



# Physiology | Lecture 4 **Plasma membrane of excitable tissues**

**Reviewed by** 

**Members of NST** 



## **Plasma Membranes of Excitable tissues**

In the past sheets, we've talked about transporting particles generally, in this sheet we'll talk about transporting again, but specifically about transporting charged particles through the plasma membrane such as K<sup>+</sup>, Na<sup>+</sup>, Ca<sup>+2</sup>, Cl<sup>-</sup> and so on, what will happen in this case?

As you know, the membrane of our cells separates two compartments: 1- The Extracellular Matrix (ECM), outside the cells. (High concentration of Na<sup>+</sup> ions) 2- The Cytoplasm, inside the cells. (High concentration of K<sup>+</sup> ions)



According to the concentration gradient, K<sup>+</sup> ions have a high tendency to move from the inside toward the outside of the cells, meanwhile Na<sup>+</sup> ions have a high tendency to move from the outside toward the inside of the cells.

Assuming a membrane that is permeable only for K<sup>+</sup> ions, these ions will move from the inside toward the outside of the cell, creating a potential (electrical) across the membrane (negative inside, positive outside) and will reach the equilibrium, but what type of equilibrium? Chemical equilibrium (equal concentrations)? Actually, it won't reach this type of equilibrium, it will get Electrochemical Equilibrium (Electro: from the potential, Chemical: from the concentration).



In this case, reaching Electrochemical Equilibrium doesn't mean reaching Chemical equilibrium, we still have a concentration gradient of K<sup>+</sup> ions, **high** inside and **low** outside, but the number of K<sup>+</sup> ions moving outside is **equal** to the ones that moving inside, and that's due to the <u>Electrochemical Equilibrium</u> part (**electrical potential**).

Another example, assuming a membrane that is permeable only for **Na<sup>+</sup>** ions, these ions will move from the outside toward the inside of the cell, creating a potential across the membrane (**positive inside, negative outside**).



Out O

In O

What if we have a membrane that is permeable only for **Cl**<sup>-</sup> ions? These ions will move from the outside toward the inside of the cell, creating a potential across the membrane (negative inside, positive outside).

What if we have a membrane that is permeable only for **Ca<sup>+2</sup>** ions? These ions will move from the outside toward the inside of the cell, creating a potential across the membrane (**positive inside, negative outside**).

As we are talking about charges, and a lipid bilayer (membrane separating them), we can think about this membrane as an electrical circuit, how is that? :) كمل دراسة بتعرف (:

The symbol A represents a Capaciter (used to separate charges), now you should know that the cell's membrane works as a capaciter, isn't it?

Here is more complicated one (Dr. Mohammad didn't say any details about it, but it's written in the slides):



## **Nernest Equation**

We can calculate the potential across membrane using the **Nernest Equation** if the membrane is permeable for only one ion.

$$E = \frac{RT}{ZF} \ln \frac{[C]_{out}}{[C]}$$

E: Equlibrium, R: Gas constant, T: Absoulte temperaturem Z: ValenceF: Faraday's constant, C: Concentration, out: outside the cell, in: inside the cell.

### **Electrochemical Equilibrium**

$$\Delta G_{conc} + \Delta G_{volt} = \mathbf{0}$$

 $\Delta G_{conc}$ : The energy difference generated by the concentration gradient.

 $\Delta G_{volt}$ : The energy difference generated by the voltage across the membrane.

$$= zFV - RT \ln \frac{[C]_{out}}{[C]_{in}} \to V = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}} \to V = 2.3 \frac{RT}{zF} \log_{10} \frac{[C]_{out}}{[C]_{in}}$$

**R**, **T** and **F** are **constants**, replacing them with their values and when **z=1** for K<sup>+</sup><sub>F</sub>

$$E_{K^+} = 61.54 \log \frac{[K^+]_{out}}{[K^+]_{in}}$$

R, T and F are constants, replacing them with their values and when z=1 for Cl<sup>-</sup>r

$$E_{Cl^-} = 61.54 \log \frac{[Cl^-]_{in}}{[Cl^-]_{out}}$$

**R**, **T** and **F** are **constants**, replacing them with their values and when z=2 for  $Ca^{+2}_{|F|}$ 

$$E_{Ca^{+2}} = \frac{61.54}{2} \log \frac{[Ca^{+2}]_{out}}{[Ca^{+2}]_{out}}$$

To avoid calculating these during the exam, memorize the next table.

lon	Extracellular (mM)	Intracellular (mM)	Nernst potential (mV)         + → positive inside in comparison to the outside.         - → negative inside in comparison to the outside.	
Na⁺	145	15	60	
Cl <sup>-</sup>	100	5	-80	
<b>K</b> +	4.5	160	-95	
Ca <sup>+2</sup>	1.8	10-4	130	

Our excitable cells have a very high permeability for K<sup>+</sup> ions and very low permeability for Na<sup>+</sup> ions, which results in creating potential, which is **negative inside and positive outside**, closer to the equilibrium potential for K<sup>+</sup> ions, but it will never reach it, because we have some permeability for Na<sup>+</sup> ions.

However, there are differences in permeabilities of membranes for ions which create differences in potentials over them, we have some membranes generate potentials equal to -70, -80, -90 and some aren't even excitable.

Let's say we have a membrane with a high permeability for K<sup>+</sup> ions and very low permeability of Na<sup>+</sup> ions, we will get a potential which will be very close to the equilibrium potential for potassium (-95mV), why close to it not equal to it? - Again, because of Na<sup>+</sup> ions, they will make the potential less negative.

As we mentioned, Nernest Equation can calculate the potential for a membrane that is permeable for only one ion, but our cells' membranes are permable for multiple ions, so we need another equation.



## **Goldman Hodgkin Katz Equation**

 $E_{m} = \frac{RT}{F} \ln \left( \frac{P_{Na^{+}}[Na^{+}]_{out} + P_{K^{+}}[K^{+}]_{out} + P_{Cl^{-}}[Cl^{-}]_{in}}{P_{Na^{+}}[Na^{+}]_{in} + P_{K^{+}}[K^{+}]_{in} + P_{Cl^{-}}[Cl^{-}]_{out}} \right)$ 

**P**: Permeability of the membrane to that ion.

The movement of the **chloride ion** from **outside** to **inside** effect is a reversal of the movement of **sodium ion** from outside to inside effect, it also has the same effect of **potassium ion** that is moving from **inside** to **outside**.

We should mention, if we used this equation in case of a membrane is permeable for only one ion, we'll get back to **Nernest equation**.

So far, we've seen two factors that play a rule in modulation of the potential across the membrane:

- 1- **High** permeability for **K**<sup>+</sup> ions.
- 2- Low permeability for Na<sup>+</sup> ions.

We can measure the potential across the membrane using the voltmeter as shown in the picture, we must place the electrodes just at the inside (**not deep**) and just at the outside (**not far**) of the membrane.



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## **Resting membrane potential**

What determines the rest potential?

1. Activity of the K<sup>+</sup> channels (most influential):

The **K**<sup>+</sup> ions move from the inside toward the outside and cause a negative potential for the membrane.

- Contribution of **K**<sup>+</sup> diffusion:

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

 $C_{out}K^+ = 4meq/I \rightarrow C_{in}K^+ = 140meq/I \rightarrow E_{K^+} = 61*log (4/140) = -94mV$ 

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

2. Activity of the Na<sup>+</sup> channels:

The membrane has less permeability for **Na**<sup>+</sup>, so the rest potential will be closer to the equilibrium potential of **K**<sup>+</sup>, but they aren't equal.

- Contribution of **Na<sup>+</sup> diffusion**:

The permeability of the membrane for  $Na^+$  is much less than that of  $K^+$ , so if the membrane is permeable only to  $Na^+$ , the calculated  $E_{Na}^+ = +61$ mV.

Because of the permeability of the membrane for these two ions, the **E** would be between (-94mV and +61mV), the calculated **E** for these two ions is –86 mV, which is not far from the  $E_{K}^{+}$  (because of the higher permeability of membrane for K<sup>+</sup> than for Na<sup>+</sup>  $\rightarrow$  200 times more for K<sup>+</sup> than Na<sup>+</sup>)

#### 3. Activity of the Na+ /K+ pump:

It pumps **3** Na<sup>+</sup> ions from the inside toward the outside and **2** K<sup>+</sup> ions from the outside toward the inside, it can alone create a membrane potential which will be negative inside.

Contribution of Na<sup>+</sup>/K<sup>+</sup> pump:
It produces -4 mV.

All these factors, during rest, will give a net membrane potential of **-90mV**, which is the resting membrane potential.

In this sheet we will talk about membrane at resting state and its properties, which means that the cell is not stimulated by any stimulus so it will have these specific resting properties.

#### NOTES:

1- membrane resting potential can be changed by a stimulus.

2-If we activated **more K<sup>+</sup> channels** the potential will be shifted to **more negative.** 

(Because normally there are more K<sup>+</sup> ions inside the cell so channels will move these ions from **the higher** concentration to **the lower** one, reducing the positive charge inside the cell while increasing it outside in addition increasing the negative potential (charge of the cytoplasm compared to the ECM charge)) **because of the ion's positive charge** 

3- if we activated **more Na<sup>+</sup> channels** the potential will be shifted to **less negative**.

(Because normally there are more Na<sup>+</sup> ions outside the cell, so these ions will move into the cell making the cytoplasm more positive while increasing the negative charge outside of it) **because of the ion's positive charge** 

4-From now on if we are at resting potential **the permeability of K<sup>+</sup> is higher than permeability of Na<sup>+</sup>**.

5-we are talking here about **ions** moving; so instead of saying permeability we say that we are changing the **conductance** of that membrane to that ion.

For example, we can increase sodium conductivity; HOW?

- Simply by activating more Na<sup>+</sup> channels.



In the adjacent pic (red square) at **resting potential** we have about 200 times conductance for potassium than sodium, and because of that we are establishing a resting membrane potential(**-ve**), because of the high conductivity of K<sup>+</sup>.

We can change the conductance by changing the

## Cord Conductance eqn of plasma membrane

### <u>Ohm's law</u>

- I = ΔV/R
- G (conductance)= 1/R
- I = G. ΔV

When we talked about the permeability of particles, we used Fick's law but here we're talking about ions, so we'll use electrical terms.

I: Current.

V: The voltage difference across the plasma membrane (the driving force that moves ions).

**R**: Resistance across the plasma membrane.

**G**: Conductance; how that membrane conducts or lets a specific ion move through it.

(Conductance is inversely proportional with the resistance; so, if we have a **high conductance** for an ion that means we have **low resistance** and vice versa).

- Also, we can measure the whole membrane voltage according to its conductivity for different ions.

It can be calculated by this equation:



## 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 the 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 the 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 is changing. These changes in membrane potential are due to changes in permeability of plasma membrane to different ions. For example, when a 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 the 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).

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

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

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  $E_{Na+} = +61$ mV.

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

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).

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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 outside 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<sub>Na</sub>). At this point, the 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 the **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

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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 full recovery in the membrane 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 a **plateau** in action potential. The presence of plateau in this type of cell 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**.

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Versions	Slide #	Before	After
V0 → V1			Prof's handout added
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