NBL 355-655 Module 4 Review Q&A

1. *Describe chemical diffusion. What does the rate of chemical diffusion in aqueous solution depend on?*

From Wikipedia: “Diffusion is the net movement of molecules or atoms from a region of high concentration (or high chemical potential) to a region of low concentration (or low chemical potential) as a result of random motion of the molecules or atoms. Diffusion is driven by a gradient in chemical potential of the diffusing species.” Chemical diffusion in aqueous solution depends on the temperature and pressure, the concentration gradient, and the chemical mass and nature (e.g. hydrophobic/hydrophilic) of the chemical.

1. *The rate of diffusion of a molecule across a lipid bilayer is dependent on what characteristics of that molecule? What is meant by “the lipid bilayer has selective permeability” (which molecules are permeable and which are not)? What is meant by “biological membranes have selective permeability” (which molecules are permeable and which are not)? How does a biological membrane produce/achieve selective permeability?*

The rate of diffusion across the lipid bilayer depends on the mass of the molecule and whether it is hydrophobic (nonpolar) or hydrophilic (polar uncharged or polar charged). Selective permeability of the lipid bilayer mean that only specific atoms or molecules can move across the bilayer. For the lipid bilayer, the selective permeability is a result of the lipid/hydrophobic nature, so only small hydrophobic molecules can diffuse easily across the lipid bilayer, while hydrophilic molecules can not. For a biological membrane, selective permeability means that the membrane allows only specific ions or molecules to move across the membrane (through transmembrane protein channels, transporters or carrier). Hence, the movement of ions or small molecules is dependent on the existence of a channel, transporter or carrier that provide a physical route for the ion or small molecule to move across.

1. *Briefly describe passive and active transport. What are the two types of passive transport? Describe each. What are the two types of active transport? Describe each. In what important ways are active and passive transport similar and different?*

The two main categories of transport across the membrane are active transport and passive transport. Active transport requires energy and moves molecules against/up their concentration gradient, whereas passive transport does not require energy and moves molecules along/down their concentration gradient. The two types of passive transport are simple diffusion (hydrophobic molecules diffuse directly across membrane) and facilitated diffusion (hydrophilic molecules cross the membrane through an open channel or carrier). The two types of active transport are primary active transport (which uses ATP hydrolysis directly) and secondary active transport (which takes advantage of another preexisting concentration gradient). Both transport mechanisms are similar in that they can move ions/small molecules across the membrane. They are different in whether they move ions along or against their concentration gradient and whether they require energy. Also many ion channels are gated (they are closed or open) while most transporters work constantly.

1. *Describe how the Na+/K+ ATPase/pump works. Why is it called an ATPase? Why is it called a pump? What gradients does it directly establish and maintain in the neuron? What gradients can it indirectly affect? What property makes it electrogenic and how much does this contribute to the resting membrane potential?*

For the Na+/K+ ATPase/pump, three Na+ are pumped out of the cell for every two K+ pumped in. It requires energy from ATP hydrolysis. In the entire cycle of ion movement, ATP is hydrolyzed into ADP and inorganic phosphate. It is called a pump because it pumps ions against their concentration gradient. It establishes and maintains the Na+ and K+ gradients. It can indirectly affect the transport of many molecules, including Cl-, glucose, neurotransmitters, amino acids, bicarbonate, phosphate, which all use either the Na+ and/or K+ gradients with secondary active transporters to move molecules against/up their concentration gradients. The Na+/K+ ATPase moves one net positive charge out of the cell per cycle. This positive ion contributes to the resting membrane potential, but only a small amount, about -10 mV.

1. *What are the five major types of primary active transporters in cells?*

The Na+/K+ ATPase, the Ca2+ ATPase, and the H+ (proton) ATPase are expressed in all cells, and the H+/K+ ATPase is expressed in cells in the stomach. There is also a family of proteins called the ATP-binding cassette transporters (ABC transporters), which are a transport system superfamily that is one of the largest and possibly one of the oldest gene families. In ABC transporters, the ATPase subunit utilizes the energy of ATP hydrolysis to provide the energy needed for the translocation of substrates across membranes, either for uptake or for export of the substrate. Different ABC transporter genes are expressed in different types of cells and are specific for the transport of different molecules, including lipids, cholesterol, steroids, peptides, ions, vitamins, and toxins.

1. *All cells, even non-excitable cells, have a Na+/K+ ATPase. What is this necessary for? What types of molecules do secondary transporters transport? Why are these important in neurons?*

All cells (including neurons) need essential hydrophilic nutrients such as amino acids, water soluble vitamins, and sugars such as glucose and lactate. For many of these, the Na+ gradient, which is established by the Na+/K+ ATPase, is used to provide the energy for secondary active transporters in both excitable and non-excitable cells, to bring these nutrients into the cell.

1. *Although there are individual ionic gradients, the overall (bulk) extracellular and intracellular solutions are isotonic and isosmotic. Why is this important? Since there is about 10 times less Cl- in the cytosol compared with the ECF, what provides the anions inside the cell that ensures it is electrically neutral? Is this an equilibrium or steady state situation and why? Are these ionic gradients fairly stable?*

Overall, even though there are ionic gradients for the individual ions, there are the same total number of positive and negative charged atoms/molecules in the cytoplasm and extracellular fluid. There are also the same number of total solutes (including uncharged molecules) inside and outside the cell. This is important to maintain the isosmotic and isotonic situation, so that cells don’t rupture or shrink, which could disrupt cellular functions and/or cause cells to die. There is 11.5 times less Cl- in the cytoplasm than in the ECF, but the cytoplasm has many proteins with negative charges (glutamate and aspartate) on their surface, as well as phosphate, F-, I-, sulfate, acetate and bicarbonate to make up the difference and keeps the negative charges balanced.

For ionic gradients, this is a steady state situation (not equilibrium) and requires a constant hydrolysis of ATP to maintain the gradients. Ionic gradients are fairly stable (since the pumps are continuously pumping ions).

1. *Intracellular organelles and vesicles also contain transporters. Name three types and where they are located.*

Synaptic vesicles contain the H+ ATPase/pump, which is a primary active transporter that transports H+ into the synaptic vesicle. Synaptic vesicles also contain neurotransmitter transporters, which are secondary active transporters that transport neurotransmitters inside the synaptic vesicle (using the H+ gradient.) The endoplasmic reticulum (ER) contains a Ca2+ ATPase/pump, which is a primary active transporter that pumps Ca2+ inside the ER.

1. *The word “transport” can be used to describe different processes in neurons, and this can be confusing. Describe the “transport” mechanisms that have been discussed in this course.*

In the previous Modules we learned about “transport” of cargoes (vesicles and organelles) in fast axonal transport in the axon, which involves microtubules and microtubule motors. In Module 4 we discussed the “transport” of vesicles in membrane trafficking, in both the secretory/biosynthetic and endosomal pathways. The transport vesicles are vesicles that contain lipid bilayers, transmembrane proteins, and in some cases they contain secreted cargoes on the inside/lumen, and are intermediates used in membrane trafficking. Secretory vesicles are the vesicles that but off the TGN and then traffic to the area near the plasma membrane and then undergo exocytosis to fuse with the plasma membrane.

In this Module (5), we’ve discussed the “transport” of small hydrophilic molecules (such as ions, amino acids, and sugars) across the lipid bilayer; this is also called transmembrane transport. This requires transmembrane proteins including transporters, channels and carriers. As described in more detail above, there are two types of transmembrane transport, called passive transport (typically involving channels) and active transport (involving primary and secondary active transporters).

1. *Active transporters use energy to establish the individual ionic chemical gradients. Because ions are charged particles, ionic gradients have electrochemical potential. Define the electrochemical potential. Every ion has its own chemical gradient and charge/valence, and thus each ion gradient has a specific electrochemical potential. The movement of ions can be used to do work. What is an important example of a chemical gradient used to do work?*

From Wikipedia: Each chemical species (for example, "water molecules", "sodium ions", "electrons", etc.) has an electrochemical potential (a quantity with units of energy) at any given point in space, which represents how easy or difficult it is to add more of that species to that location. If possible, a species will move from areas with higher electrochemical potential to areas with lower electrochemical potential; in equilibrium, the electrochemical potential will be constant everywhere for each species (it may have a different value for different species). For example, if a glass of water has sodium ions (Na+) dissolved uniformly in it, and an electric field is applied across the water, then the sodium ions will tend to get pulled by the electric field towards one side. We say the ions have electric potential energy, and are moving to lower their potential energy. Likewise, if a glass of water has a lot of dissolved sugar on one side and none on the other side, each sugar molecule will randomly diffuse around the water, until there is equal concentration of sugar everywhere. We say that the sugar molecules have a "chemical potential", which is higher in the high-concentration areas, and the molecules move to lower their chemical potential. These two examples show that an electrical potential and a chemical potential can both give the same result: A redistribution of the chemical species. Therefore, it makes sense to combine them into a single "potential", the electrochemical potential, which can directly give the net redistribution taking both into account.

The electrochemical potential is defined as the electrical energy stored in the chemical gradient for a charged ion or molecule. Work is involved in the production of ATP by the proton motive force used by the ATP synthase in mitochondria. The H+ gradient (proton motive force) is used to do work and produce ATP in cellular respiration.

1. *The Nernst equation calculates the \_\_\_\_\_ potential stored in a chemical gradient. The Nernst potential is also called the Equilibrium potential (a term used for a single ion in an isolated system). The Nernst/Equilibrium potential is the membrane potential at which there would be no \_\_\_\_. State the Nernst equation. What does the Nernst potential for each ion depend on? Given the ionic gradients provided in the lecture notes, be prepared to show the calculation of the Nernst/equilibrium potential for K+, Na+, Cl- and Ca2+.*

The Nernst equation calculates the electrochemical potential stored in a chemical gradient (for a charged atom or molecule). The Nernst/Equilibrium potential is the membrane potential at which there would be no net movement of ions across the membrane (for a particular chemical gradient).

Nernst equation: Ex = 60 mV/z x log [ion]out /[ion]in  where z is valence/charge of ion.

The Nernst potential (Ex) depends on only the concentration gradient of the ion and the valence/charge of the ion. The chemical gradients are stable and do not change significantly when healthy neurons signal and the valence of an ion does not change. Therefore, the Ex for each ion in a healthy neuron is essentially constant. However, the Ex for each ion can be different for different neurons and muscle cells, depending on their specific ion concentration gradients. Note the Nernst Potential is the same as the Equilibrium Potential and is usually denoted as Ex, such as ENa+

Note, some of you may have learned about the Nernst Potential in previous courses. You may have seen the constant as +58, -58, +59, or -59 mV instead of +60 mV in my lecture. How can this be?

The constant depends on temperature and thus if the cell is at room temperature the constant would be about 58 mV, but at body temperature, the constant is about 62 mV. I use 60 mV which is about the average between these, and I find easier to use for mental calculations. What about the +58 or -58. You remember that the log of x = -log 1/x. In my version of the equation, it’s +60/z x log [outside]/[inside]. But for the other versions you may see, if the concentration ratio is expressed as [inside]/[outside], then the constant would need to be negative. In other words +60/z x log [outside]/[inside] equals -60/z x log [inside]/[outside].

I think my version is easier for quick calculations.

1. *Define a) electric charge; b) an ion; c) the Coulomb force; d) an electric field, e) electric potential energy; f) electric potential and g) membrane potential.*

a) Electric charge is the physical property of matter that causes it to experience a force when placed in an electromagnetic field. There are two types of electric charge: positive and negative (commonly carried by protons and electrons respectively). If there are more electrons than protons in a piece of matter, it will have a negative charge, if there are fewer it will have a positive charge. The unit of electric charge is the coulomb.

b) An ion is an atom (or group of atoms) that has lost one or more electrons, giving it a net positive charge (cation), or that has gained one or more electrons, giving it a net negative charge (anion). Monatomic ions are formed from single atoms, while polyatomic ions are formed from two or more atoms that have been bonded together, in each case yielding an ion with a positive or negative net charge.

c) The Coulomb force is the electrostatic force that acts between two electric charges. The Coulomb force (F) depends on the Coulomb constant (C), the amount/magnitude of each of the charges (q1 and q2), divided by the square of the distance between them. F= C q1 x q2 /r2. Hence the closer charges are to each other, the greater the Coulomb force.

d) An electric charge has an electric field. (Sometimes it is described that an electric charge produces or induces an electric field, or that an electric field surrounds an electric charge.) An electric field is a region around a charged particle, within which a force would be exerted on other charged particles. The strength of an electric field is described as Newtons per coulomb, or volts per meter. A Newton is a unit of force, and equals a force that produces an acceleration of one meter per second (s) per second on a one kilogram (kg) mass.

e) When a charged particle (such as an ion) is placed in an electric field, it has electric potential energy that describes how much stored energy it has. Electric potential energy is the potential energy stored when charges are out of equilibrium. To instill a charged particle (such as an ion) with electric potential energy, we have to do work to move it over a distance and separate it from other charges. The unit of electric potential energy is the Joule.

f) The electric potential (also referred to as the electric potential difference) is the electric potential energy per unit charge (Joules per coulomb). The electric potential is defined as the amount of work needed to move a unit of charge from a reference point to a specific point inside an electric field without producing acceleration. The unit of electric potential is Volts, which is equal to Joules per coulomb.

g) The membrane potential is a type of electric potential and is expressed in millivolts (mV). Sometimes it is called the potential difference between the outside and inside of the membrane. It should technically be called the transmembrane potential since it’s the potential difference across the membrane.

1. *What are the two mechanisms that neurons use to communicate? What are the two types of electrical signaling? Describe the overall information flow through neurons.*

The two mechanisms that neurons use to communicate are electrical signaling and chemical signaling. The two types of electrical signaling are the action potential and graded/electrotonic potentials. The action potential is for long distance signaling from the cell body along the axon to the presynaptic terminus. Chemical synaptic transmission involves the release of neurotransmitters from the presynaptic axon and the binding of neurotransmitters by receptors on the postsynaptic neuron. Neurotransmitters bind to ionotropic receptors and lead to the generation of postsynaptic potentials: EPSPs and IPSPs (which are graded/electrotonic potentials). EPSPs and IPSPs are generated at synapses, which are predominantly located on dendrites, dendritic spines and the cell body. Membrane potentials flow/move along the membrane and summate with each other to increase or decrease the membrane potential at the cell body. If there is sufficient depolarization of the membrane at the initial segment of the axon hillock, an action potential will be generated and then propagated along the axon to the presynaptic terminus where it leads to synaptic transmission, and activation of either EPSPs or IPSPs at the postsynaptic neuron.

1. *About how many synapses does an average neuron have (how many different synaptic inputs does a neuron receive)? Where are these synapses located? What responses do synapses produce?*

A typical neuron receives thousands of synaptic inputs from other axons. The majority of these occur on dendrites, dendritic spines if the neuron has spines, and on the cell body/soma. A few can occur on the axon and/or presynaptic terminus. In synaptic transmission between neurons, the responses are called excitatory postsynaptic potentials (EPSPs) which are depolarizing responses and inhibitory postsynaptic potentials (IPSPs) which are hyperpolarizing responses.

1. *What is the membrane potential? Describe the movement of electrons in aqueous solution. What aspects of the membrane potential involve the movement of electrons?*

The membrane potential is the difference in electric potential between the inside and the outside of a membrane (expressed in voltage), produced by separation of charges across the membrane. The membrane potential is present only at the surface of the membrane. The membrane potential is found on all regions of the plasma membrane in all cells. The size of the membrane potential depends on how many ions are separated across the membrane that are affecting each other. Free electrons **DO NOT** diffuse or flow in aqueous solution and therefore **NO** aspects of the membrane potential involve the movement of free electrons. **ALL** charge movements in cells involve only **IONS**.

1. *What are the three main types of membrane potentials that neurons have and what are the features of each? Which of those involve a change in the membrane potential? Why are IPSPs, EPSPs, and receptor potentials called graded potentials (or electrotonic potentials)? How are graded potentials different from the action potential?*

The three main types of membrane potentials that neurons have/use are the resting membrane potential, the action potential (AP) and the graded/electrotonic potentials. The AP and graded/electrotonic potentials are the membrane potentials that involve rapid changes. IPSPs and EPSPs are called graded because their size (magnitude) and duration (time course) depend on how much synaptic signaling occurs. They can be small or large depending on how much synaptic signaling occurs. In contrast, the action potential is all-or-none. If threshold is reached, an AP will be generated and it doesn’t reflect how large the summed response was that produced it. Graded/electrotonic potentials are usually smaller than action potentials, and can be depolarizing (EPSPs) or hyperpolarizing (IPSPs).

1. *In addition to water, what are the three components required to establish and change the membrane potential? What two properties of biological membranes make them good components for their role in establishing and maintaining the membrane potential?*

To establish and change the membrane potential, a neuron needs ions, ion transporters, and ion channels. The fact that biological membranes are thin and selectively permeable makes them good components for their role in establishing and maintaining the membrane potential. By being thin, the separated charges can influence (attract) each other (producing the electric potential).

1. *What the two main categories of ion channels and types of channels in each category?*

The two categories of ion channels are ungated and gated ion channels. The ungated channels are called leak channels. There are four types of gated channels that include the voltage-gated channels, ligand-gated channels, mechanically gated channels and temperature-gated channels (which are not depicted in the lecture notes).

1. *What are leak ion channels? How are they different from gated ion channels? How is the resting membrane potential (RMP) established? What is the relative ratio of K+, Na+, and Cl- leak channels in the neuronal plasma membrane? What is the basis of this ratio? What effect does the greater abundance of leak K+ channels have on the RMP?*

Leak channels are ion channels that are always open at all times, unlike gated channels, which are only open during certain times (e.g., at a specific membrane voltage or when they bind a neurotransmitter or are activated by pressure). There are ~20-40x more K+ leak channels than Na+ leak channels, and ~3-15x more K+ leak channels than Cl- leak channels. This ratio is based on the number of ion channel proteins that are expressed for each specific type of channel in the plasma membrane. The number of proteins expressed is regulated by gene expression.

Since there are many more K+ leak channels than Na+ and Cl- leak channels, more K+ will flow out across the membrane (down its chemical gradient) than the other two ions flowing in. Because more K+ flows from inside the cell to outside via the K+ leak channels (leaving behind the anions), a net negative charge is established on the inside of the membrane and a net positive charge is formed on the outside of the membrane. Eventually when the electric force of the membrane potential opposes the force of chemical diffusion, and there will be no net movement of K+ across the membrane.

1. *How much does the Na+/K+ ATPase directly contribute to the RMP?*

The Na+/K+ ATPase is electrogenic (it pumps 3 Na+ ions out for each 2 K+ ions in) and contributes only about -10 mV to the RMP. One reason the Na+/K+ ATPase may not have a more significant contribution to the RMP is because many of the Na+ ions that are pumped across the membrane are immediately used by secondary active transporters to move nutrients inside the cell.

A summary from Wikipedia: Because the membrane permeability for K+ is much higher than that for other ions, and because of the chemical gradient for K+, K+ ions flow from the cytosol into the extracellular space carrying out positive charge, until their movement is balanced by build-up of negative charge on the inner surface of the membrane. Again, because of the high relative permeability for K+, the resulting membrane potential is almost always close to the Nernst/equilibrium potential for K+. (But it’s often slightly more positive because there is a small contribution from the leak Na+ channels and leak Cl- channels.) In order for this process to occur, a concentration gradient of K+ must first be set up. This work is done by the ion pumps/transporters and/or exchangers and is powered by ATP.

1. *What would the RMP be if there were no leak channels? What would the RMP be if there were the same number of K+ and Na+ leak channels? What would the RMP be if ATP were depleted from the cell (by poisoning the mitochondria)? (How would depleting ATP affect the chemical gradients?)*

If there were no leak channels, the resting membrane potential would be about -10 mV, since the Na+/K+ ATPase is electrogenic but there would be no additional movement of ions across the membrane through ion channels. If there were the same number of Na+ and K+ leak channels, the membrane potential would also be about -10 mV. If ATP was rapidly depleted from the cell, the RMP would be close to 0 because the Na+/K+ ATPase/pump would not be able to function, and with no concentration gradient, ions would not have a chemical gradient. Without a chemical gradient, there would be no diffusion of ions, and the resting membrane potential would be 0 mV.