Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission & neurotransmitter systems

Topic 1
Action potentials and synaptic transmission – part 3 of 5

Dr Philip Holland
Department of Basic and Clinical Neuroscience

Lecture transcript

Slide 3

In the last section, we discussed how these neurons can integrate information from their presynaptic partners or from the surrounding, and we spoke about how this can be very divergent with up to 400 inputs.

Now after the signal is transmitted through the dendrites and the cell body to the axon initial segment, this is where it can then trigger an action potential, and that's what we're going to focus on today. We're going to focus on how that action potential generation works here at the axon initial segment, this highly specialised component in the start of the axon.

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To do this, we're really going to focus on voltage-gated sodium channels and voltage-gated potassium channels. You see this mechanism here by which we have the usual ionic gradient that you're now becoming familiar with, whereby sodium is at much higher concentration outside the cell than inside the cell. Remember that sodium is the light blue.

Therefore, if you remember back to the electrostatic and diffusion force section, sodium wants to enter the cell because it wants to be drawn towards the negatively charged intracellular space, but also it wants to enter the cell because it wants to go to the area of lower concentration within the cell.

In response to an electrical stimulus, which opens this voltage-dependent gate, sodium will rapidly flux into the cell, making the intracellular space more positive with respect to the extracellular space.

Slide 5

In the context of the voltage-gated potassium channel, which we now see here in the purple, the opposite is true, where potassium is higher concentrated inside the cell and lower concentrated outside the cell. If you remember that the electrostatic force, the charge component, is pulling potassium into the cell via the leak channels, but the diffusion forces want potassium to leave the cell because it's a lower concentration outside the cell.

In this circumstance, the same electrical stimulus triggering the voltage-gated potassium channel will cause potassium to leave the cell and move to the extracellular space, rendering the intracellular space more negative, and this is the hyperpolarising response. So when we talk about

hyperpolarisation, we're talking about the inside of the cell becoming more negative. When we talk about depolarising, we're talking about the inside of the cell becoming more positive with respect to the extracellular space.

Slide 6

If you remember what we spoke about in terms of graded potential is that this incoming signal causes a localised graded potential that decays electrotonically as it traverses across the cell body. If this reaches this specialised axon initial segment at too low a threshold, we do not see a response. However, if this response is significant and above the threshold, minus 55 millivolts in this case, we see this significant depolarisation phase. So this positive phase, followed by a hyperpolarising phase, the negative phase. What we're going to focus on now is how these channels respond to allow these phases to happen.

The axon initial segment is uniquely designed to do this. It has a very high concentration of, for example, voltage-gated sodium channels, voltage-gated potassium channels, and chloride channels. So it makes it uniquely responsive to changes, and are uniquely excitable compared to other regions of the axon to trigger these action potentials, and this is very important in that context.

Slide 7

The action potential-- this is a classic graph of an action potential-- is divided into a number of phases, which we'll talk through now. First of all, we have the resting membrane potential. We've discussed this. We know what's happening here. This is the polarisation of the cell that's set up via the balance of the sodium-potassium ATPase pumps and the leak channels present on the membrane.

Then in response to a depolarising stimuli, so an electrical stimuli or a graded potential, as we've discussed, some of these sodium channels in the postsynaptic cell might open. Now if this stimuli is large enough to pass the triggering threshold-- that's the main 55 millivolts in the previous section-- then these voltage-gated sodium channels at the axon initial segment start to open, and sodium rushes into the cell. So we get this positive depolarisation phase.

This rapid entry of sodium further depolarises the intracellular space of the neuron, opening more sodium channels. So we get this very rapid flux of sodium into the cell here, in this case.

The sodium channels - and we'll come back to this - have what's called an inactivation phase. About half a millisecond after they open, they become inactive - and we'll come back to the mechanism for that - so they can no longer flux sodium.

Slide 8

At the same time, the voltage-gated potassium channels begin to open. Now we discussed that they cause potassium to leave the cell and the cell to become more negative, but they also respond much slower than the sodium channels. They open more slowly, and they close more slowly.

So as they open now, and the sodium channels are inactive, we can see here that potassium starts to leave the cell. So we're now starting to hyperpolarise the cell. It's becoming more negative, moving towards its resting membrane potential.

Potassium continues to leave the cell, because even after the cell has been hyperpolarised back to the resting membrane potential, these channels are slower to respond, so they close more slowly. So we get this after hyperpolarisation, this overshoot of negativity, and the response to this.

Then these channels close again, and in response to, potassium starts to now leak back into the cell via the leak channels, if you remember back to the leak channels. So the potassium will slowly start

to leak back into the cell, rendering it more positive and moving towards the resting membrane potential. Of course, this is helped by the sodium-potassium ATPase pump, and then we have resurrection of the normal, resting membrane potential out here. So the axon is now back at its resting state and ready to fire again.

Slide 9

There are two important phases with response to these changes, and we call these the refractory period. These are the points at which the axon of the neuron either can't fire or will find it more difficult to fire subsequent action potentials. The absolute refractory period is that point at which the sodium channels are inactivated so they can't flux sodium. This lasts until the resting membrane potential has been restored, and we'll come back to that. But safe to say that at this point, no action potential can be triggered in that neuron.

This has two effects. It allows the neuron to control its excitability, but it also prevents back propagation. If you imagine that we only want this action potential moving in the one direction, towards the terminal field of the neuron, this helps to prevent that signal from travelling back towards the cell body.

The relative refractory period is the period during this after polarisation overshoot where the potassium channels, because they are slow to close, render the membrane potential lower, so more negative, than the resting membrane potential.

During this point, an action potential can be triggered, but because the membrane potential is below the resting membrane potential, it will require a greater input to do so. So this is the relative refractory period, whereby the same stimulus that end just in action potential in the previous section of the resting membrane potential may now not be sufficient, and we would need a greater stimulus.

Slide 10

We just want to focus now on these different stages here. I mentioned the inactivation state of the sodium channel. It's important to know that channels have three main states that we're going to discuss for the purpose of these talks. They are the closed state, which is when the gate is closed and they can't flux ions. They have the open phase in which the gate is open, and they can flux ions across the membrane. But sodium, for example here, has this inactive state and this refractory period whereby, in this case, a ball and chain mechanism is taken up into the pore and physically blocks the pore. This is a charge-dependent mechanism. Although the gate is open, as you can see - the black line here in the middle - no sodium can flux into this cell, into this membrane, so the cell can't fire an action potential.

Not all channels have the three states: voltage-gated sodium channels have all three of these states, but voltage-gated potassium channels don't have an inactivation phase, and that's important for their hyperpolarisation.

Slide 11

It's worthwhile now to just look in more detail at how the voltage-gated sodium channel moves between these three states across the actual action potential. In number one, number two and number three, we have the channel and how it's responding, and in number four and number five, we have the trace of the action potential that you saw in the previous couple of slides. In number one here, at the resting condition, the gate is closed. No sodium can flux across the ion, and the neuron is at its resting membrane potential, at rest.

Number two, we have this incoming electrical stimuli. This causes voltage-dependent activation of the gate, and as you see now, this starts to allow sodium to flux into the cell down towards number three. This sodium causes a depolarisation of the cell, moving it from a more negative to a more positive

component. And if this component is above the minus 55 millivolt triggering threshold, then we get rapid opening of many more sodium channels, and we get this large depolarisation phase classically seen in the action potential.

As mentioned here now in number four, about half a millisecond after this activation state, because of the change in potential - if you look, the intracellular space has become more positive because of this sodium - this charge-dependent mechanism causes this ball and chain mechanism to be taken up into the pore of the ion channel, and it physically blocks the ion channel, preventing sodium flux, so the cell can't become more depolarised.

For example, equilibrium potential - if you remember back to the resting membrane potential - for sodium is somewhere in the region of 50 millivolts. But you can see here in this example, because it's now blocking sodium influx, we're only getting to about 30 millivolts on the depolarisation phase here.

As the potassium channels now begin to open in the background and we have this hyperpolarisation phase - you can see that on the right here, number five - and as the resting membrane potential is restored, the normal charge spread across the membrane, where it's more negative in intracellular space, is recovered, and the ball and chain mechanism simply is removed from the ion channel. At this stage, the gate closes again, so the channel is back in its resting condition ready to fire the next action potential.

It's this ball and chain mechanism that's considered important, or is important, for the absolute refractory period, this important point when a neuron cannot fire another action potential until it has restored its normal mechanism and its normal gate in the closed state.