Physiology | Lecture 5

Plasma membrane of excitable tissues

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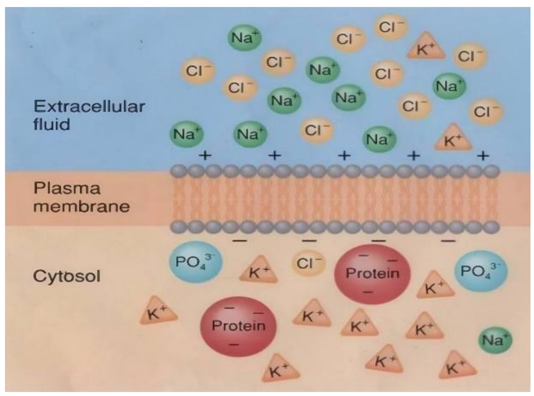
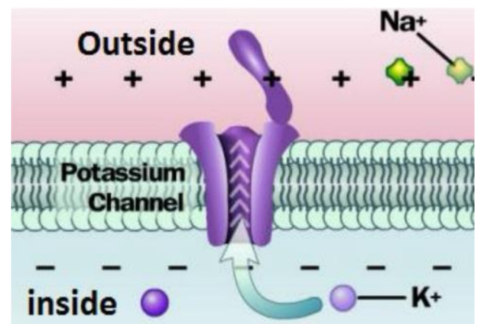
Plasma Membranes of Excitable tissues

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^+, Na^+, Ca^{+2}, Cl^- and so on, what will happen in this case?

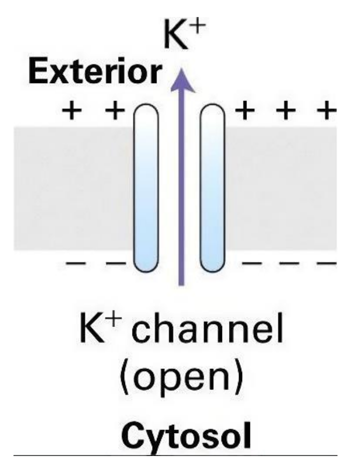
As you know, the membrane of our cells separates two compartments with different compositions:
1- The Extracellular Matrix (ECM), outside the cells. (**High concentration of Na^+ ions**)
2- The Cytoplasm, inside the cells. (**High concentration of K^+ ions**)



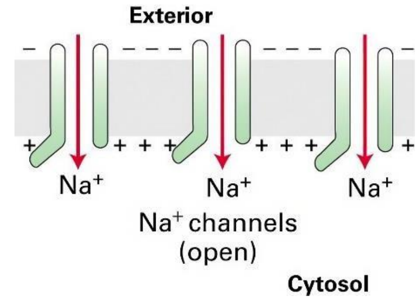


According to the concentration gradient, **K^+** ions have a high tendency to move from the inside toward the outside of the cells, meanwhile **Na^+** ions have a high tendency to move from the outside toward the inside of the cells.

Assuming a membrane that is permeable only for **K^+** 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^+** ions, **high** inside and **low** outside, but the number of **K^+** ions moving outside is **equal** to the ones that moving inside, and that's due to the **Electrochemical Equilibrium** part (**electrical potential**).



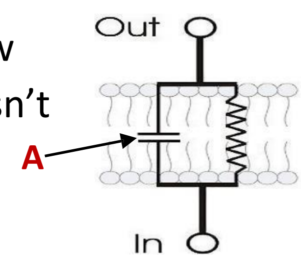
Another example, assuming a membrane that is permeable only for **Na^+** ions, these ions will move from the outside toward the inside of the cell, creating a potential across the membrane (**positive inside, negative outside**).

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

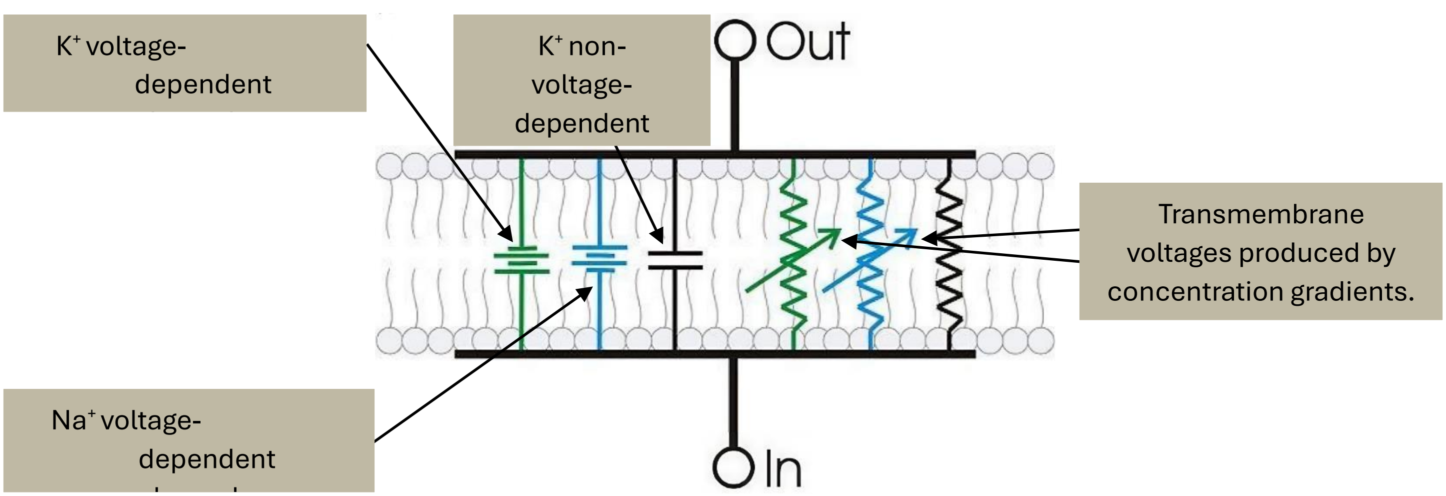
What if we have a membrane that is permeable only for **Ca^{+2}** ions? These ions will move from the outside toward the inside of the cell, creating a potential across the membrane (**positive inside, negative outside**).

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.

$$E_{ion} = \frac{RT}{zF} \ln\left(\frac{[ion]_o}{[ion]_i}\right)$$

E: Equlibrium, R**:** Gas constant, T**:** Absolute temperature **Z**: Valence
F: Faraday's constant, **C**: Concentration, **out**: outside the cell, **in**: inside the cell.

Electrochemical Equilibrium

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

Then we can say that:

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

ΔG_{conc}: The energy difference generated by the concentration gradient.

ΔG_{volt}: The energy difference generated by the voltage across the membrane.

(It depends on charge which depend on the valance of the particle **(z)**)

$$0 = zFV - RT \ln \frac{[C]_{out}}{[C]_{in}} \rightarrow V = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}} \rightarrow V = 2.3 \frac{RT}{zF} \log_{10} \frac{[C]_{out}}{[C]_{in}}$$

R, **T** and **F** are **constants**, replacing them with their values and when **z=1** for K^+:

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

R, **T** and **F** are **constants**, replacing them with their values and when **z=1** for Cl^-:

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

لماذا وضع تركيز ايون الكلور في الداخل في الأعلى؟

Z for Cl^- **= -1** :وبتطبيق القانون باستخدام هذه القيمة تصبح

$$E_{K^+} = \frac{61.54}{-1}\log\frac{[Cl^-]_{out}}{[Cl^-]_{in}}$$

وباستخدام خاصية اللوغاريتم:-log(a/b) = log(b/a) نعود لصورة القانون المكتوبة سابقا حيث اجعل التركيز بالداخل في الاعلى

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

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

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

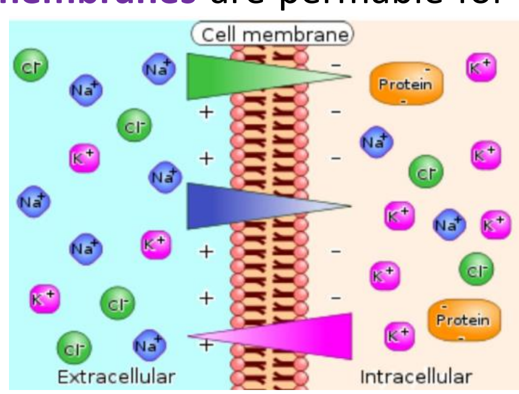
Ion	Extracellular (mM)	Intracellular (mM)	Nernst potential (mV) + → positive inside in comparison to the outside. - → negative inside in comparison to the outside.
Na^+	145	15	60
Cl^-	100	5	-80
K^+	4.5	160	-95
Ca^{+2}	1.8	10^{-4}	130

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

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

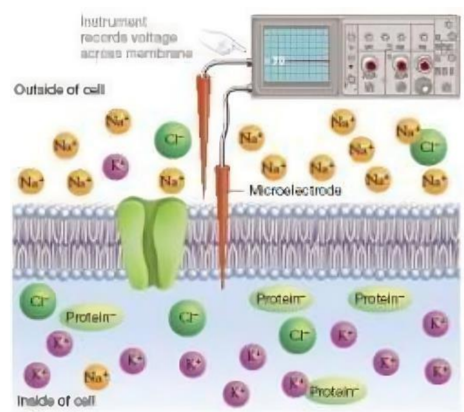
We should mention, if we used this equation in case of a membrane is permeable for only one ion, we'll get back to **Nernest equation**.

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

1- **High** permeability for **K^+** ions.

2- **Low** permeability for **Na^+** 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.



Resting membrane potential

What determines the rest potential?

1. Activity of the K^+ channels (**most influential**):
The K^+ ions move from the inside toward the outside and cause a negative potential for the membrane.

- Contribution of **K^+ diffusion**:
As mentioned earlier, if the membrane is permeable only for K^+, the calculated $\mathbf{E_K^+}$ is about (-94mV):
$C_{out}K^+ = 4meq/l \rightarrow C_{in}K^+ = 140meq/l \rightarrow E_K^+ = 61*\log(4/140) = -94mV$

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

2. Activity of the Na^+ channels:
The membrane has less permeability for Na^+, so the rest potential will be closer to the equilibrium potential of K^+, but they aren't equal.

- Contribution of **Na^+ 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 $\mathbf{E_{Na}^+}$ = +61mV.

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 $\mathbf{E_K^+}$ (because of the higher permeability of membrane for K^+ than for Na^+ → 100 times more for K^+ than Na^+)

3. **Activity of the Na+ /K+ pump**:
It pumps **3 Na^+** ions from the inside toward the outside and **2 K^+** ions from the outside toward the inside, it can alone create a membrane potential which will be negative inside.

- Contribution of **Na^+/K^+ 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^+ channels** the potential will be shifted to **more negative.**

(Because normally there are more K^+ 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^+ channels** the potential will be shifted to **less negative**.

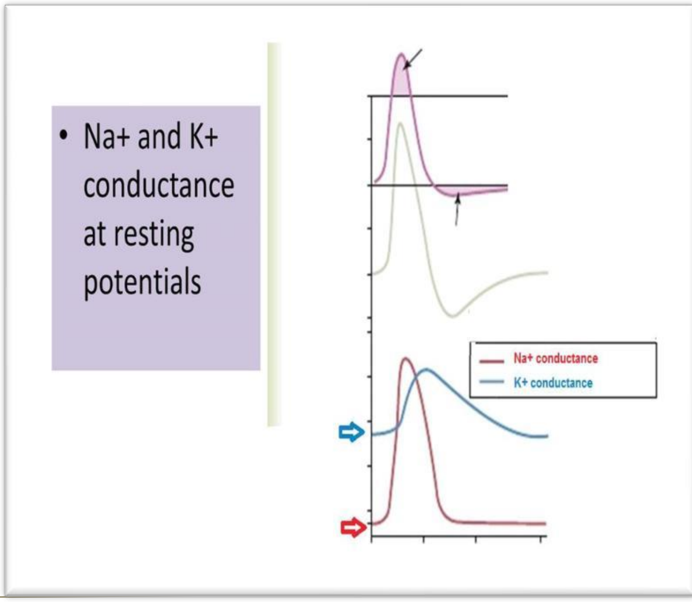
(Because normally there are more Na^+ ions outside the cell, so these ions will move into the cell making the cytoplasm more positive while increasing the negative charge outside of it) **because of the ion's positive charge**

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

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^+ channels.



In the adjacent pic (red square) at **resting potential** we have about 100 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^+.

We can change the conductance by changing the activity of these channels.

Cord Conductance eqn of plasma membrane

Ohm's law

- $I = \Delta V/R$
- G (conductance)= 1/R
- $I = G.\ \Delta V$

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:

The cord Conductance equation describes the contributions of permeant ions to the resting membrane potential

G: Conductance for the ion

G_{tot}: Total conductances

E: Equilibrium potential.

$$V_m = \frac{g_K}{g_{tot}} E_K + \frac{g_{Na}}{g_{tot}} E_{Na} + \frac{g_{Cl}}{g_{tot}} E_{Cl}$$

Measuring currents at a specific membrane potential

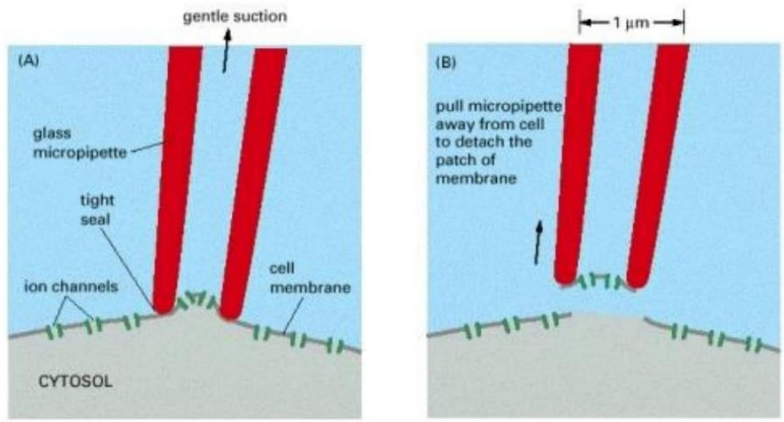
Patch clamp technique

We can measure the activity of different channels at different voltages by measuring the currents of the ions that are moving.

Patch clamp technique: This technique helps to study the behavior of voltage gated ion channels at different membrane potentials.

1.The tip of the pipette that is very small, smaller than the cell, is brought close to the membrane and a gentle suction is applied to seal off a part of the

membrane which contains voltage gated ion channels.



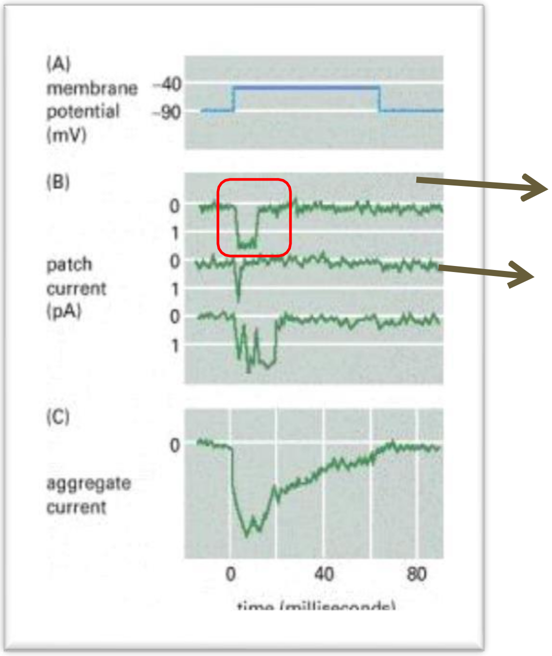
2. A solution that is similar to the ECF (high concentration of Na+) is placed in The pipet and then the whole tip of it is placed in a solution that is similar to the ICF (high concentration of k+).

3. We can change the voltage on the membrane to observe the activity of the voltage gated channels at different membrane potentials. For example, when clamping the membrane potential at +60, there is no Na+ current, whereas there is a current at –60. This means that this channel is voltage gated and opens and closes at specific voltages.

Note: when clamping the potential at –95 mV which is the equilibrium potential for K+ there are no K= currents because it is at equilibrium.

Watch these short videos for more understanding

https://youtu.be/mVbkSD5FHOw



This picture shows the recording of currents in patch
clamp.

A) Shows the voltage applied across the membrane, the potential shifts from -90mV to -40 mV indicating a depolarization.
B) Shows the activity of individual ion channels in
response to voltage change, the downward deflections as the one circled in red indicates ion channel opening.
C) Shows the sum of the currents from multiple channels. The initial sharp downward deflection corresponds to a rapid openinng of channels in response to depolarization

Additional Resources

رسالة من الفريق العلمي:

Success is the sum of small efforts, repeated day in and day out

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