**Neurobiology**

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**Week - 04**

**Lecture 4.3: Chemical Synapses**

Hi everyone, welcome back to Neurobiology. In this series of videos we have been looking at synapses, the contacts between neurons. In the last video we looked at electrical synapses, in which the two neurons are directly connected to each other and electrical signal in the form of charged ions can flow directly from one neuron to the next. In this video we will look at chemical synapses, in which the neurons are not directly connected to each other, there is a small gap between them and the communication happens in the form of neurotransmitters that are released by one neuron and are received by the next neuron. These kinds of synapses are much more common in the brain, so contacts between neurons are usually chemical synapses, as well as in the peripheral nervous system. The communication between the neurons and muscles happens in the form of chemical synapses.

And in fact if someone uses the term synapse without specifying what kind of synapse they are talking about, then it is fair to assume that they are talking about chemical synapses. So here is the standard representation of a chemical synapse. We are looking at two neurons here. On the left is the exon terminal of the first neuron that is giving information and on the right here is the dendrite of a second neuron that is receiving that information.

So this whole assembly is called the synapse and these two neurons are the synaptic partners. The exon terminal can be called the presynaptic terminal and the dendrite terminal can be called the postsynaptic terminal, which is receiving information. And the gap between these two neurons can be called the synaptic cleft. So this gap is very small on the order of 20 to 40 nanometers. And through this gap the communication happens in the form of small chemical molecules, which are also called neurotransmitters.

So these neurotransmitters can go and bind to receptors on the dendrite. So these receptors are called the postsynaptic receptors. And before they are released, the synaptic vesicles are contained in small bags or pouches in the exon terminal, which are also called the synaptic vesicles. Each of these vesicles may contain a few hundred or a few thousand of these

neurotransmitters. And when the time is right, then these vesicles can fuse with the membrane and release the neurotransmitters into the synaptic cleft.

And this releasing happens only at specific regions in the membrane. These regions have the required protein machinery that allow this process to happen. And these regions are known as the active zones. Now I'm going to show you the real image of a chemical synapse from electron microscopy. And one thing you will immediately notice is that it looks quite different from this diagrammatic representation that we have been seeing so far.

The main difference will be in the spacing between neurons. So here we see a lot of space around these two neurons. But in the real brain tissue, the neurons are very densely packed against each other, and there is hardly any free space. So let's look at it now. So this is a zoomed in image of a slice of brain.

This structure here is the first neuron. This is the axon terminal. And on the other side here is the dendrite of a second neuron. You can see some cell organelles in these neurons. And these small balls here are the synaptic vesicles in the axon terminal.

Each of these balls would contain thousands of neurotransmitters. And this very small space here is the synaptic cleft into which the neurotransmitters would be released. So let us look at the processing at a chemical synapse in a bit more detail. We have earlier said that action potentials are important because they allow release of neurotransmitters at a chemical synapse. And here we will understand how that happens.

The main link between action potentials and release of neurotransmitters are calcium ions. And this happens because there is a high density of voltage-gated calcium channels that are present at the axon terminals on the membrane here. So when action potential reaches here, that raises the membrane potential, and that increased membrane potential causes these voltage-gated calcium channels to open, and so calcium ions can flow into the membrane. Remember that calcium ions are more abundant outside compared to inside, so they would like to flow in. And also because the inside is negative, calcium ions are likely to flow in.

So both the chemical and electrical gradients make the calcium ions move from outside to inside. And as these calcium ions come in, they can bind to various proteins that are particularly present at the axon terminals, such as synaptotagmin. And these proteins, along with other protein complexes, make the synaptic vesicles come to the membrane and fuse with it. So as you know, the membrane is made up of lipids, and the synaptic vesicles are also made up of similar lipids. So they can come and fuse with the membrane.

And as that happens, we get these kinds of structures where the vesicles are now open towards outside, and the neurotransmitters can come out into the synaptic cleft. Now once the neurotransmitters are in the synaptic cleft, they can diffuse through the extracellular medium, and they can go and probabilistically bind to the receptors on the postsynaptic side. These receptors are directly or indirectly connected to various ion channels. And as these channels open, they allow movement of ions into the membrane. And depending on the types of ions that move in, so let's say if sodium ions move in, they would cause depolarization of the membrane here.

And if some other types of ions move in, they might cause hyperpolarization. This is how we can get change in the membrane potential of the postsynaptic neuron. So a change in the membrane potential at the presynaptic neuron triggered by an action potential can result in change in the membrane potential on the postsynaptic neuron. So when the action potential arrives at the exon terminal, the neurotransmitters are released, and they can go and bind to the postsynaptic receptors. But we don't want the postsynaptic receptors to be activated forever.

We want the communication to happen when the action potential comes. The duration of one action potential is only about a millisecond or so. And so the neurotransmitter should remain in the synaptic cleft for some milliseconds but then should be cleared up after that. Then only we will be able to have precisely timed communication between the two neurons. So there are a few mechanisms by which neurotransmitters are cleared up from the synaptic cleft.

One of these mechanisms is reuptake. So after the neurotransmitter is released, there are ways in which it can be reuptaken back into the exon terminal. And this happens through specialized proteins that are present on the membrane, which are the transport proteins or the reuptake proteins, which move the neurotransmitters back into the neuron. And then they can be packed back into the synaptic vesicles. The second mechanism is enzymatic degradation.

For this there are specific enzymes in the synaptic cleft that can degrade the neurotransmitters. One such enzyme is cholinesterase that degrades acetylcholine. And similarly for other neurotransmitters, there are other degrading enzymes. And the third mechanism is simply passive diffusion. So some of the neurotransmitters can diffuse out to longer distances.

And then these neurotransmitters can be either reuptaken somewhere else or they can be flushed out of the system. So through these various mechanisms, the system is able to remove the neurotransmitters and the synapse can be ready for communication when a new action potential arrives at the exon terminal. In summary, we have seen that whenever there is an action potential in the presynaptic neuron, it causes release of neurotransmitters and that causes some change in the membrane potential in the postsynaptic dendrite. So this change in the membrane potential on the postsynaptic side can be called a postsynaptic potential or PSP. And if this is positive or depolarizing in nature, then it can be called an excitatory postsynaptic potential or EPSP.

And if it is on the other side that it is inhibitory or hyperpolarizing in nature, then it can be called an inhibitory postsynaptic potential or IPSP. Let's think about what would determine whether the postsynaptic potential is excitatory or inhibitory. Well, of course, it would depend on what kind of ions move in and that depends on what kind of channels are opened by the neurotransmitters. So if positive ions are able to move in, then we will see an excitatory postsynaptic potential. Whereas if the positive ions are moving out or negative ions are coming in, then we would see an inhibitory postsynaptic potential.

We can also observe there is a small delay between the action potential in the presynaptic neuron and the postsynaptic potential here. So this is small delay here is of course because it takes time between when the action potential arrives here and then the fusion of the vesicles, release of neurotransmitters and opening of channels here. All that process takes some time and that causes a small delay on the order of a millisecond or a few. This delay can also serve as a useful experimental tool to tell us whether two neurons are directly connected to each other. So if we put electrodes in the two neurons and we observe that whenever there is action potential in one, there is a postsynaptic potential in the other, we will know that the second neuron is getting input from the first neuron.

But this input can be direct or indirect. There may be a direct synapse between these two neurons or it is also possible that maybe this neuron A is giving input to some third neuron C which is then activating the second neuron B. So how do we decide whether it is a direct connection from A to B or whether it is an indirect connection from A to C to B? Well if it is a direct connection then the delay would be small one or two milliseconds. But if this is an indirect connection then the delay can be long. So by looking at the amount of this delay we can figure out whether the connection is direct or indirect.