Computational Neuroscience

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Week – 02

Lecture - 08

Lecture 08 : Ion channels

Welcome. Continuing on with our discussions on excitable membranes and all or none action potentials and neural activity in the second week. So, we will now turn to what exactly makes the membranes of neurons excitable. And as we have mentioned that there are ion channels that are present on the membrane that provide conductance of to the different ions to flow into the neuron or out of the neuron. So, what are the ion channels? So, if we recollect from our patch recordings that we had talked about, we can in our whole patch recordings and sometimes in our recordings from single ion channels, if we can get a single ion channel on membrane tip in an inside out or outside out recording, we can actually characterize the electrical properties of the single ion channels by measuring single ion channel currents. That is, what the nature of the current is? What sizes of the current are? And so on.

So, what are these ion channels? These are essentially proteins that are transmembrane proteins and they are generally of two kinds and that is the two kinds that we will talk about mainly in this course. One that is voltage gated on the left and the others that is ligand gated. So, what we mean by that is that these ion channels are proteins that have a particular sensor in them which is in this cartoon form marked by this plus sign in such a way that when the membrane potential changes that is this $V_{in} - V_{out}$ as we have discussed earlier. Once this $V_{in} - V_{out}$ changes, the ion channels opening and closing probabilities change.

So, I already bring in a new term probability in this context. So, there because these ion channels are stochastic in nature and so the term probability comes in. But given that we have a huge number of ion channels, we will assume that overall the conductance due to the ion channels is proportional to the probability of ion channels being open. So, here we have examples of four different ion channels that will that we have in our course that that is heavily involved in our course that is the voltage dependent sodium channel,

voltage dependent calcium channels, voltage dependent potassium channels and voltage dependent chloride channels. We will go into a little more detail about how this voltage dependence occurs and later on we will be modeling this in our Hodgkin Huxley system of equations to look at how this voltage dependence ultimately provides the dynamics required to produce action potentials.

So, in terms of the other kinds of ion channels the ligand gated ones, it is such that there is always some binding site on the outside or inside of the neuron or inside of the ion channel that is the in the part that is outside the exterior part or the part that is inside. So, here are examples of three types of ion channels that are ligand gated and usually we will see that the neurotransmitter receptors that are present in the synapses we have referred to the term we will go in more detail in the next lecture. So, they have a binding site for the neurotransmitter itself and this neurotransmitter then when released in the synaptic cleft onto the postsynaptic site it goes and binds to the binding site of the receptor and the binding process itself provides a conformational change that opens up the receptor and that itself is an ion channel. So, for example, we will see AMPA receptors or NMDA receptors or even GABA receptors they are ion channels themselves allowing cations to flow in or out of the neuron or anions in the case of GABA receptors like the chloride ions will move in or out of the and out of the neuron. Similarly, we have some calcium activated potassium channels where the internal calcium decide it actually provides the range of the concentration of the calcium inside the neuron determines the opening probability of the potassium channel and can provide the range of conductances for these channels.

And similarly we will in other cases see some nucleotide gated channels that are present let us say in the retina and so on and they are they have the binding site for the cyclic AMP in this case or calcium in this case in the inside of the neuron. So, then again in a similar manner when calcium or the cyclic AMP goes and binds to the binding site then these ion channels open. So, there are further types of ion channels and like that are activated by stretch that is due to mechanical force or pressure similarly heat activated and so on. So, in our course we will be limited to primarily these two types of ion channels that are voltage gated and ligand gated. So, we will come across the ligand gated primarily in the context of a synapse on the postsynaptic side where the person the neurotransmitter receptors themselves are these ligand gated ion channels.

And the voltage gated ion channels will primarily be on the soma in order to understand the potential and also the calcium voltage gated calcium channel will we will see that comes into play in the synapse as well on the presynaptic side it has a role to play in terms of neurotransmission. So, if we consider let us say somehow we are able to measure sodium currents in a neuron let us this is just assume that and let us say we

provide a depolarization of the neuron and we are measuring the sodium current. So, it is this is the voltage this is V_{rest} or the membrane potential at rest and this is the change in voltage provided that is let us say it goes from V_{rest} to V_1. And parallelly we are able to measure the sodium current this is basically a voltage clamp that you are aware of now. And so if we repeat this experiment if we do this experiment once then we may get a reading something like this.

So, here we are measuring the I sodium in across the neuron membrane in this axis is time. So, we are getting at the initial stage a blip of sodium current and then it goes back to 0. Another time it may be something like this and another time it may be some something else another time may be something even more different and so on. So, overall the way we actually will be talking of properties of the ion channels is based on what we would expect to see by averaging all these different trials all these different repeats. So, if I change the depolarize the neuron and actually measure the sodium currents then overall for this kind of a pulse of current a pulse of membrane depolarization what we will see is an overall current somewhat like this which we will get like this smooth curve if we average multiple repeats over 10s to 50 of the order of 10s of repetitions.

And this is what will be reflecting our sodium current overall and based on the voltage we will later on see how we can determine the conductance of the sodium channels based on these current measurements of a particular ion. And by varying the voltage V_1 that we have by varying this size of the depolarization we can determine the levels rather we can determine the different conductances or the voltage dependence of this sodium conductance and that we will come across later on when we do the Hodgkin-Huxley model. So, here in the ligand gated ion channels case also instead of voltage we may provide a different. So, if we have the concentration of the ligand is what determines the voltage. So, similar to this voltage experiment if we vary the concentration of the ligand inside the neuron in these two cases or outside in the in the other case in the neurotransmitter receptor that the glutamate binding case.

Then again we can measure the currents very similar to the nature of this kind and then based by varying this we can get a dependence of the conductance of this particular ion channel for as a function of or dependence on the concentration of the ligand for the conductance. So, essentially for an as an electrical element or an electrical circuit when we will talk about these ion channels we will be replacing them by conductances and what we mean by that is if we have sodium conductance then we have this g_{Na} which will be a function of V and this function of voltage is what is the most important thing. Similarly, any other ion let us say g_K that will also be a function of V and what we mean

by V is the membrane potential and these will be mainly empirically determined as we will see through the measurements of the kind that we have shown here. Similarly, for the ligand gated case it is say g some other ion as a function of the ligand concentration and so on. So, in in conclusion in this case what we have seen is that we have ion channels are stochastic in nature that is their conductance is not exactly the same for every trial or the current flowing through them is not exactly the same, but overall on average we see the effect and from that we can determine the conductance.

The other thing is that there are two types that is voltage gated and ligand gated. The voltage gated ones are going to be important in our discussions of spiking and ligand gated ones are going to be important in the case of neurotransmitter receptors in case of synapses where we have current injection into the postsynaptic neuron. And if we delve a little more into the structures of the ion channels then we can get a better idea of what they are like what the sensors are so to speak that is what provides the voltage dependence how it functions and how they obtain the selectivity that we have talked to the we have just mentioned implicitly. That is we said that we have a sodium channel which means that it only allows sodium to go through and not the other kinds of channels. We also said potassium ion channel which means it is selective to potassium only and not the different other ions.

So, if you think about it potassium the ion potassium is larger than the sodium, but somehow these potassium channels have selectivity for only potassium to go through. So, but not sodium which is smaller than the potassium channel. So, there are what we will see important selectivity filters within these ion channels. So, what are the ion channels as we said that they are proteins and transmembrane proteins with variety with a number of subunits that are present. So, as you can see in the examples shown here the particular sodium channel voltage created calcium channel with a beta subunit number of potassium channels and the chloride channel structure is shown where these barrel like structures are essentially the transmembrane part of parts of the protein and so this is this has a helical structure in general as we see in transmembrane proteins and they make an arrangement in such a way that multiple such subunits come together to form a pore.

So, if we think of let us say the voltage gated potassium channel then essentially there are 6 subunits like the one shown in this case that come together. So, and let us say if we look from the top. So, let us say this is the membrane and we have the potassium channel somehow represented in there where it allows potassium to go through from outside to inside or inside to outside depending on the gradient of potassium. So, now if we look from the top that is on top of the membrane then what we will see is there are these an arrangement like this that there are 4 subunits. So, we have membrane all around this and this these have these are the 4 parts of the ion channel that have come together to form a

pore in between that provides the path for the ion to flow through and it is not always open in the sense that depending on the voltage with a conformational change in this protein structures that the opening is made to close or made to open depending on the voltage.

So, if we go into a little more detail from work that was done earlier there were a number of hypothesis in terms of how the gating of the ion channels occur. So, as we were saying if you look at the cross section. So, this is just some of the subunits being shown here. So, there this you have this pore here which is closed in one particular conformation and there is a charged helix is a part of the protein that depending on the voltage can rotate that was one of the hypothesis here and then provide a conformational change such that the pore opens up compared to when it was closed and that allows the ion to go through and the selectivity that we have is actually present at based on the amino acid residues that are present at the pore opening and that will allow either a particular ion to go through and stop the other kinds of ions to go through. So, later on gradually the hypothesis about the potassium channels came out with the final ideas that showed that if we have a membrane if membrane like this then each of the units of the potassium channel is made up of 6 transmembrane domains and they are basically S1, S2, S3, S4, S5 and S6.

So, here we have the membrane which is a lipid bilayer as usual. So, we have the S5 here, S6 here. So, what we have here is the protein backbone here we have what the section that is the pore which goes into the membrane and the final protein ends inside here and there is a linker segment from the S4 to S5 protein. So, this is what we call the linker and then the rest of them are connected in the same manner and this is the inside of the domain. So, this S4 domain is supposed to be the segment that provides the gating that allows it to open or close.

So, what we will see is from X-ray crystallographic studies here on the right what is shown here in the top view here is that you have the 4 domains on the 4 side that is each of these are showing the S5 and S6 domains that is only this part is being shown here and the other parts are also there, but in this structure it is absent and the 4 of them together make up the central part of the ion channel the together and that part is through which the potassium ion goes through. And as you can see again in the other part as we had mentioned the selectivity filter is present at this location depending on the kind of side rest side chains that are present in the protein over there and this part is the pore loop which is the outer and which is between the outer and the inner helix that is the S5 and the S6 part. So, now, if we put all this together with the S1, S2, S3 outside and the S4 that provides the way in which the ion channel opens or closes that is shown here that is either it slides rotates down or goes up depending on depolarization and

hyperpolarization. So, as you can see the positive charges are towards the inside of the membrane here when it is closed and when the voltage increases there is a depolarization that is there is a build up of positive charge here the positive potential here then this is repelled and made to move out and that pulls back the pore open. So, that from X-ray crystallographic studies again as you can see here is represented at the bottom in the closed state and in the open state.

So, based on our ideas of from the X-ray crystallographic studies what we now know about the potassium ion channel is as we had described earlier we have this S 4 segment that acts as the sensor and we have the linker segment down here. So, in this current state the ion channel is open. So, that means, actually not means I mean at this point the neuron is depolarized that is the inside is more positive and at rest when it is closed is shown at the bottom here and that is in this case the linker the S4 segment is pushed in which pushes the linker and closes the pore shut physically. So, that the potassium ion cannot flow through into the or out of the neuron in any case. So, when the neuron is depolarized in this case gradually what happens is the S4 segment with its positive charges is pushed out of the through the membrane and that pulls the linker protein with it and that actually physically opens up the bottom of the pore and this is the final state when it is activated and open that is when the neuron is depolarized.

Then again it the opposite movement would occur if we now reduce the voltage and go towards lower and lower and then back to the resting membrane potential or even lower when the ion channel is closed. So, in this scenario there are a few more things that we need to consider and that is that if you think of an ion in let us say this kind of a positive ion that is present let us say extracellularly it is present in a very stabilized form in the in the aqueous medium from because of the hydrogen bonding of the ions that are present let us say sodium or potassium all of them are in a hydrogen bonded state which is very stable energy people. So, now if you think of the membrane the liquid bilayer and an ion channel that is present. So, let us say this is the outside of the neuron, this is the inside of the neuron, this is the membrane. So, this is stabilized by hydrogen bonding with the water molecules on here.

So, it has to break open those hydrogen bonds in order to go in to the inside of the neuron. So, in between there must be some stable locations for through which the ion can travel into the inside of the neuron or opposite way from the inside to the outside of the neuron. So, again here it is at a hydrogen bonded case. So, this is also very stable. So, if we think of the energetics of the whole scenario we have a very stable state outside and a very stable state inside the neuron and in between there is a barrier that it has to go through.

What happens is that by providing those stability sites in here we get intermediate stages that allow us allow the ion to actually jump and travel through. This increases the probability of going through the membrane because of the stapler or somewhat stable internal locations within the pore and that provides the ion to flow through. And even these have come about from studies where by doing mutations point mutations on those locations we can see that ion cannot flow through anymore. And so, while there are many intricate details in the proteins that we need to understand for a more detailed understanding of these ion channels to maybe even do biophysical models of these and do molecular dynamics simulations. In our case we will abstract all these ion channels down to a conductance that is voltage dependent in this particular case the potassium channel or a conductance that is dependent on the concentration of the ligand let us say glutamate or calcium and so on.

So, while the gating mechanism is important and we will see how that becomes important we will not go into all the detailed modeling of this we will bring it down to the level of a non-linear conductance. And with that let us in the next class talk about how the ligand gated receptors or the ligand gated ion channels which are the neurotransmitter receptors in the neurons allow a current flow into the neuron or current injection into the neuron.