Human Physiology
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Lecture - 02

Hello everyone, welcome to another new class in human physiology. In the last class, you remember we discussed the first class of neurotransmission, where we tried to cover topics like resting membrane potential and how the resting membrane potential is attained in the cells, mainly in the neuronal cells. Then we also discussed the graded potential; we also saw how the EPSP and IPSP work. And very importantly, we mentioned that whenever the neuronal cells attain this threshold potential, which is about minus 55 millivolts, the signaling process that starts initiates inside the neuronal cells, which is also called an action potential. So, in this class, we will see how the action potential happens inside the cells. and we will also see how different types of ion channels are involved in it.

So, let us stay with it. So, what concepts will be covered? So, mostly as we said in this class, we will cover action potentials; we will see what different types of ions are involved in the ion channels in cases of action potential, and then further we will discuss different types of refractory periods. So, let us see them one by one. So, what is basically the action potential or the neurons' electrical signal? Action potentials are generally like very rapid or transient electrical signal changes that occur across the neuron's membrane, and whenever these rapid transient changes in the electrical potential happen, neuronal cells transmit a signal.

From the axon hillock area of the neuronal cells, if we have an axon, this is like the cell body, and we have the axon hillock area. So, basically, initially, we had this resting membrane potential, which was about minus 55 millivolts, mostly in this axon hillock area, and then whenever it attains the threshold potential. So, initially it was like minus 70 millivolts, which was the resting membrane potential. And then, from the resting membrane potential, what we get are the EPSP signals, right? From the stimulatory signals, we attain about minus 55 millivolts, which was about the threshold potential. So, whenever the cell attains this threshold potential, a cascade of ion channel movements occurs, and for that, we will observe a wave of electrical signals across the neuronal cell.

This is only called an action potential. And unlike the graded potential, action potentials are mostly all-or-none events. So, either it will happen or there will not be any action potential. Basically, as we said, the initial threshold potential is minus 55 millivolts. And in the next few slides, we will see what the different types of voltages would be based on the movement of ion channels.

So, in cases of action potential, the first step, or the first crucial step, is the fast stages of the movements that happen, which is also called depolarization or the influx of sodium. So, let us see in this diagram how the depolarization wave is created. So, what we said again let us recapitulate: initially, the cell or the cell membranes have the resting membrane potential, which was about minus 70 millivolts, and then, through a lot of IPSP signals or stimulatory signals near the axon hillock area, the cell reached this threshold potential, which was minus 55 millivolts. And whenever this minus 55 millivolt threshold potential is attained near the cell, you see the neuron in the axonal area of the axon. So, basically, these are the axonal areas of

the neuron, right? So, in the axonal area of the neuron, there are a lot of voltage-gated ion channels.

So, what are these? These are voltage-gated ion transport channels, and you can see what these channels are, basically sodium. So, you remember in our ion transport class, we discussed different types of ion transport channels for facilitated diffusion, some were leaky pore channels, and some were ligand-gated channels, but these are the voltage-gated ion channels. So, whenever the cell attains this threshold potential, which is about minus 55 millivolts, let us consider that in this ion channel, there is a gate or door that generally stays closed. When it is close, for example, initially the cell had a resting membrane potential of about minus 70 millivolts, right? So, at rest, generally the cells will have their ion-gated channels closed, but whenever the cells reach this threshold potential of minus 55 millivolts, these ion-gated or voltage-gated channels get activated. So, if the voltage-gated channels get activated, what will happen is the gate will open up, right? The gate will open, and as you know, the sodium concentration outside the cells is higher and the sodium concentration inside the cells is lower.

So, basically what will happen is diffusion will occur and sodium ions will move from outside of the cells, where sodium ions were more concentrated, to the inside of the cell. So, some of the sodium ions will basically come inside the cell, and as you know, sodium ions carry a positive charge, right? As the positive charge of sodium ions comes rapidly inside the cell, the potential, which was initially at minus 55 millivolts or threshold potential, will rapidly change from minus 55 millivolts to plus 30 millivolts. So, basically, what happened again? Let us recapitulate that initially we had a resting membrane potential of minus 70 millivolts, and after that, through the EPSP signal, it reached the threshold potential of minus 55 millivolts. Now, in the neuronal cell, mostly in the axonal area, we have a lot of voltage-gated channels. So, whenever this voltage or the charge of the cells becomes minus 55 millivolts, these gates will open up, causing a lot of positive sodium ions to come inside, and the charge will completely change from minus 55 millivolts rapidly to plus 30 millivolts.

And you know what will happen; this charge will basically propagate, moving from this area to the area near the second ion channel. So, initially, how much was that like potential here? Initially, it was like minus 70 millivolts to minus 55 millivolts, and now a lot of sodium positive charges are moving slowly near this channel. So, basically from minus 70 millivolts, because of this positive charge, it will become like minus 55 millivolts, which is also called the threshold potential. And what we just said is that whenever this ion channel reaches the threshold potential, these ion channels will open up again, sodium ions will come in, causing the positive charge to build up again; in the same way, the potential will change from minus 55 millivolts to plus 30 millivolts. In the same way, this positive ion will move to the next channel.

Again, this channel, which was initially at rest, was minus 70 millivolts. Once some positive ions move, it will become minus 55 millivolts, and this is the threshold potential. At threshold potential, this third channel will open up, causing a lot of sodium to come inside. Again, this localized potential from minus 55 millivolts will go to plus 30 millivolts. So, basically, this way one depolarization wave will kind of be generated.

So, this potential, which eventually changes from minus 55 millivolts to plus 30 millivolts, and this movement of this potential will create a depolarization wave, okay. And let us see what happens next, okay? And one more crucial thing just to finish before we go to depolarization. At this end point of the axonal terminal area, you also see that there are a lot of calcium ion channels, right? And these calcium ion channels are generally closed, but whenever the inside

of the cell attains plus 30 millivolts. So, whenever the inside of the cells attains this plus 30 millivolts, the calcium ion gated channels open, causing a lot of calcium ions to move inside. Now, in a few slides, I will discuss the importance of this calcium ion, but just try to remember that this way, the cells in the upper part of the neuronal cells are basically attaining around minus 55 millivolts to positive 30 millivolts, and our depolarization waves are created.

And once this depolarization wave reaches the external terminal area, it activates the calcium ion channel, causing calcium ions to move inside. The role of the calcium ion will be discussed very soon. Then, simultaneously, for example, what we just said in the last slide, let us consider that we had this initial depolarization wave on top of here, causing a lot of sodium ion channels to open, causing sodium ions to flood in, and the voltage initially changed from minus 55 millivolts to plus 30 millivolts. Now, let us see what happens in this down area of the neuron. So, basically, how much we initially got the cell potential was 70 millivolts right at resting membrane potential; now, after some EPSPs, it got to about minus 55 millivolts, which was the threshold potential.

And after that, what happened was depolarization; it caused the cell potential to become minus 55 millivolts to plus 30 millivolts, and at this 30 millivolts, we said that this created a depolarization wave. Now, as the inside of the cells got this 30 millivolt potential, what it does basically is inactivate the sodium ion channel. So, in the last slide, as we said, like the minus 55 millivolts when it is going to the next, it activates the next potential channels, but whenever it reaches plus 30 millivolts, it automatically deactivates the sodium channel or inactivates that sodium channel. I will discuss a little more very soon, but just remember that whenever the cell attains plus 30 millivolts, two things happen. First, it inactivates the sodium ion channel, right? Second, what happens is that it activates various potassium voltage-gated channels which are present in this area.

So, a neuronal cell also has a lot of potassium voltage-gated channels. So, at plus 30 millivolts of potential, these potassium ion gated channels or voltage-gated channels get activated or opened. So, what will happen is that basically these potassium voltage-gated channels will open at plus 30 millivolts, causing a lot of potassium ions to come out. Why? Because generally you know that potassium ions are higher inside the cells and lower outside the cell. So, basically, simple facilitated diffusion happens.

So, facilitated diffusion causes a lot of potassium ions to move out of the cell. And what it would cause to the potential. So, initially what we said was that the potential was plus 30 millivolts due to the depolarization wave, and now a lot of potassium, a huge number of potassium ions which are positively charged, will basically move out from the neuronal cell and come outside. And as a lot of positive charge is coming out from the cell, it will leave a lot of negative ions on the inside of the cell, causing the potential to rapidly change from plus 30 millivolts to minus 90 millivolts. So, you see such kinds of rapid changes are happening here.

And this way, which is generated, the ion potential changes from plus 30 millivolts to minus 90 millivolts; this is also called repolarization or the repolarizing wave. So, basically, in the last slide, we saw how the depolarization wave was created, right? So, depolarization, which was about minus 55 millivolts to plus 30 millivolts, occurs at the very same time we will also see a repolarizing wave, which would have about plus 30 millivolts to minus 90 millivolts. And basically, both this depolarization and repolarization happen simultaneously. There is not a significant time lag, and using this depolarization and repolarization wave, neurons basically send these transmission signals towards the terminal area and from one presynaptic neuron to

a postsynaptic neuron. So, this is the overall scheme of the thing where you initially saw that cells were at resting membrane potential, or minus 70 millivolts.

From there, we reached the threshold potential using the IPSP, and now, on top of this neuron, a depolarization wave has been created, causing the potential to move from minus 55 millivolts to plus 30 millivolts, and whenever this plus 30 millivolts is attained here. It opens up the calcium ion channel, and as it opens up the calcium ion channels, a lot of calcium ions come outside. And I will discuss what the role of these calcium ion channels is very soon. At almost the same time, this positive 30 millivolt also activates or opens up the potassium voltage-gated ion channels. And as potassium is high inside and low outside, a lot of positive potassium ions move out of the cell, causing a significant buildup of negative potential or negative ion charge, which basically attains about minus 90 millivolts.

This is also a hyperpolarizing condition because the cells eventually move beyond the threshold of the resting membrane potential. So, you remember that initially at rest, the resting membrane potential was minus 70 millivolts, right? And then the depolarizing wave costs like plus 30 millivolts. And now, when the depolarization is happening, eventually, due to a lot of extra potassium ion movement, the cells, like the potential movement, cannot get stopped at minus 70 millivolts; it eventually comes to about minus 90 millivolts. So, although this is called repolarization, this excess negative potential that is attained by the excess movement of potassium ions from the cell can also be called hyperpolarization. Hopefully, the steps of depolarization followed by repolarization are clear to you.

Now, briefly discuss the involvement of calcium ions. So, as you see, one more thing very importantly, whenever the cell attains minus 90 millivolts, here there are also calcium ion channels you can see. So, this minus 90 millivolts, what it will do is basically inhibit the calcium ion. So, what will happen is no further calcium ions can move inside. So, no further calcium ions can move inside.

Now, let us see what the role of the calcium ion is. So, as you see, there are a lot of vesicles; they have neurotransmitters in them. So, these vesicles that are present at the axonal terminal area have a lot of neurotransmitters, and they can be like glutamate, which is a stimulatory neurotransmitter, or they can be GABA, which is an inhibitory neurotransmitter. So, basically, what it is trying to do is use this potential to open up the calcium ion, and this calcium ion has a specific role in the release of this neurotransmitter from the axonal terminal area to the postsynaptic junction. If I consider, there may be one more kind of neuron here.

So, how is the calcium ion helping with it? So, you see this vesicle has a lot of proteins in it, and in the same way, the axonal terminal area also has some protein. What this calcium ion does is basically create a bridge between the neurotransmitter vesicles and the membrane. So, initially, the neurotransmitter vesicles are not very near to the axonal terminal membrane area, right? They do not have any connections between the vesicles and the terminal area. But whenever the calcium ions come inside, this calcium ion kind of creates a bridge between the proteins that are present on the vesicles of this neurotransmitter. with the proteins that are present in the membrane of this axonal terminal area.

And whenever this bridging happens, what it does is that this bridging causes these vesicles to kind of pull near to this membrane. And whenever these vesicles get pulled near to the membrane, they basically get fused. So, basically this vesicle gets fused and exocytosis happens; you can see that this process of exocytosis happens and the neurotransmitter

molecules are basically removed in the postsynaptic junction area or between the two neuronal areas. So, in this way, calcium ions have a very important role because they basically create a bridge between the proteins of these neurotransmitter vesicles along with the membranes. Using this bridging, they pull the neurotransmitter vesicles towards the membrane area of the axonal terminal site, and eventually, via exocytosis, the neurotransmitter molecules, which can be either excitatory like glutamate or inhibitory like GABA, are ejected into the postsynaptic junction.

And once these neurotransmitter molecules are removed, what will happen? It will again create a IPSP or EPSP signal. in the next neuron. So, in this way, the signal will basically continue, and this whole process of depolarization and repolarization, followed by the removal of neurotransmitter to the next neuron, is called action potential. It is clear to you. So, basically, this is a neuronal action potential in a diagram, and all these ion channels are involved.

So, this is like a pictorial presentation. So, now we will discuss two important things, which are the refractory period, and we will also try to represent the whole potential of the action potential sequences on a graph. So, let us first go to the graph and then we will discuss the refractory period. Let us go directly to the graph. So, before we go to the graph, one last time.

So, what was the depolarization wave? The depolarization waves were from minus 70 millivolts to plus 30 millivolts, right? You remember, due to the opening or activation of the sodium ion channel, there is a generation of a depolarization wave. Which was initially from the resting membrane potential of minus 70 millivolts; eventually, it goes to the threshold potential of minus 55 millivolts, and from the threshold potential, it goes to plus 30 millivolts, which is called a depolarization wave. From the same way, when this plus 30 millivolts was attained, it opened up those potassium ion channels, causing the potential to drop from plus 30 millivolts to about minus 70 to minus 90 millivolts. So, up to minus 70 millivolts, we can call it repolarization, and as we know, it does not stop at minus 70 millivolts, right? Basically, because a lot of potassium ions come outside, it goes via more kind of polarization, which is about minus 90 millivolts, and this stage can be called hyperpolarization. Now, let us see the whole thing in the plot where we have the x-axis, which is the, and the y-axis, which is the potential.

So, basically, we have the y-axis, which is the potential, and the x-axis, which is the time in milliseconds. So, where we are, let us see the different levels. This is the resting membrane potential, which was minus 70 millivolts, right? And then this is the minus 55 millivolts, which is the threshold potential, right? So, what happens basically at a resting cell is that it is at minus 70 millivolts. Now, we said that there are graded potentials or IPSPs, right? There are graded potentials or IPSPs; basically, it is the integration of different stimulation signals. If that happens, the cells from minus 70 millivolts touch minus 55 millivolts, which is also called the threshold potential.

Whenever the cell reaches this special potential, the action potential initiates, and how it initiates you see in this ion channel where initially the ion channels are, so basically let us consider this as the sodium ion channel. So, basically, let us consider these: the sodium voltage-gated ion channel, and each ion channel can have 2 gates. One is the activation gate, which can be called AG, and the other is the inactivation gate, also known as IAG. So, initially at rest, you can see the activation gate is closed; right, initially at resting membrane potential, you see the activation gate is closed. But whenever the cell reaches this threshold potential, here you see what is happening: the activation gate of the sodium ion channel, which was initially closed.

It closed, it got open right whenever it reaches the threshold potential, which was minus 55 millivolts. The activation gate, which was initially closed, basically opens up. See, the activation gate opens up, and whenever the activation gate opens up slowly, the inactivation gate also opens up. So what happens is that along with the activation gate opening up, the inactivation gate also opens up. And when both the gates open up, what it will do is cause a lot of sodium ions to come inside the cells, and not only will the sodium ions move from outside the cells towards the membrane, but because these inactivation gates are also open, it will also facilitate the movement of those ions towards the cell.

inside the cytoplasm. So, due to this inactivation gate opening up, the sodium ions will eventually come inside the cell, causing the cell membrane potential to rapidly rise to almost plus 30 millivolts. So, at plus 30 millivolts, we said that this is also called the depolarization wave, and we discussed what will happen at plus 30 millivolts; this will basically deactivate or inactivate the inactivation gate. So, at this point, this is the peak point; you can see this is the peak point. Where the potential is about plus 30 millivolts, the activation gate is still open. But this 30 millivolt basically inhibits this deactivation gate, so it will inactivate; what it will do is inactivate this inactivation gate, causing the closing of this inactivation gate, and what will happen here is that the inactivation gate is closed.

as much as ion comes inside. So, if you try to give more stimulation, more signal, more IPSP, as much stimulation as you generate, the sodium ions will eventually not be able to come inside the cell, right? Because this gate is closed, this inactivation gate is closed. So, even though sodium ions can come inside the ion channel, the ions cannot come inside the cell. At this peak point, and now from this peak point, what we said the same way is that the potassium ion channels will open. The potassium ion channels will open because at this plus 30 millivolts, they get activated, the potassium voltage-gated ion channels, and a lot of potassium ions will come outside of the cell, causing the voltage to drop rapidly from plus 30 millivolts to about minus 90 millivolts, you see.

How hyperpolarization is happening. So, basically from the peak point of plus 30 millivolts, the potential will drop to minus 90 millivolts. So, eventually, this initial step from minus 70 to plus 30, which is called depolarization, and then from plus 30 to about minus 70 can be called repolarization, and the transition from the resting membrane potential of minus 70 millivolts to minus 90 millivolts can be called hyperpolarization. Now, let us see what the two refractory periods are that we have mentioned. So, there are two refractory periods. One is the absolute refractory period, and the second is the relative refractory period.

So, at this peak point, from this point to almost like one-third of this potential, as we said, as much stimulation as you can generate, there cannot be any further generation of action potential because this is already like the peak point, and at the peak point of plus 30 millivolts, the inactivation gates are closed. So, even though some sodium ions come inside, they will not be able to go into the cell. causing no further neurotransmission. So, this is the time lag or the refractory period, which is called the absolute refractory period; whereas, no matter how much you create the EPSP or give the stimulation signal, it will not be able to translate into an action potential. And whenever the cell or the potential reaches the hyperpolarizing state at minus 90 millivolts, it basically takes some more time from minus 90 millivolts to the threshold resting membrane potential, which is minus 70 millivolts, right? So, this time lag where the cells eventually come to the hyperpolarizing state, and from the hyperpolarizing state, it goes up to the resting membrane potential followed by the threshold potential.

So, this time lag where you can give a lot of stimulation signals, but it takes a few extra folds of stimulation because it has already come to the hyperpolarizing condition. But here, if you give extra stimulation of IPSP or a stimulatory signal, eventually that summation or integration happens, and the potential can eventually reach the threshold potential. So, this gap or this period is called the relative refractory period. But just remember that in cases of the absolute refractory period, no matter how much you provide additional stimulation or IPSP, it will not be able to translate to an action potential because its inactivation gate is closed. But in the case of the relative refractory period, you can increase the fewfold amount of extra stimulation that can translate to basically attaining the threshold potential, followed by the process of action potential.

So, hopefully everything is clear; we already discussed synaptic transmission, and you can go through the notes here. An important thing is that there are a few proteins you have to remember; for example, this type of VSNARE protein, or synaptobrevin, which are present on the vesicles. So, this type of snare protein, like V-snare or synaptobrevin, is generally present in the vesicles. In the same way, there are proteins that are present on the membrane known as T-SNARE proteins or Syntaxin. So, what we just said is that in cases of the vesicles, we will see some proteins called V-snare protein or synaptobrevin.

You will also see some proteins in cases of this membrane that are called T-SNARE proteins or syntaxin. And what we said is that whenever these calcium ion channels open, whenever this membrane potential reaches from minus 55 to plus 30 millivolts, the calcium ion channels move and then these calcium ions come here, causing the bridging between these two proteins. Like V-snare and T-snare, whenever this bridging of the protein happens, they will pull the vesicles near the membrane, and whenever they pull near the membrane, eventually it will fuse, and through the exocytosis process, these neurotransmitter molecules will eventually come out. So, we have already discussed going through the note. Hopefully, you like the classes on neurotransmission, both part 1 and part 2.

If you have further questions, please discuss them with us during live sessions. You can also drop your questions by email. So, activity questions: how do drugs or diseases that affect ion channel function alter action potential propagation and synaptic transmission? You can also provide some specific examples. So, try to answer this question. Hopefully, you are enjoying the different classes of human physiology.

Let us meet with you very soon for another new class. Thank you very much.