Computational Neuroscience
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Week – 10
Lecture – 46

Lecture 46 : Long Term Plasticity

Welcome. So we have been discussing plasticity particularly synaptic plasticity of the short term and long term kind and in the last week classes we have covered models of short term plasticity theoretical models of short term plasticity which are based on different phenomena that has been experimentally observed that modulate short term plasticity either short term depression or short term facilitation. So now we shift gears and move on to how to understand long term plasticity and how to model long term plasticity in neural models. So if you recollect we had introduced the idea of long term plasticity in contrast to short term plasticity as the form of plasticity that is longer lasting or more permanent than short term plasticity. So we had said that STP or short term plasticity is a temporary effect and it recovers to its original strength that is synaptic strength that you start with after activity for a period of time you leave it undisturbed and the synaptic strength goes back to what you originally started with and the changes in between is short term plasticity. Now in contrast long term plasticity is that you do manipulation is that is more permanent in an stage depending on what mechanisms come into play afterward and that is maintenance of the synapse that leads to keeping the synapse equally strong for longer and longer periods of time may be even entire life.

So that requires other mechanisms and that will not be part of our discussions initially and so we will be focusing on how the long term plasticity comes into play and how what are the ideas behind keeping it stable for hours. So as we have discussed before in long term plasticity so given a presynaptic spike of two in and we are passed on to two neurons that are connected through a chemical synapse and this is the postsynaptic spike we get let us say an EPSP with a particular amplitude. Now in over time we can produce long term plasticity with certain manipulation and then we again measure the synaptic strength with the presynaptic spike and let us say with increase in synaptic strength where this is the EPSP has increased in size which is potentiation and we let it stay and measure again let it stay undisturbed and measure again and we see that we are maintaining the synaptic strength. So we measure again and we are still at the same synaptic

strength so and this carries on for period of hours I mean couple of hours I mean it is difficult to record for very long periods of time being passed on to both neurons simultaneously that are connected to each other.

So people have looked into it into couple of hours sometimes and that is the direct observation of long term plasticity that we can see in terms of measuring directly EPSPs or EPSCs or IPSCs IPSCs. So however we say that if the synaptic strength is maintained beyond half an hour or so that is what will we will consider as long term plasticity and this comes from a long line of work and include which focuses on the mechanisms behind the long term plasticity or LTP. So why half an hour that is so what this involves is LTP involves protein synthesis. So in order for protein synthesis to happen due to triggered which is triggered by some event in the synapse with transcription translation and so on and finally, having proteins that are leading to stronger synaptic strength that requires at least 20 minutes to half an hour because of the processes that are involved. So what we mean then in LTP is with new proteins with new proteins in that is also transported to the synapse and which makes it stronger then we say that this is LTP or with protein synthesis removal of or reduction in synaptic strength which is long term depression that also requires protein synthesis.

So the what are the kind of proteins that we are talking about so these are again we will talk about the postsynaptic side let us say this is the spine on the dendrite. There is a narrow neck and dendrite. So as we know let us think that this is glutamatergic and the postsynaptic side is releasing glutamates that is glutamatergic neuron the postsynaptic side has AMPA receptors and we can say we are considering only AMPA receptor that is ionotropic transmission. So in this case so we have these receptors here and actually this whole region that is part of the synapse is held together I mean with proteins that are called the postsynaptic density 95 which provides structure to the synapse. There are many other proteins that are involved in providing this structure giving stability to the receptors and so on and so this makes the synapse be maintained for long periods of time.

So here with flow of sodium or calcium and calcium with increase in potential in here we can finally see that with long term potentiation we require we can have more receptors in the spine that itself with increase the flow of sodium and calcium these cations into the postsynaptic side making it a stronger synapse. So up regulation of the neurotransmitter receptors so these are proteins as you know and this AMPA are ion channels which are allowing these cations to flow in. So if we if the protein synthesis ultimately increases the number of neurotransmitter receptors that are then transported to the spine and added on top of the existing ones then the synapse would get stronger. Similarly we if there is up regulation in

the proteins involved in the transport of the proteins to the synapse that also would increase the transport towards the synapse and lead to more neurotransmitter receptors and also other proteins in the postsynaptic side which can be increase in the psd 95 or other linking proteins that are there in the postsynaptic side. Similarly we can also get increase in the size of the spine.

So essentially there may be free neurotransmitter receptors there that are not even placed into the spine because of lack of space within that region. So we now know from quite a bit of work that size of spine also matters immensely because that essentially increases the allows an increase in the number of neurotransmitter receptors that it can hold and is proportional to the strength of the synapse. So very recently with a large body of work on the spine size and synaptic size it has been shown that actually synaptic strength is indeed very related to the size of the synapse. So increase in the spine size would mean increase in cytoskeleton protein production. Cytoskeletal proteins must be increased these are these are basically proteins that provide structure to the spine and like the skeleton of our body and so those need to increase to increase the size of the spine.

So in long term depression the opposite mechanisms come into play in terms of you get to reduce the neurotransmitter that is you also increase the population of proteins that actually recycle the neurotransmitters or remove the neurotransmitters from the membrane and actually get them degraded and similarly if you reduce the transport of proteins to the dendrites then also we will have decrease in synaptic strength decrease in size of the synapses would or the spine can lead to finally, reduction in number of neurotransmitters there and that can also lead to reduction in synaptic strength. So these are basically the ways in which the long term plasticity is occurs and an important factor is then how do how is it triggered. So we have said how long term plasticity happens in terms of mechanisms in the biology. So but we have to trigger it through some mechanisms the neuron must be told that now you have to do I mean you have to start synthesizing these proteins. So in that sense we know that actually calcium is the key player in terms of starting of LTP.

So we will be discussing the LTP long term potentiation or long term depression long term plasticity so to speak based on that are mediated by NMDA. So NMDA is N-methyl-D-aspartate a kind of glutamate receptor and this glutamate receptor allows is a cation channel but it allows a high influx of calcium. So if you think of a postsynaptic spine again so as discussed we have the AMPA receptors and these allow sodium and some amount of calcium to come in and depolarize the neuron. With this depolarization if the receptor if the spine has another receptor type that is NMDA then there is an associative build up of calcium. So

how this happens is so we have the glutamate neurotransmitter which is let us say glutamate which comes and binds to it that gets the AMPA receptors allows sodium to come in into the spine and that gradually increases the inside potential or depolarizes the inside I mean depolarizes the spine.

Now NMDA receptors are special in the sense that they also have glutamate binding to it they require glutamate to bind to it to get them but under normal circumstances their pore is blocked by magnesium ions that is the pore at the mouth of the NMDA receptor is very suitable I mean energetically very favorable for a magnesium ion to just fit in and so the NMDA receptor remains blocked. Even though the glutamate has bound to the NMDA receptor and the gate has opened that is the gating has occurred it will not conduct unless the magnesium ion is thrown out. So this magnesium ion to be thrown out requires sufficient depolarization to happen in the spine that is it has to be sufficiently positive inside so that it can repel the magnesium out. So with depolarization the magnesium is kicked out of the pore and once the magnesium gets removed then buildup of calcium can happen in the spine because NMDA receptors conduct calcium ions much more than any other kind of cation channels and so the calcium that comes in through the amper receptors are extremely small in amount compared to when NMDA channels open. So that leads to this buildup of calcium which is the trigger the calcium then the after the increase in level of calcium there are a number of pathways that get activated including phosphorylation I mean a PKC that protein kinase C and protein kinase A number of them are required which ultimately goes and activates the transcription factor.

So that finally, leads to protein synthesis and this buildup of calcium thus can happen when we have very high activity in a very short period of time that is we have a large amount of flow of cations in the through the amper receptors which depolarize the neuron and additionally with the glutamate being bound to the NMDA and the magnesium being kicked out by the initial flow of the cations from the amper receptors that leads to the calcium entry. So essentially we have a strong short period of depolarization or in the high activity that can lead to this process and the calcium concentration is again crucial for even LTD and the lowering of it below a certain level finally, leads to the opposite phenomena being occurring and that does not require the NMDA actually very low amount of activity for a long period of time finally, leads to LTD. So that brings us to the manipulation that we were talking about let us say we measured the presynaptic we produce a presynaptic spike and this is the postsynaptic neurons measurement we measured the EPSP and this manipulation can be a high frequency stimulation that is we produce a huge number of spikes for a short period of time that is I

mean 100 hertz for a few seconds and that finally, leads to long term potentiation in other words if we measure it again we get increase in synaptic strength. Now let us say this was 1 milli volt this now is 2 milli volts and this may initially reduce little bit, but it will stay on at a saturated I mean finally, it would saturate at a level that is higher than the previously measured strength. So that is what we mean when we induce long term plasticity long term potentiation with high frequency stimulation or a tetanic burst stimulation this was the initially this is the way that long term plasticity was induced.

In an opposite manner if we have low frequency stimulation at about 0.5 to 1 hertz for many minutes then we actually see depression and that depression keeps on staying for a long period of time for a measurable periods of time and leading to long term depression. So these ideas so essentially what this means is that if we have very high frequency stimulation we have similarly very high frequency response in the postsynaptic site given the huge burst of activity. And so that would mean that there is correlated firing in the presynaptic and postsynaptic site that is the both the pre and post are firing together. And in the LTT if the if we think of it in this way that the low frequency stimulation is extremely low and it is not causing any effect on the postsynaptic site.

And let us say that the postsynaptic site fires action potentials randomly in a spontaneous manner which is true for neurons. In that case what we are seeing is that the activity between the presynaptic and postsynaptic sites are uncorrelated which leads to long term depression. And so this brings up the idea of a of a hebb in hebbian synapse and what hebb postulated is neurons that fire together wire together. That is they are connected strongly more strongly together neurons that fire together wire together. And neurons that modify a synapses that modify themselves in this manner that when you have high activity and sort of a correlated activity.

Then you have increase in synaptic strength and when you have de correlated activity you have decrease in synaptic strength. Those kind of synapses are basically called hebbian synapses. And so we will be considering hebbian synapses as well as synapses that are not hebbian or anti hebbian. So, it is not true that all synapses behave in this manner. In fact there are synapses that are exactly the opposite and that is what we mean by anti hebbian or they are neither anti hebbian or hebbian and so we will call them non hebbian.

So there are a variety of possibilities and the basic idea we will be using in when we model this whole process in our subsequent lectures. It is going to be the correlation between the pre and post synaptic neurons or causal relationship. So, if pre synaptic spikes cause the post synaptic neuron to fire that will be taken

as a increase in synaptic strength. So, if this kind of thing happen for a long period of time then we get strengthening of the synapse. And if the pre synaptic spiking is not causing the post synaptic spike and rather the post synaptic spike in fact is occurring just before the pre synaptic spike then it is totally a causal and so that would lead to long term depression.

So this idea will be the basis for our next discussion on long term plasticity where we will be discussing spike timing dependent plasticity which is often used in modeling neural systems with synapses showing plasticity or STDP. So with this we come to the conclusion of today's discussion on long term plasticity and we will continue in the next lecture with STDP and then follow up with basically how to model long term plasticity in networks or networks of neurons. Thank you.