NBL 355-655 Module 7 Review Q&A

1. *For graded/electrotonic potentials, the membrane potential decreases (decays) as a function of time and distance away from where the transmembrane current is produced. Why?*

The membrane potential will decrease/decay with time and distance away from where the initial transmembrane current occurred that changed the membrane potential. (This decrease is also said to dissipate or spread.) This happens because ions move/diffuse in the cytoplasm and along the inside of the membrane. Ion movement is current. Ions move in solution (either within the cytoplasm, in the extracellular solution or across the membrane) because of the two forces on an ion: chemical diffusion and Coulomb forces. (The same forces that produce the driving force which affect an ion’s ability to move across the membrane, also affect the movement of those ions once they are in the cytoplasm or ECF.) As the ions move away from their source of entry, the ions will diffuse away from the membrane and into the cytoplasm or be transported back across the membrane, or leak across the membrane via leak channels. The movement of ions along the inside of the membrane and in the cytoplasm is called the axial current. As the ions move away from the inside of the membrane, the membrane potential will return to the RMP.

2*. Why do neurons need an “active” change in the membrane potential (the action potential) for long distance signaling? (What does the action potential overcome?)*

If there were only passive flow of current (and passive change in the membrane potential) down the axon, the membrane depolarization would decrease/decay with distance and time, and return to resting potential before reaching the end of the axon. (Hence the signal from the presynaptic cell would be very weak or nothing, and no or only a little communication at the synapse would occur.) The action potential overcomes the issue of decay/decrease by providing a mechanism for regenerating a change in the membrane potential. The AP is regenerated without loss (without decrement) all the way to the end of the axon, the presynaptic region.

*3. When a neuron receives synaptic inputs and produces postsynaptic potentials (the graded potentials), where do these membrane potentials spread in a neuron and where does summation of membrane potentials occur? Where in the neuron is this summation most important?*

The current and changes in membrane potential they produce spread everywhere in the neuron. The currents spread/travel along every membrane in the neuron (dendrites, cell body, even axons) and change the membrane potentials. Therefore summation occurs at every membrane all the time. However, the place in the neuron where summation is important is at the initial segment of the axon hillock, because this is where the action potential is generated.

*4. What are the three main functions of the axon? Describe the general features/characteristics of the action potential.*

The three main functions of axon are to trigger/generate action potentials, transmit/conduct action potentials along the length of the axon, and induce synaptic transmission at the axon presynaptic region (which involves transforming the action potential electrical information into the release of neurotransmitter). An action potential, or nerve impulse, is produced, when the summed membrane potential reaches a value greater than threshold, which is about -55 mV at the axon hillock initial segment. Threshold can be different for different types of neurons and ranges from about -47 mV to -57 mV. The AP is a transient (very short-lasting) change in the membrane potential (rise-depolarization and fall-repolarization). Features of the AP: All or none and usually lasts about 3-4 msec. The AP is regenerated so it is transmitted without decrement as it propagates in space and time along the axon. The AP only occurs in excitable cells (neurons and muscles). Usually APs don’t occur only once but occur in sets/trains/series. Information is encoded (the neural code) in the rate/frequency and/or pattern and/or total number/unit time. For a given neuron, the AP has a characteristic shape, time course and speed of propagation (that is similar but not identical to other APs).

*5. In evolving action potentials for long distance signaling, neurons overcome the passive decay/dissipation/spread/decrease of the membrane potential with time and distance away from the cell body. However, in evolving action potentials, what big “problem” did the neuron then encounter?*

As discussed above, if there were only passive flow of current (and passive changes in the membrane potential) down the axon, the membrane depolarization would decrease/decay with distance and time, and return to close to the resting membrane potential before ever reaching the end of the axon and presynaptic region. (Hence the signal from the presynaptic cell would be very weak or nonexistent and no or little synaptic communication would occur.) The action potential overcomes the issue of this decrease/decay by providing a regenerating change in the membrane potential. The AP is regenerated without loss all the way to the end of the axon. However, the problem that is created is that the action potential is all-or-none (requiring only threshold to produce it). Thus, the neuron loses the ability to encode information about how much summed graded activity that is present in the neuron, in the output of a single AP itself. Therefore, neurons must encode information about how much activity is occurring in the neuron by using some aspect of the number of APs being fired, in the frequency and/or timing and pattern of action potentials being generated.

6. *Why is the action potential generated at the initial segment of the axon hillock? What determines threshold for a neuron to fire an action potential?*

Threshold is determined by the voltage sensitivity of the voltage gated (VG) Na+ channels, and their localization and density at the initial segment of the axon hillock. Threshold can be different for different types of neurons and ranges from about -47 mV to -57 mV. The initial segment is where the action potential is generated because it is the first place along the axon where the VG Na+ channels are localized and concentrated. Beyond the initial segment, the VG Na+ channels are localized and concentrated along the entire length of the axon in an unmyelinated axon, but only at the nodes of Ranvier in a myelinated axon (we have not covered this yet but will describe it in subsequent lectures).

*7. Describe the phases of the action potential in terms of changes in the membrane potential and the ionic currents that underlie the AP, as a function of time. What specific types of ion channels underlie each phase of the AP?*

First, the membrane potential must reach the threshold membrane potential, about -55 mV. This is produced by summed graded potentials generated by synaptic responses. Once threshold is reached, when an action potential is triggered, the membrane potential increases rapidly (the rising phase) to between +20 to +40 mV (the peak) within about 1 msec. This is followed by a repolarization of the membrane potential back to the resting membrane potential which takes about 1.5 msec (the falling phase) and then a hyperpolarization when the membrane potential drops even lower (more negative) than resting membrane potential (the undershoot) for about 1 msec, and then the membrane potential increases back to the resting membrane potential (-67 mV).

Activation/opening of the voltage gated Na+ channels produces the increased permeability/conductance to Na+ and an inward Na+ current, during the depolarization/ rising phase, and then the Na+ conductance decreases during the repolarization/falling phase. Activation/opening of the voltage gated K+ channels produces an increased permeability/conductance to K+ during the repolarization/falling phase and leads to the outward K+ current. This is followed by an additional outward K+ current that occurs by opening of additional types of K+ channels. These additional K+ channels eventually close and the membrane potential returns to the resting membrane potential.

Summary:

Rising Phase (0-1 ms):

Membrane potential increases from -55 mV to +20-+40 mV

Increased Na+ conductance (because of activation of VG Na+ channels)

Inward current (into the cell due to Na+ influx)- this is considered a negative current

Falling Phase (1-2.5 ms):

Membrane potential decreases from +40 mV to about -67 mV

Increased K+ conductance (because of activation of VG K+ channels)

Outward current (out of the cell due to K+ efflux) –this is considered a positive current

Undershoot Phase (2-3 ms):

Membrane potential falls below -67 mV and then increases back to -67 mV

A small amount of K+ conductance (additional K+ channels are activated)

Outward current (because additional K+ channels are open)

*8. Describe the overall structure of and how voltage gated Na+ channels work, including what the three states of the channel are, where is and what is the role of the voltage sensor region, and what is meant by the inactivation gate and channel inactivation. What does the inactive channel require to get back to the closed-activatable state? How do you think VG Na+ channels are so selective for Na+ over other ions?*

Voltage gated Na+ channels open in response to the change in voltage (the depolarization) of the membrane potential above about -55 mV. The three states of the channel are closed-active, open, and closed-inactive. The channel protein is composed of four sets of six membrane spanning domains (24 MSDs in all). The transmembrane region S4 is the “voltage sensor” region that senses the membrane potential voltage and changes its position (conformation) when there is a depolarization of the membrane potential beyond threshold. When S4 moves, it transmits a conformational change to the channel region, opening it. S4 is composed of an alpha helix with positively charged amino acids (arginine and lysine) on one side of the alpha helix. After the channel is open, the channel-inactivating segment (aka the inactivation gate) binds to the channel pore regions and blocks the channel, keeping it closed. The only way that the VGNa+ channel can open again is by returning first to the closed-active state, which requires repolarization to the resting membrane potential (RMP). Then if threshold is reached again, the VGNa+ channels can be activated/opened.

*9. What effect does the inactivation of the voltage gated Na+ channel have on the amplitude and duration of the AP? What would the AP amplitude and duration look like if voltage gated Na+ channels did not inactivate? What impact would that have?*

Inactivation of the VG Na+ channels contributes to the repolarization of the membrane potential back to the RMP. If VG Na+ channels didn’t inactivate then the membrane potential would initially depolarize to a level between the normal peak (of about +30 mV) and the Nernst potential for Na+ (+60 mV) and then very slowly repolarize as the VG K+ channels open and allow K+ to flow out. Without VG Na+ channel inactivation, since both VG Na+ and VG K+ channels would be open, the membrane potential would slowly repolarize but to only about 0 mV. The axon would become persistently depolarized to 0 mV, which would induce continuous synaptic transmission output from that neuron, even without any synaptic input to that neuron.

*10. Describe the fast positive cycle of the AP. If VG Na+ channels rapidly inactivate, what does the fast positive cycle of the AP affect and lead to?*

In the fast positive cycle, activation of VG Na+ channels leads to an inward Na+ current, which further depolarizes the membrane potential, which activates more VG Na+ channels. Once the first group of VG Na+ channels are activated, they inactivate, so even though the membrane potential is depolarized at the initial segment, the channels that opened originally become closed-inactivated. However, if there are nearby closed-active VG Na+ channels in the neighboring membrane region, they will become activated and opened by the membrane depolarization produced by opening the first set of VG Na+ channels and they allow Na+ to flow in, depolarizing the membrane. Hence the fast positive cycle allows for the initial generation of the AP and then propagation (movement) of the AP along the axon.

*11. Describe the structure of a voltage gated K+ channel. What are the two states of the channel? Where is and what is the role of the voltage sensor region? What aspect of the AP do the voltage gated K+ channels affect?*

VG K+ channels are similar in structure to VGNa+ channels except that they are composed of four separate proteins that each have 6 transmembrane spanning domains (TSD). They are also called delayed rectifier K+ channels. In each subunit, the S4 TSD is the voltage sensor, and it has several positively charged amino acids along one side of the TSD. VG K+ channels are different from VGNa+ channels in that they open more slowly, and in addition, the majority of VG K+ channels don’t have an inactivation domain/gate, and hence most VGK+ channels don’t inactivate. VG K+ channels affect the peak amplitude of the AP and the rate at which the AP repolarizes. The time it takes to repolarize the AP determines the relative refractory period.

*12. Why is it important that voltage gated K+ channels open more slowly than voltage gated Na+ channels? What would happen (to the amplitude of the AP) if VG K+ channels activated/opened at the same rate as the VG Na+ channels? What would this impact?*

It is important that VG K+ channels open more slowly than VG Na+ channels, since it ensures there will be an initial large depolarization of the membrane potential, from the RMP of -67 mV, up to about +20 to +40 mV. If the VG K+ channels opened at the same rate as the VG Na+ channels, the membrane would depolarize to only about 0 mV. This would mean that the AP amplitude (magnitude) would not be as large. This might affect both AP conduction and synaptic transmission.

*13. Describe the slow negative cycle of the AP. Thinking about this, why don’t voltage gated K+ channels need to inactivate to close? Describe the mechanism underlying the undershoot phase.*

In the slow negative cycle, membrane depolarization activates VG K+ channels, which open and K+ flows out, which repolarizes the membrane potential back to the RMP. When the membrane potential repolarizes back to the RMP (through the activity of the VGK+ channels), the VG K+ channels will close (since they require depolarization above threshold to open). Therefore, the VG K+ channels don’t need to inactivate because their activity (which allows K+ to flow out and repolarize the membrane potential), brings the membrane potential back to the level that closes the VG K+ channels.

*14. In what ways do the driving forces for Na+ and K+ change during the AP? Consider before, peak, and undershoot. What are the two reasons why the peak of the AP gets close to but not as positive as ENa+? Why does the undershoot of the AP get very close to the EK+?*

Initially, at the RMP, the driving force for Na+ is very large (-67 mV -60 mv)= -127 mV. But as the AP proceeds and the membrane potential becomes depolarized to its peak of about +30 mV, the driving force for Na+ decreases to (+30mV -60 mV)= -30 mV. At the undershoot the DF for Na+ increases (-67 -84 mv = -151 mV). Then as the membrane returns to the RMP, the DF for Na+ returns back to -127 mV.

The reverse is true for K+, where initially (at the RMP), the DF for K+ is small (-67- -84 mV)= +17 mV. But as the AP proceeds to the peak of +30 mV, the DF for K+ increases to (+30 - -84 mV) = +114 mV. As the membrane potential repolarizes and at the undershoot, the DF for K+ would be -84mV - -84 mV =0. Then as the membrane potential returns to the RMP, the DF for K+ returns back to +17 mV.

*15. What is the absolute refractory period, and what determines it? What does the absolute refractory period affect concerning the direction of AP conduction and maximal frequency of AP generation, and why?*

The absolute refractory period (ARP) is the time during which the VG Na+ channels are closed-inactivated, and thus are unable to facilitate any further Na+ current and membrane depolarization, no matter how much excitatory activity the neuron receives. During the ARP, no matter how much summed activity that is occurring in the neuron, the neuron can’t generate another action potential. The ARP (about 1 msec) sets the theoretical maximum rate of AP generation. (Since the ARP is ~ 1 msec, the max rate of APs is about 1000/sec, or 1000 Hz.) The ARP also ensures that the AP travels in one direction toward the presynaptic terminus and not back along the axon to the cell body.

*16. What is the relative refractory period, and what determines it? What would the AP time course look like if there were a lot more or a lot f ewer voltage gated K+ channels? How could that affect the rate/frequency of AP generation?*

VG K+ channels affect the time course of the falling phase of the AP, and therefore determine the relative refractory period (RRP). More VG K+ channels would lead to faster AP repolarization, and a shorter RRP, which would mean that a new AP could be produced more rapidly, which would allow a faster rate/frequency of APs. Fewer VG K+ channels would lead to a slower AP repolarization and a longer RRP, and would mean that a new AP could not be generated for a longer time, and decrease the rate/frequency of APs. VG K+ channels also have a small effect on decreasing the peak magnitude/amplitude of the AP. It contributes (along with the inactivation of the VG Na+ channels) to make the peak of the AP less than the Nernst potential for Na+.