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Membrane physiology and the basis of excitability

Ref: Guyton, 12th ed. pp: **57-69**, 11th ed: **p57-71**, 10th Edition, **p52-66.**

MEMBRANE POTENTIALS AND ACTION POTENTIALS:

MEMBRANE POTENTIAL:

If we assume that a cellular membrane is permeable **only** to K+, which is found in a very high concentration inside the cell. K+ will diffuse to the extracellular fluid because of the concentration gradient. The diffusion of K+ will result in a movement of positive charges outside the cell and leaving behind negative charges inside the cell. This will create an electrical potential difference across membrane (positive outside and negative inside). Creation of this potential difference will oppose diffusion of K+ to the outside at a certain concentration difference. When you reach a point at which diffusion of K+ is completely opposed by the potential difference created across membrane and the net diffusion for K+ is zero even though you still have a concentration gradient, you have reached the equilibrium potential for K+ (E_K). The equilibrium potential for any univalent ion at normal temperature can be calculated by Nernest equation:

$$E\ (mV) = -\ 61.\log\ (Ci/Co)$$

E = equilibrium potential for a univalent ion
Ci = concentration inside the cell.
Co = concentration outside the cell.

When more ions are involved in creating the potential, we can calculate the potential according to Goldman-Hodgkin-Katz equation.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{Na+}[Na^+]_o + P_{K+}[K^+]_o + P_{Cl-}[Cl^-]_i}{P_{Na+}[Na^+]_i + P_{K+}[K^+]_i + P_{Cl-}[Cl^-]_o} \right)$$

P = permeability of the membrane to that ion.

In this equation, Goldman and his colleagues considered that these ions are mostly involved in the development of membrane potential.

According to this equation the permeability of the membrane to an ion is very important in determining the membrane potential. If the membrane is permeable only to K+ and not permeable to Cl- and Na+, the membrane potential will be equal to E_{K+}.

Resting membrane potential:

In excitable cells the membrane potential is not constant. When the cell is stimulated, the membrane potential changes. These changes in membrane potential are due to changes in permeability of plasma membrane to different ions. For example, when neuron is stimulated, this will result in increased permeability to Na+. This will bring the membrane potential closely to E_{Na}. The recorded membrane potential for a cell under resting conditions when no stimulus is involved is known as **resting membrane potential**. For neurons the recorded resting membrane potential is about (– 90 mV). This represents a potential difference between the inside to the outside when neuron is not active.

Origin of resting membrane potential:

Contribution of K+ diffusion:

As mentioned earlier, if the membrane is permeable only for K+ the calculated E_{K+} is about (-94mV).

Co_{K+} = 4meq/l , Ci_{K+} = 140meq/l

E_{K+} = -61. log 140/4 = -94mV

Which is not far from the recorded membrane potential but not exactly.

The contribution of Na+ diffusion:

Membrane is also permeable to Na+. The permeability of the plasma membrane for Na+ is much less than that of K+. If the membrane is permeable only to Na+, the calculated E_{Na+} = + 61mV.

…… (Co_{Na+} = 142meq/l , Ci_{Na+} = 14meq/l).

Because of the permeability of the membrane for the two ions, the E would be between (-94mV and +61mV). The calculated E for the two

ions is –86mV, which is not far from the E_{K+} because of the higher permeability of membrane for K+ than for Na+ (100 times more).

So the Na+ contribution in resting potential is by bringing the membrane potential to a lower value than the calculated E_{K+}.

Contribution of Na+ - K+ pump:

As mentioned earlier, this pump is electrogenic. It moves more positive charges outside the cell (3 for 2). This will induce loss of positive charges from the cell and bring the membrane potential to a higher negativity (about –4mV additional negativity).

Therefore all these factors, during **rest**, will give a net membrane potential of –90mV (called **Resting Membrane Potential**).

ACTION POTENTIAL:

As we have seen, the plasma membrane is **polarized** (has ability to separate opposite charges) during resting state. When the membrane potential decreases (becomes less negative), the membrane is in **depolarization** stage. While the change in membrane potential in opposite direction (becomes more negative than resting potential) is known as **hyperpolarization**.

When a cell is depolarizing, it reaches a maximum according to stimulus, then the membrane potential returns to its resting state. The phase of returning from depolarized state to resting state is known as **repolarization**. These changes in membrane potential can be recorded by placing one electrode inside the cell and the other out side the cell. By recording of whole action potential in this way, we will obtain a **monophasic action potential**.

Let us consider the changes in membrane potential of an excitable cell to understand the events that appear during changes of membrane potential. To induce a change, a stimulus must be applied to change activity of channels at the membrane. Any increase in permeability of membrane to Na+ will result in diffusion of (+) charges inward. This event will decrease the membrane potential (becomes less negative). And conversely any increase in K+ diffusion (movement outward) will result in an increase in membrane potential (becomes more negative). The diffusion of these ions depends on the activity of Na+ and K+ channels that are found on the membrane. Activation of Na+ channels will induce depolarization, while activation of K+ channels will increase the potential difference across membrane.

Action potential and the role of Na+ channels:

On the membrane, most Na+ channels during resting state are inactive (closed). According to channel type, these channels can be activated by a chemical stimulus (in case of chemical gated channels), electrical stimulus (in case of voltage gated channels), or mechanical stimulus. In the case of chemical gated channels, binding of ligand to its receptor will induce activation of chemical gated Na+ channels. Once activated, the membrane potential will decrease (becomes less negative). Which means that the membrane depolarizes. The voltage changes in the membrane will cause the other type of channels (Na+ voltage gated channels) to be activated. Activation of these channels will cause more changes in membrane potential (more depolarization). More and more depolarization will occur in the membrane by a positive feed back mechanism. If we reach a point at which most voltage gated Na+ channels are activated, this will cause a sudden increase in Na+ permeability. This increase in Na+ permeability will even reverse the membrane potential (becomes positive inside and negative outside) (this is known as the **overshot** in the action potential), because Na+ is trying to approach its equilibrium potential (E_{Na}). At this point membrane has reached maximal changes in membrane potential (a peak of an action potential).

As we have seen, during depolarization there is a point at which a sudden increase in Na+ influx which induces rapid and maximal change in membrane potential. This point is known as **threshold** of an action potential. The rapid change in membrane potential during the raising phase of an action potential is known as **firing stage**. When a stimulus causes a depolarization that brings the membrane potential to the threshold, the membrane will respond by the firing stage of an action potential. If depolarization in the membrane has not reached threshold, the membrane will not enter firing stage, and instead, the potential returns to its resting level. Therefore the response in the membrane will be either by an action potential when threshold is achieved or no appearance of an action potential when the membrane potential has not reached threshold. For that reason induction of an action potential in excitable cells follows the **NONE OR ALL PRINCIPLE**.

The voltage changes in membrane potential not only activate voltage dependent Na+ channels, but also inactivate these channels at certain potential difference. This inactivation appears because channels

have changed their state from opened channels to closed channels due to voltage changes. The closing event of Na+ channels does not make these channels as the only responsible for bringing membrane potential to its resting level. But also, activation of voltage dependent K+ channels is the main player in returning the membrane potential to its resting level.

Action potential and K+ channels:

Although there is some leakage of K+ during resting state, which maintains the resting membrane potential close to E_{K+}, depolarization causes activation of voltage gated K+ channels. The activation of these channels is much slower than activation of Na+ channels. This results in a delay in the maximal activation of K+ channels.

The delayed activation of K+ channels combined with inactivation of Na+ channels will result in a rapid returning of the membrane potential to its resting level causing the **falling phase** in the action potential. The membrane potential may go for a while to more negative potential than during resting potential, which is known as **positive afterpotential (after hyperpolarization)**. Followed by a full recovery in membrane potential (returns completely to its resting level). The positive after potential is probably due to an excess in K+ efflux, which causes more deficit of positive ions inside the cell.

Action potential and Ca++:

As discussed before, the raising phase of an action potential results by fast activation of Na+ channels. These are called *fast channels*. In some excitable cells, like cardiac muscle and uterine muscle, cells are equipped with another type of channels known as *slow* Na+ – Ca++ *channels*. These channels are activated at slower rate than Na+ channels. The slow and prolonged opening of slow channels will cause mainly Ca++ to enter the cell and prevents the rapid fall induced by activation of K+ channels, and the membrane potential is maintained for a while then the potential falls to its resting level. This is known as **plateau** in action potential. The presence of plateau in this type of cells is important in prolonging the time of an action potential, giving more time for the cell to be able to respond to another stimulus, because the cell remains longer time in **refractory period**.

Refractory periods of an action potential:

During action potential the cell is not able to respond to another stimulus. From the firing stage to the end of first third of falling phase the cell will not respond at all even by a stronger stimulus. In this stage the cell is said to be in **absolute refractory period**. From the beginning of the second phase until the resting membrane potential is achieved the cell

cannot respond the usual stimulus, but a stronger stimulus can change the membrane potential. In this period the cell is in **relative refractory period**.

The periods depend on the activity of Na+ channels. These channels pass three states during action potential. During resting potential, Na+ channels are **closed but capable for opening** when stimulated. During the raising phase (firing), almost all Na+ channels are **opened**. And any other stimulus (even stronger one) will not cause activation of more Na+ channels. During this period the membrane is in absolute refractory period.

In the third state, when voltage dependent Na+ channels become closed after the membrane potential has reached positive values. At this state Na+ channels are not capable for opening. During all the falling phase of an action potential, these channels remain **closed and not capable for opening**. They can pass to the first state (closed and capable for opening) when the membrane potential returns to its normal level or to a more negative potential than resting potential. During this period, the membrane is in relative refractory period. This means that a stronger (suprathreshold) stimulus may activate the closed channels that are not capable for opening by normal stimulation. In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals.

Na+ -K+ pump and action potential:

This pump has **no** role in the electrical activity that are taking place during action potential. But it plays an important role in restoring ionic composition that has been altered during action potential. This role is important in maintaining the ionic composition of the intra-and the extra-cellular fluids.