Neurobiology

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Lecture 3.1: Ion Channels

Hi everyone, welcome back to Neurobiology. In the last few videos, we have been looking at various electrical properties of neurons and in particular we understood what determines the membrane potential. So we saw that the final value of membrane potential is somewhere in between the equilibrium potentials of different ions. And we have also looked at why the membrane potential changes slowly if a current stimulation is applied. But there is one observation that we have not explained yet. And let me refresh your memory by this graph.

So if we apply a small pulse of current, we see small changes in the membrane potential. So we can see a small depolarization if a positive current is applied or we can see hyperpolarizations if negative current is applied. But if a large positive current is applied, then we see a very different type of response in the neuron. So we see these action potentials which have a large and a rapid increase in the membrane potential and then there is a rapid fall.

So what determines these action potentials? What makes these very different from the regular depolarizations or hyperpolarizations? This is what we will try to understand in the next few videos. And this is important because action potentials are the main currency of neural activity. The magic actually lies in the ion channels. Although so far we have thought of ion channels as passive holes in the membranes through which ions can pass whenever there is a driving force. But that is not the whole picture.

Ion channels are actually more complicated. They come in different varieties and their state can change. So they may be in open state at some point and they may go into other states at other points. So to understand how action potentials are generated, we will try to first understand how ion channels function. So again these ion channels are not formed by creating holes in the bilepate layers of the membranes.

Rather the ion channels are formed by protein molecules that are embedded in the membrane. So here is one such protein molecule which is coming out on the outside of the neuron and its one end is in the inside of the neuron and it is spanning the whole bilipid layer. If we look at it molecule from top then we can see that there is a cavity in between or a pore in between and this pore is typically filled with water and the ion molecules can pass through this cavity. Let's look at some of the properties of ion channels. The first property is that the channels allow the ions to move at very high speeds.

So a single ion channel molecule may allow up to 100 million ions per second to pass. That's a staggeringly large number to pass through a single ion channel and these numbers are much larger than what an active transporter like the sodium potassium exchange pump can allow. The second property is that the ion channels are quite specific to specific ions. For example, the potassium channel allow almost 100 times more potassium ions to pass through than sodium. So it is not 100% specific but these are pretty specific and similarly sodium channels allow 15 times more sodium ions than potassium ions to pass through and we will later look at how these specificities are achieved.

And finally the ion channels can open or close in response to specific events that are taking place in neurons. So they are not always in the open state or always in the closed state but they can dynamically change as per requirement. So let us think about how do the ion channels become selective to specific ions and for that it would be useful to look at the sizes of the different ions. So here are the sizes of the potassium and sodium ions. The atomic radius of the potassium ion is about 0.

133 nanometers and the atomic radius of sodium ion is about 0.095 nanometers. So it is slightly smaller than the atomic radius of the potassium ion. Now we can understand how a channel can become specific to sodium. So if that channel has a smaller pore then one can expect that that pore would allow the sodium ions to pass through and may be able to block the larger potassium ions if the pore size is somewhere in between these two values.

But that does not explain how a channel can become specific to potassium because if a channel has large enough pore that allows potassium ions to pass through with this radius then it should certainly be able to allow the sodium ions to pass through as well. So how do we get channels that are specific to potassium and that block sodium ions? So that remains a puzzle. A part of the solution lies in the fact that the ions are present in an aqueous medium inside or outside the neuron. So this aqueous medium contains a lot of water molecules and if we look at a water molecule more carefully so the water molecule has an oxygen atom shown in red here and two hydrogen atoms shown in white here. And because the oxygen atom is more electronegative than the hydrogen atoms it tends to attract the negative charge towards it.

So there is a partial negative charge on the oxygen and partial positive charges on the hydrogen atoms. And the sodium ion or the potassium ion because these are positively charged they tend to attract these partially negative oxygen atoms towards them. So as a result this sodium ion is not present in isolation. Rather it is always surrounded by a bunch of water molecules with their oxygen atoms getting attracted towards the positively charged ions. And this results in the effective diameter of the whole ion.

So this bunch of water molecules is known as the hydration shell and this ion along with the hydration shell has a much larger radius than the ion alone. So the actual ion molecules along with the hydration shells are much larger than the isolated ion atoms. And because the atomic size of the sodium ion shown in red here is smaller than the atomic size of the potassium ion shown in yellow here but because this same charge is localized in a small region this tends to attract more oxygen atoms towards it. And as a result the overall hydration shell for the sodium ion is actually larger than the hydration shell for the potassium ion. So the hydration shell seem to provide a possible explanation for how a potassium channel can become specific to potassium ions.

So if the pore size is such that the hydration shell of potassium can pass through it but it is not large enough that the larger hydration shell of sodium ion can pass through that then this channel will be specific to potassium ions and will block sodium ions. But this raises the opposite problem that how does a sodium channel become specific to sodium ions because now the sodium channel needs to have a larger pore to allow the larger hydration shells of sodium to pass through and that pore should also allow the hydration shells of potassium to pass through. So how does this channel stop the potassium ions from passing that becomes a puzzle. We are running into this dilemma because we are making a mistake. The mistake is that we are thinking of ion channels as rigid tubes through which the ions are passing.

In reality these ion channels are not just passive tubes but they are made up of proteins and proteins are made up of amino acids and these amino acids have various kinds of side chains. So when the ions are passing through the ion channels they are actually interacting with the side chains of amino acids that are present inside these ion channels. And typically in the ion channels there is a narrow region which is also known as the selectivity filter and in this narrow region the hydration shells cannot pass through fully. So these water molecules are stripped off from the hydration shells and only the sodium atom or the potassium atom remains. And this removal of water molecules is an energetically unfavorable reaction but this can take place because the sodium atom or the potassium atom can be stabilized by interaction with the negatively charged amino acids.

So this interaction with the amino acids is what facilitates the removal of this hydration shell and after this the ion can pass through and it can regain its hydration shell. The key thing to note here is that the interaction will depend on the exact positioning of these various amino acids. So in a sodium channel the positioning of the amino acids is such that the sodium atom can be fully stabilized. So it is optimized for the size of the sodium atom and in a potassium channel the arrangement of the amino acids is optimized for the size of the potassium atom. So even though a sodium atom may be able to fit in the potassium channel or a potassium atom may be fit into the sodium channel they may not be stabilized as well as they are stabilized within their respective channels.

And that is what facilitates the removal of these hydration shells and the movement of the ion through the ion channel. So the key solution is not based on the size of the ion but based on the interaction of the ion with the neighboring amino acids. Another property of ion channels that is important for generation of action potentials is that the channels can be gated and by this we mean that the channels may be present in different stable states. The channel may be in an open state or it may be in a closed state and the channel can transition from one state to another. So this process of going from an open state to a closed state or vice versa is known as gating.

And channels that have gating are known as the gated ion channels. So not all channels are gated ion channels. The leakage channels that we have seen before so some of the sodium potassium chloride channels are always open and they do not have a closed state. So those are non-gated channels or passive channels whereas other channels may have different states and they may transition between these states. So those are the gated ion channels and these channels may play an important role in the neural activity in determining the responses of neurons in response to various kinds of inputs.

So how does this gating take place? How do the ion channels open and close? There are many different gated ion channels and they may have different mechanisms but broadly these mechanisms can be grouped into three classes. In the first class there is typically a change in some local region within the protein. So let's say this is an ion channel and there is this narrow region here and if this narrow region becomes even narrower then the pore may be blocked. So this may be the closed state of the ion channel and this may be the open state of the ion channel. The second type of mechanisms may involve a global change in the protein structure.

So this is the open ion channel and if the whole protein folds more compactly and the whole pore becomes narrow so the ions cannot pass through. So this may be a closed state. And in the third type of mechanisms there is some loosely attached part of the protein which may be called a blocking particle. So if this is away from the pore then the channel is open and if in response to some external stimulus if this blocking particle comes and blocks the pore then the channel may be closed. So usually it's one of these three types of mechanisms that is used by an ion channel to go from one state to another.

So what are the stimuli that control the opening or closing of ion channels? In other words what type of triggers control the gating of the ion channels? One type of stimulus are small molecules that can come and bind to the ion channels. So these are known as ligands and these ion channels can be called the ligand gated ion channels. So if a ligand comes and binds on the ion channel it interacts with the amino acids on the channel and these interactions can result in the change in the 3d conformation of this protein. So the channel can go from the closed state to an open state or vice versa. These kinds of ligand gated ion channels are found commonly in neurons.

When neurons communicate with each other they release neurotransmitters and some of these neurotransmitters perform this role of the ligand. So they go and bind to ligand gated ion channels on other neurons and result in change in the activity of these other neurons. The second type of stimulus is voltage. So as we already know that there is a voltage inside the neuron and if the ion channel involves charged amino acids, these charged amino acids may be affected by the voltage of the neuron and if the voltage changes then these amino acids will change their conformation and that conformational change can result in the opening or closing of the ion channels. These kinds of voltage gated ion channels are very important in the generation of action potentials as we will see in the subsequent videos.

Can you guess the third kind of stimulus that can affect the ion channels? Well it can be mechanical force. So you can imagine that if some mechanical force is applied on the ion channel that can also result in the change in conformation. So such kind of channels are called the pressure gated or a stretch gated ion channels and one way in which this can happen is if the ion channel is connected to the membrane through some linker chains then if the membrane is stretched or some pressure is applied then that will result in the change in conformation of the protein and so it can go from closed to open state or vice versa. And you can imagine that these kinds of ion channels are important in the sensation of touch. So these are the three major types of stimuli that can control the gating of ion channels and in particular these voltage gated ion channels are going to be important for the generation of action potentials.

So given these external triggers the channels can go in different states and we have already been talking about the open state and the closed state but in some channels there are actually two types of closed states. So one closed state is the normal closed state where the channel is closed so it's not conducting ions and it is ready to be activated. So if the appropriate external trigger comes then it can open. So the second state is of course the open state where it's open and it's conducting the ions and there is a third state which is also closed and also non-activatable. So if the channel is in this state then the channel is not connecting the ions and even if an appropriate trigger comes it will not be able to open.

So it will remain in this closed state also known as the refractory state. So that's the main difference between these two closed states. Here the channel is closed but it is available for opening whereas here the channel is closed and not available for opening and the channel may remain in this state for some time but eventually it will go back to the resting state and then it will become available for opening again.