Neurobiology

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Week - 03

Lecture 3.5: Properties of action potentials

Hi everyone, welcome back to neurobiology. In this series of videos, we have been trying to understand action potentials. We have seen the role played by voltage-gated sodium and potassium conductances. We have seen how the technique of voltage clamp can be used to see how the conductances depend on the voltage. And we also saw how Hodgkin and Huxley were able to come up with a very neat description that tells us the shape of an action potential in terms of the voltage-gated conductances. We have also seen some very interesting properties of action potentials very briefly earlier.

For example, action potentials have a fixed amplitude. So, they are all or none events. They require an input above a certain threshold to be generated. So, only if there is a sufficiently large depolarization, an action potential can be generated.

Action potentials can be conducted over long distances without losing their amplitude. And there is a minimum time that must be given before a next action potential can be generated after the first one. So, in this video, we will try to understand how these very interesting properties arise from basic mechanisms. So, let us look at the phenomenon of the threshold first. So, just to refresh your memory, if we give some current stimulus to a neuron that can cause some depolarization in the neuron.

So, if you give a small stimulus, you may see a small depolarization. If you give a slightly larger stimulus, you can see a slightly larger depolarization. And if depolarizations are not large enough, then we do not see action potentials. But if the depolarization is large enough, then we can see an action potential being generated. So, there is a threshold and only if the depolarization exceeds the threshold, then an action potential is generated.

So, now can we figure out what causes the presence of this threshold? Actually, this threshold can be explained in terms of the channel properties that we already know. Maybe you want to pause your video here and think about it for a minute before we discuss the answer. Okay, so when we give a current stimulus and cause a depolarization, two things start to happen in a

neuron. The first thing is that the voltage-gated sodium channels will open as the voltage increases. And when the voltage-gated sodium channels open, they will bring sodium ions in and they will make the membrane potential more positive.

So, that is a factor that will try to further increase the voltage. And there is an opposing factor, which are the leakage channels, which will try to decrease the voltage. So, whenever the voltage increases, the leakage channels will flow current in the opposite direction so that the membrane potential can come back to the baseline. Now, this second factor, the leakage channels can be thought of as a linear factor. The more the voltage increases, the more the amount of current that will be there through the leakage channels.

And this first factor, the voltage-gated sodium channels, is somewhat of a nonlinear factor. So, the number of sodium channels that open with increase in voltage increases nonlinearly. For smaller increases, the opening is very small. But as the voltage increases, the number of sodium channels that are open increases at a much higher pace. And these two factors compete.

And because they depend in different ways on the voltage, for smaller depolarizations, the second factor dominates. And for the larger depolarizations, the first factor dominates. So, if you have a very small depolarization, then the number of sodium channels that is open is relatively small, but the leakage currents are larger. So, they bring back the membrane potential down and it's not able to reach the threshold. But if the depolarization is large enough, then the number of sodium channels that is open initially is large and they are able to dominate the leakage currents and therefore the membrane potential can keep on rising.

So, this explains why we have a threshold on the depolarization. Now, if we give an even larger input that could potentially cause an even larger depolarization in a neuron, we would still see an action potential of the same size. Why is that? Why don't we get larger action potentials for larger inputs? Well, the reason is that the size of the action potential depends on the voltage-gated sodium conductances. So, the reason the membrane potential is rising very fast here is because of the positive feedback loop that is caused by the voltage-gated sodium conductances. The increase in voltage opens more sodium channels and more sodium channels cause a further increase in voltage.

So, that loop is responsible for this peak and the height of the peak is determined by how many voltage-gated sodium channels are actually present in the neuron. So, those channels will open regardless of the size of the input that is given. And the more sodium channels we have, the closer we can get to the equilibrium potential of sodium ions which is +55 millivolts that is the upper limit. But there are also voltage-gated potassium channels that are opening. So, this tussle between sodium and potassium channels will determine how close we can go there.

So, it does not matter what size of input is given. It just has to be above a threshold but beyond that the size is determined by the number of sodium and potassium channels. It is like the amount of brightness that you get from burning a candle does not depend on whether you light the candle by one small matchstick or you light it by a big gas lighter. The initial ignition has to be strong enough that you can burn it but then the amount of light that you get depends on how much wax was there in the candle and does not depend on how you lighted it. It's the same thing here with action potentials.

You just have to trigger it enough so that the action potential can be generated but beyond that the size is determined by the number of channels and not by the size of the input. One interesting property of the voltage-gated sodium channels is that they get into an inactivated state. So, as we have seen before, if we look at the voltage-gated sodium conductance as a function of time for different values of voltages. So, when we increase the voltage the sodium conductance increases but after that it gets into an inactive state. So, it's closed earlier.

Here it's open and then here it's inactivated. In terms of the molecular structure, an ion channel may be in a closed state earlier and then when there is depolarization the channel opens but after that it does not go back into the same closed state as it was before. Rather a blocking particle comes and blocks the channel so that it becomes inactivated and it is not available for opening and it takes some time before it can get into the normal closed state and it is available for opening again. So, this inactivation has some very interesting effects on the neuron and this happens only with the voltage-gated sodium channels. The voltage-gated potassium channels do not inactivate.

We can visualize the inactivation of the voltage-gated sodium channels using a voltage clamp experiment. So, let's say we have a neuron at -60 millivolts of resting membrane potential and then we clamp the voltage at 0 millivolt for a short duration and then we bring it back to -60 and then after a short duration we do this again. So, we clamp it back at 0 millivolts and then bring it back to -60 and these two pulses are of the same duration. Now, for the first pulse this depolarization from -60 to 0 causes a rise in the sodium conductance. So, this can be measured by measuring the current and then using pharmacological agents we can separate out the sodium conductance.

So, we know that the sodium conductance increases to this level for the first pulse, but the same pulse given again after a short duration elicits a much smaller response. So, the number of sodium channels that open here is much smaller than the number here which tells us that there were fewer sodium channels that were available for opening during this time. If we increase the gap between these two pulses then we see a somewhat larger increase in the sodium conductance and if this gap is further increased then we see that the sodium conductance is normal. So, we see the same increase in sodium conductance as we saw for the first pulse. So, this tells us that

certain time is required before the sodium channels can go from the inactive state to the normal closed state and they are available for opening again.

Now, this was in the voltage clamp case. In a normal neuron or in a current clamp experiment where we are not controlling the voltage, so then also the same thing is happening when we give a first pulse some stimulus then we see an action potential that causes the sodium channels to inactivate. So, after some time if we want to generate another action potential then we have to give a much larger stimulus then only an action potential can be generated and there is some duration within which if we give no matter what amount of stimulus we cannot generate an action potential. So, this shorter duration is called the absolute refractory period. This is the period in which no matter how strong a stimulus you give you cannot generate an action potential because there are no sodium channels available for opening or very few channels are available for opening which are not sufficient for causing an action potential.

But after some time when the absolute refractory period is over then some sodium channels become available for opening but because this number is smaller than the default state you may need a larger stimulus to cause an action potential. So, here you need this much stimulus to generate an action potential. After some delay a smaller stimulus might suffice and after some more delay even a smaller stimulus might suffice and then after this period is over then a normal stimulus would suffice. So, this longer period is known as the relative refractory period. The period in which you can generate an action potential but you need a larger stimulus to generate it.

So, just to recap the absolute refractory period is the period in which no action potential can be generated after the first action potential and the relative refractory period is a period in which an action potential can be generated but it needs a larger stimulus. So, overall these are the two refractory periods and then after the refractory period is over then a normal action potential can be generated with a normal stimulus. And the reason for the presence of refractory period is the fact that the sodium channels inactivate so they are not available for opening and also the fact that the potassium channels open and remain open for some time after an action potential. Therefore, a larger stimulus is required to overcome both the leakage channels as well as the voltage-grated potassium channels that are open. One interesting property of action potentials is that they can travel along the length of an axon to long distances without losing their amplitude and this is quite important for the functioning of our nervous system because there are several neurons in the brain that have long axons.

For example, there are some neurons that go from the brain to the end of the spinal cord and there are neurons that connect the spinal cord to various parts of the body. So, these neurons can be several feet long sometimes. Now, as we have seen before that if we cause a depolarization in some part of a neuron then the depolarization can travel along the length of the dendrite or the axon but as it travels it loses its amplitude and this is an exponential decay and how far it can go

depends on the length constant and length constants are typically on the order of millimeters or sometimes even smaller than that which means that if you have a neuron that is several centimeters long, in other words the length is 10 times or more longer than the length constant then we will have basically nothing left by the time the signal reaches the end of the axon. So, how do the action potentials manage to travel long distances without losing their amplitude? Let us understand that in a bit more detail. To understand this we will have to look at the anatomy of a neuron in more detail.

So, here is our sample neuron. This is the cell body and we have several dendrites connected to the cell body and then there is one long axon that is coming out. The neuron receives inputs on the dendrites and these inputs cause depolarization in various dendrites and these depolarizations can also travel passively along the neuron. Now, wherever the depolarizations exceed the threshold, there an action potential can be generated and the threshold in turn depends on the number of voltage-gated sodium channels. The interesting thing is that the number of sodium channels is relatively small in the dendrites. So, it is really hard to generate an action potential there.

The density of the voltage-gated sodium channels is relatively high in the axon and it is particularly highest at the axon hillock, which is the initial part of the axon that is connected to the cell body. So, this is the region where the action potentials are most commonly generated because of the high density of the voltage-gated sodium channels. So, before the action potential is generated, this is the neuronal membrane. It is negative inside relative to outside and when the action potential starts, then the sodium ions flow in and as these ions flow in, the membrane becomes more positive transiently and then we have an action potential and then this side can become hyperpolarized again after the action potential is over. Now, these sodium ions that flew in during the action potentials can also diffuse to nearby regions.

So, let us say they go from site A to site B and as these ions go to site B, the site B gets depolarized and that triggers an action potential in this neighboring region. So, now we have an action potential here in site B and this causes further depolarization of the membrane, more sodium ions flow in and then these sodium ions can then again flow to the nearby regions. So, they can go from site B to site C and now we have an action potential here. So, this is how an action potential keeps on flowing. So, it can go from again to the next region, site D.

So, the action potential is not just passively flowing along an axon. It is in fact getting regenerated at every point of the axon. So, this is a very active transmission. It is not just a passive transmission and this will consume some energy also. Now, one thing you might be wondering, why is the action potential moving only in one direction? So, the sodium ions from site C are going to site D, but they can also go to site B.

So, why don't they cause an action potential again at site B? Well, we know the answer to this already from the previous slides. The sodium channels in site B are already in the inactive state because there was an action potential just moments ago here and it will take some time for these inactivated sodium channels to be available again for opening and also the potassium channels the voltage-gated potassium channels that had opened had still not closed. So, this region is still in the after hyperpolarization phase. So, these two factors, the slow closing of potassium conductances and the inactivation of the sodium channels, these two factors together ensure that the action potential does not move in the backward direction. It can only move in the forward direction and this is really helpful because that saves energy.

We don't want the action potential to be moving back and forth because that will not convey any additional information, but will just waste energy in the neuron. So, regenerating action potential at every point of the axon can maintain the amplitude of the action potentials, but it comes at a cost. The cost is that the ion channels have to be opened at every point in the axon and the opening of ion channels will be a slow process. So, the conduction along the axon becomes pretty slow and also because there is a lot of movement of ions at every point, it also becomes an energy consuming process because the gradients will have to be maintained back with the use of pumps. On the other hand, if we were conducting action potentials in a passive manner, then we would not have these costs because we will not be opening ion channels at every point.

The speed of conduction will simply depend on the speed of movement of ions along the length of the axon which can be quite fast and it will not involve opening of many ion channels. So, the overall movement of ions would be relatively smaller. So, the energy cost would also be lower, but then in the passive conduction, we would not be able to maintain the amplitude for very large distances. So, can we do something better for action potentials? Can we somehow make them more efficient? Can you think of a solution? Well, how about a hybrid approach where we allow the action potential to move passively for some distance and it will reduce in amplitude, but before it reduces too much, we can regenerate it again so that it reaches its full amplitude again and then again we allow it to move passively. Well, actually nature has implemented something like this.

So, this passive movement of action potentials happens in parts of the axons that are insulated and this insulation happens in the form of myelin. So, there is a myelin sheath wrapped around parts of axons. This myelin sheath is basically glial cells that tightly wrap around the axon and they cover the ion channels that represent on the membrane. So, it is basically an insulated tube in those regions and in such regions, the action potentials just travel passively. They do reduce in amplitude, but before they have reduced too much, they encounter a region where there is no myelination.

So, these unmyelinated regions are called nodes of Ranvier and these are present throughout the axon at regular intervals. So, the action potential reaches here, regenerates again, then it again travels passively, reduces in amplitude, but again it regenerates at the next road of Ranvier. So, this is how it can travel passively, then regeneration, then passive conduction, regeneration and so on. This kind of hybrid conduction is sometimes called the saltatory conduction. Saltatory is a Latin term that basically refers to dancing or jumping because here we can think of the action potential as jumping from one node of Ranvier to the next.

If we look at how much time the action potential takes to travel along the axon, so this is the position along the axon and on the y-axis we have the time. So, it takes some time for generating at a node of Ranvier, then from one node to the next, it takes very little time to go a long distance. Then again, it takes some time to regenerate here and then it takes very little time to go to the next node. So, we have basically slow conduction in these regions and then fast conduction in the myelinated regions. Overall, by using myelination, we can get up to 10 times faster speed of conduction as compared to an unmyelinated axon.

So, this concludes our series on action potentials. But before I close, I want to emphasize that what we have seen so far is a somewhat simplified description of what happens in a neuron. We have talked about voltage-gated sodium and potassium channels, but in reality there are actually many more types of channels that are present. So, there are also voltage-gated calcium channels and chloride channels. And even among sodium and potassium, there are multiple types of channels that are present. And these may add more complexity to how the action potentials are generated.

And because these channels are proteins, they may also be affected by various events happening in a neuron. So, just like other proteins, they may be affected by post-translational modifications such as phosphorylation and they may also be affected by the amount of calcium that is present in a neuron. We have also not discussed about the differences that may be there in different branches of a neuron. So, the number of channels that are present or the variety of channels that are present might differ in different parts of a neuron that might allow those parts to perform slightly different functions. And finally, there may be quite a bit of variety among neurons.

So, some neurons may express certain types of channels while other neurons express other types of channels. And that might result in some differences among the neurons. For example, some neurons may have smaller spikes while some may have large amplitude spikes. Some neurons may respond with few action potentials while some may tend to have huge bursts of action potentials. So, this variety of channels can result in variety of responses.

So, we just have to be aware that in real brains, there is quite a bit of variety that comes from the variety among the channels.