**Neurobiology**

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**Lecture 4.5: Synaptic Integration**

Hi everyone, welcome back to Neurobiology. In this series of videos we have been looking at synapses, the contacts between neurons. We have seen both electrical synapses and chemical synapses in the last few videos. So synapses tell us how one neuron affects the other neuron at a particular point. But if you consider a large neuron that has multiple dendrites, it would be receiving inputs from many other neurons at various contact points. So how are all these inputs combined together to determine the final activity of the neuron? That is what we will try to understand in this video.

A neuron may have multiple dendrites and each of these dendrites may form multiple synapses. So the final activity of the neuron will depend on all these inputs that the neuron is receiving. And this combination or integration of all these inputs to determine the final activity of the neuron is known as synaptic integration. These inputs are nothing but basically the postsynaptic potentials that are generated in a neuron when neurotransmitters come and bind to its receptors.

These postsynaptic potentials can be excitatory EPSPs or inhibitory IPSPs. So basically the same neuron can receive both excitatory and inhibitory inputs. So inputs can vary in terms of their polarity. They can also vary in terms of their magnitude because different synapses can have different strengths. They can also come at different locations on the dendrites relative to the cell body and they may also come at different time points.

So how are these variable inputs combined together? This is what we will understand as we go along. We can observe the process of synaptic integration by looking at a simple circuit. And one such simple circuit is the circuit underlying the knee-jerk reflex that we have seen in one of the introductory videos. So just to refresh your memory, if the kneecap is hit with some object, then that causes a small extension in the quadricep muscle that can be sensed by a sensory neuron. These sensory neurons then go to the spinal cord and they directly contact with motor neurons that come back to the same muscle.

So when these sensory neurons are activated, they would activate these motor neurons and these motor neurons will cause the contraction in the muscle. At the same time, these sensory neurons also connect to some inhibitory interneurons and these inhibitory neurons then connect to motor neurons that go to the opposite muscle. So as a result, whenever these sensory neurons are activated, they would cause the contraction of the quadricep muscles and they would also cause the extension of the flexor muscles on the other side. And because the leg is hinged at the knee and this muscle contracts and this muscle extends, so the leg would move forward. Now one thing to note here is that this is not just one single sensory neuron.

It is actually a bundle of sensory neurons. So it's a nerve that is going from this muscle to the spinal cord containing multiple sensory neurons. And similarly, there are multiple motor neurons, but each of these motor neurons receives input from many of the sensory neurons. So as shown in this schematic here, this motor neuron is getting input from three sensory neurons here. Now if we activate one of these sensory neurons by injecting current in that neuron, so if we inject current and the amount of current is enough, then we can produce an action potential in the sensory neuron as shown in the black trace here.

And because this neuron is making synapse with the motor neuron, so the activation of this neuron will cause an effect in the motor neuron. And what we observe is that the activation of the single sensory neuron generates a small EPSP, an excitatory postsynaptic potential in the motor neuron. Because it's an excitatory synapse, so we see some excitatory postsynaptic potential here. But we do not see generation of action potentials and that's because the amplitude of this postsynaptic potential is small and it is not able to cross the threshold for generating an action potential. But we observe that if we stimulate this whole nerve using some extracellular stimulating electrodes, so these are basically big loop electrodes that loop around the nerve and pass a lot of current that can cause excitation in this whole bundle of neurons.

Then we see that there is a larger EPSP and it crosses the threshold and results in generation of an action potential in the motor neuron. And what that tells us is that if you activate multiple of these neurons at once, then an action potential can be generated in the motor neuron. But action potential in just one of these neurons is not enough. So basically the synaptic input that the motor neuron is receiving at just one synapse is not enough to generate action potentials. It needs multiple of these synapses to be activated to get enough input for action potentials.

So in this circuit, there were two types of motor neurons, one that were receiving direct input from the sensory neurons and one that were receiving input via inhibitory interneurons. These motor neurons go to the opposite muscle on the thigh. So now let's consider the activity of these motor neurons that are receiving input from the inhibitory interneurons. We can do a similar kind of experiment here as well. So if we inject current in one of these inhibitory interneurons, what effect do we expect to see on the motor neuron? Well, since this synapse is inhibitory from the

interneuron to the motor neuron, we should see a reduction in the membrane potential of the motor neuron if an action potential is generated in the interneuron.

And that is what we see. So if you have an action potential in the interneuron, you see a small inhibitory postsynaptic potential in the corresponding motor neuron. Now if we activate many of these interneurons together, which we can do by stimulating the whole sensory nerve, and this stimulation of whole sensory nerve will generate a lot of activity in the sensory neurons, which would cause activity in the inhibitory interneurons. So if by doing this, if we activate a lot of the inhibitory interneurons together, we see a larger IPSP in the motor neuron. And that's because a lot of these synapses are activated together on the motor neuron and their effect is accumulated.

So we see a larger IPSP. And of course, this large hyperpolarization will not result in an action potential because there is nothing like a negative action potential. And since there is no action potential, this will not result in release of any neurotransmitters from the motor neuron. So you might be wondering what is the point of having these IPSPs if they do not result in release of neurotransmitters. Well, if the neuron receives only IPSPs, then it might seem that IPSPs are not of particular relevance.

But if a neuron receives both IPSPs and EPSPs, then IPSPs can have an impact in reducing the effect of the IPSPs. So the inhibitory input can counter the excitatory input that the neuron receives. And we can see this in an example here. So this is a neuron that is getting a lot of excitatory input and so it is firing many action potentials with certain frequency. And this is when it is not receiving any inhibitory input.

But if the same neuron also receives inhibitory inputs at certain time points, then we see that the number of action potentials is now reduced. As opposed to this trace, this trace has fewer action potentials. And we can see the timing of these IPSPs here. So by looking at this trace, you can see there is a dip and then it comes back to baseline.

So that is an IPSP. Similarly, here there is a fast dip and it comes back to baseline, dip, baseline. So these are IPSPs. And wherever we see IPSPs, there the action potentials have been lost. And what that tells us is that the IPSPs were countering the excitatory input that the neuron received at this time. And that prevented the membrane from getting depolarized and generating an action potential.

So that is the effect of IPSPs. They can counter the depolarizations that would have been generated by the excitatory inputs. Let's consider a typical neuron. So it is receiving inputs on its dendrites. And these inputs may be causing some depolarization in the membrane.

And if this depolarization exceeds the threshold, then an action potential can be generated. But if it does not, then the depolarization will just travel passively in the neuron. So it may have this amplitude here and by the time it reaches the cell body, it would have a reduced amplitude. And by the time it reaches the axon hillock, it may have further slightly reduced amplitude. But if it exceeds the threshold here, then the action potential can be generated.

And the reason that a smaller depolarization can generate an action potential here, but a larger one cannot generate here is because the thresholds are different at these different regions within the neuron. So the threshold depends on the density of the voltage-gated sodium channels. And that density is pretty low in the dendrites. So the threshold in the dendrites tend to be high. And then as we get closer to the axon hillock, the threshold drops suddenly.

So even though we had a larger depolarization in the dendrites, this depolarization was not enough to cross the threshold. But when the depolarization reaches the axon hillock, there it might cross the threshold and so we are able to generate action potentials in the axon hillock. Now let's consider multiple inputs coming on the dendrite. So these inputs can come at different times or they can come at different locations. And we will look at these two factors one at a time.

So let's first consider the case where two inputs are coming at different times but at the same location. So this is our neuron of interest that we are recording. And it is getting input from some presynaptic neuron A at this junction. So whenever neuron A spikes, there will be some neurotransmitters that will come and bind to our neuron of interest. And they would cause opening of some ion channels.

So let's say there is some sodium current coming in to the neuron. So if the neuron A spikes two times, then we will see sodium current into our target neuron two times. And each of these currents will cause depolarization of the target neuron as we can see here. So the first input causes some depolarization and once the current stops, then this depolarization will start decaying. And if the second input comes here, before this depolarization has completely decayed, then the membrane potential will start rising from this point.

And if it reaches the threshold, then an action potential can be generated. Now this rate of decay depends on the time constant of the membrane. So if the time constant is long, then the decay would be slower. But if the time constant is short, then the decay would be faster. Then the depolarization would have decayed before the second input came.

And in that case, the second input also would raise the membrane potential to the same level as the first input. And we will not be able to cross the threshold. So there will be no action potential. So in cases when the time constant is short, or if the gap between the two inputs is large, then we will not see an effective summation of the inputs to cross the threshold. But if the time constant

is large, or the two inputs come in close succession to each other, then we will see a good summation and we will be able to cross the threshold.

Now let's consider the case where the two inputs are coming at two different locations on the neuron. So the neuron is receiving input from a presynaptic neuron A at this synapse and another neuron B at this synapse. So if neurons A and B fire, then they would produce certain amount of synaptic current in the neuron that would produce some depolarization here and here. And these depolarizations can travel throughout the neuron passively and their amplitude will decay as they travel farther away. Now the action potential we know is likely to be generated at the axon hillock because that's where the thresholds are lowest.

So by the time the amplitude from synapse A reaches here, it would have decayed depending on this distance between synapse A and the axon hillock and also the length constant of the neuron. So if the distance is equal to the length constant, then this amplitude would have become 37% of the original value. Similarly, the input from synapse B would have also decayed by the time it reaches here. So if we look at the membrane potential at axon hillock, when input A is received, we see some depolarization and this depolarization is reduced depending on the length. And further, when input from B comes, it gets added up to the membrane potential that was there at this point and if it crosses the threshold, then we see an action potential.

But if the neuron received the same inputs but had a smaller length constant, so say 250 micrometers instead of 500 micrometers, it had half the length constant that would mean that now these inputs are two length constants away from the axon hillock. And that would mean that they would have decayed to 0.37 times 0.37 of the original magnitude. So the first input causes a much smaller depolarization at axon hillock and the second input adds to that but it is still not able to cross the threshold.

So we do not see an action potential in this case. So in summary, inputs from different synapses can get added up at every point in the neuron. But the magnitude of these inputs depends on how far they are from the point of origin of action potential and the length constant. Before I close the discussion on synapses, I want to highlight one more thing. We have discussed that the synapses are formed between the axon terminal of one neuron and the dendrite of another neuron.

But if we zoom in, then the location of the synapse on the dendrite can be in two forms. It can either be on one of the main branches of the dendrite, like here, in which case it can be called a shaft synapse. And in some cases, the synapses are formed on small protrusions that are coming out of dendrites, like here. So these protrusions are known as spines and such synapses are known as spine synapses. So here is the axon terminal of one neuron which is forming a synapse with the dendritic spine of a second neuron.

These dendritic spines are actually quite dynamic structures. So their numbers can change over time. And as we have discussed that memories are stored in synaptic strands. So it has been shown that many of the long term memories can involve changes in the number of spines. So connections between two neurons can increase if there are new spines that are formed that receive synapses and or they can also decrease over time.

So these kinds of synapses that include axon terminal of one neuron and dendrite of another neuron are known as axodendritic synapses. And these are the most common type in the brain. But there are synapses that are also formed on the cell body or on the axon of another neuron. So these kinds of synapses may be called the axosomatic synapses and axo-axonic synapses. And these synapses also function in essentially the same way as normal axodendritic synapses in that the synaptic input will cause a change in the membrane potential of the postsynaptic neuron, either in the cell body here or in the axon here.

And that can affect the voltage-gated channels in the postsynaptic neurons and eventually affect the release of neurotransmitters.