens in this case the biggest class of metabotropic receptors are G protein coupled receptors. And, here in this case the receptors are not ion channels themselves.

So, what happens usually they again are ligand they have a binding site for the neurotransmitter. And, what happens is that they actually open or close or modulate another ion channel indirectly via second messengers or other molecules in the pathway. So, the biggest class as I was saying the G protein coupled receptors.

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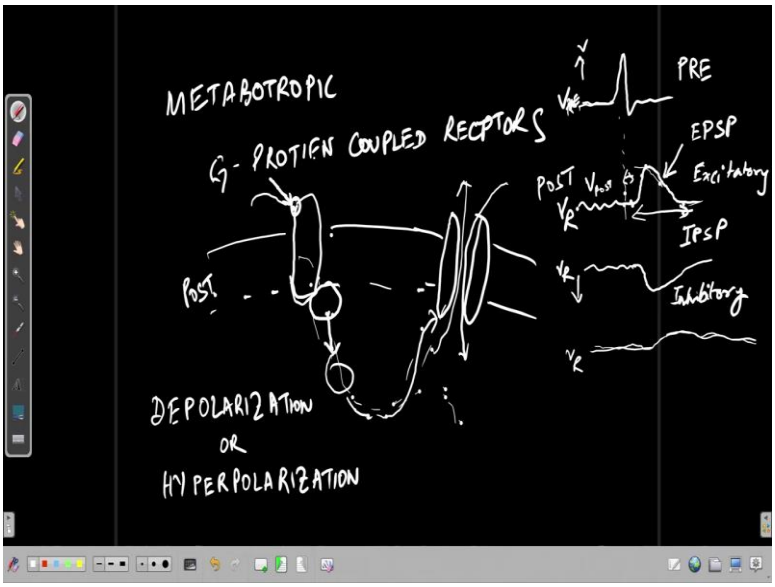

So, metabotropic so, they are G protein coupled. So, these are; so, they are actually a large class of them are like this, that they have a binding site for the neurotransmitter. So, if this is the postsynaptic spines membrane, they are also transmembrane. They have the binding site, then the neurotransmitter goes and binds there.

And, that activates a second class of molecules inside the neuron and then another kind of molecule or maybe more. And finally, go and modulate or open or close or gate and ion channel that then allows the flow of ions in or out of the postsynaptic neuron. So, this

is a indirect way of causing the information flow and usually this is a much much slower process and the effects are longer lasting.

So, there are mechanisms depending on the type of receptor. There are mechanisms to stop the effect of the neurotransmission; that is once this pathway is activated, there are other ways in which self-control mechanisms are there that actually stops this after some period of time. So, in both the cases there is ultimately a current flow into the neuron in the postsynaptic site or a positive current flow in or a negative current flow in whichever way you want to look.

So, that causes either a depolarization in the postsynaptic site or a hyper polarization in the postsynaptic site. So, given that the postsynaptic site is also at V rest like this. A spike in the presynaptic site, this is the voltage of the presynaptic neuron that there is a spike occurring in the presynaptic site.

This is the pre and this is the post, which is the V of the post, V of the pre. So, if it is an ionotropic transmission and let us say it depolarizes with a little delay usually of the scale of milliseconds; there is a depolarization that happens and then decays.

This is what we call as the Excitatory Post Synaptic Potential or EPSP. So, the this is the voltage axis, this scales are different. This may be some a few millivolts depending on the strength of the synapse, this can be of different sizes. And, when I introduce the term strength that is key that is involved in the plasticity process, that modulation of that strength of the synapse that how much effect it is causing on the postsynaptic neuron.

So, this depolarization is excitatory, that is it causes the next neuron to go towards action potential, producing an action depolarization. If the postsynaptic effect is a hyper polarization, that is the voltage goes down from V rest; then it is called an Inhibitory Post Synaptic Potential or IPSP. So, we will discuss a little more later about the excitatory and inhibitory types, inhibitory types.

So, the two main types of synapses that is one that is helping the postsynaptic neuron to get excited or go towards the spiking threshold and inhibitory, that is taking it away from the ability to spike or make an action potential. So, it is not that the same synapse will switch between excitatory and inhibitory, if it is at V rest or at V R. The particular

neurotransmitter will try to produce either an excitatory postsynaptic potential or an inhibitory postsynaptic potential.

But, there are also ways in which the same neurotransmitter can cause excitatory as well as inhibitory effects, like let us say glutamate. There are inhibitory metabotropic glutamate receptors also rather metabotropic receptors, that cause inhibition or hyper polarization in the post synaptic neuron. And, they are metabotropic in nature, glutamate itself is the neurotransmitter.

But so, it can produce excitation as well as inhibition depending on what receptors are present in the postsynaptic site of that particular neurotransmitter. So, the effect of the ionotropic receptors is fast and it finishes also fast, that is in the scales of a few milliseconds both for excitation and inhibition. But, the metabotropic receptors are the effect are small, but much longer lasting. If it is excitatory in nature, they will last longer can be even in the scales of minutes, seconds to minutes for the effect to go away.

And so, they are for more fine and longer term changes in the postsynaptic site. So, with this introduction of excitatory and inhibitory neurotransmission and the mechanism of neurotransmission, the types of neurotransmission being ionotropic and metabotropic; we will come to the closure of this lecture. And, we will continue further to go on into how the synaptic strength that I introduced today that gets modulated to incorporate plasticity.

Thank you.