
PHYSIOLOGY
Lec: 12
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Lecture objectives

- Define the resting membrane
- Review the different types of ionic channels in the cell membrane
- Understand ionic basis of resting potential by applying the concept of diffusion potential
- Describe the relation between the resting membrane potentials and K and Na equilibrium potentials
- Describe the contribution of Na-K ATPase pump to the resting potential
- Know the resting membrane of different cell types including neurons, muscle cells (Excitable Tissues)and other cell types of the body
- Describe the effects of hypokalemia, hyperkalemia and hypocalcemia on resting membrane potentails of excitable cells

Excitable tissues and none excitable tissue

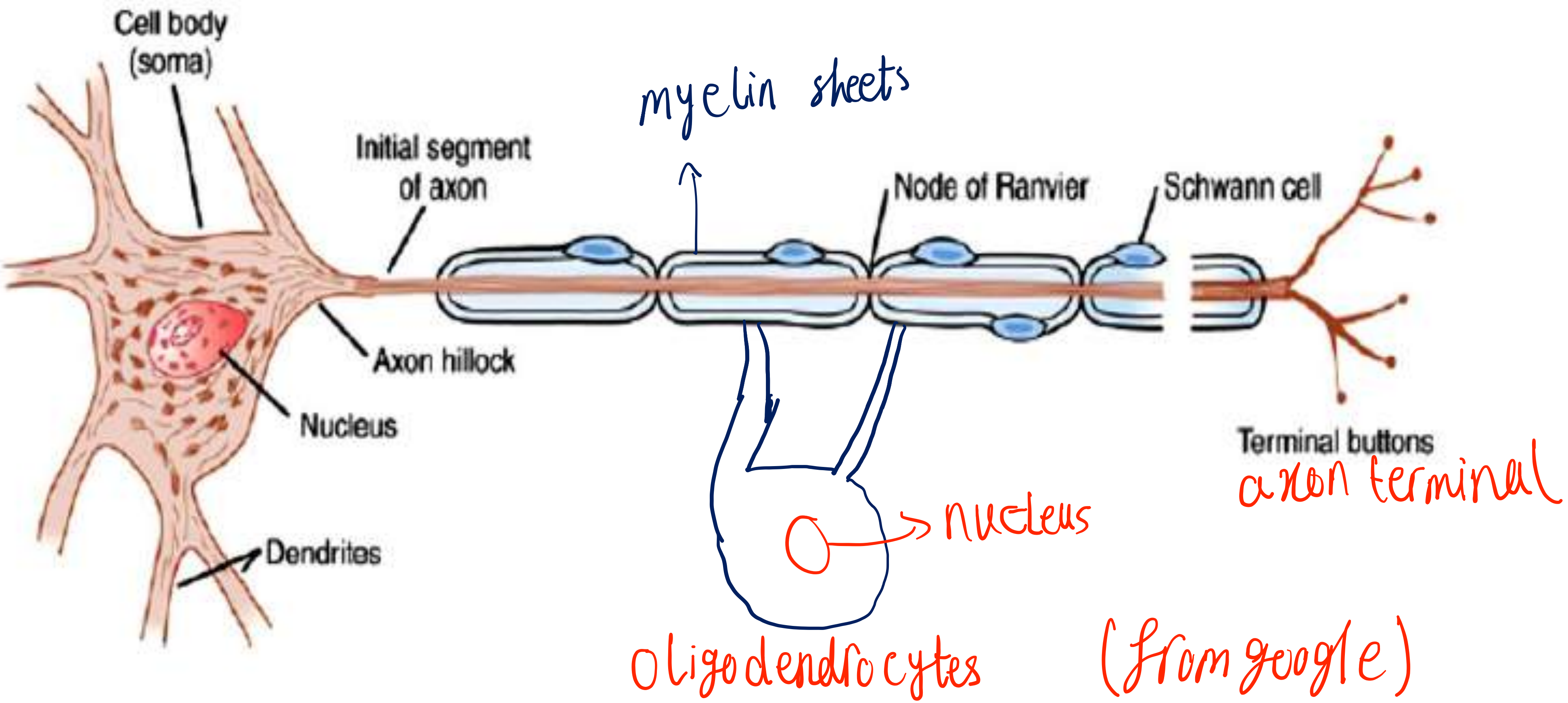
- All cells have resting potential
- None excitable cells like RBC Epithelial cells in the kidney tubules in the gut have lower resring potential the excitable cells
- Excitable tissues include nerve cells and muscle cells . Usually have higher resting potential compared to none excitable cells . Excitable cells such as nerves and muscles have the ability to generate signals(action potential) that may be quickly transmitted to other nerve cells or muscle cells

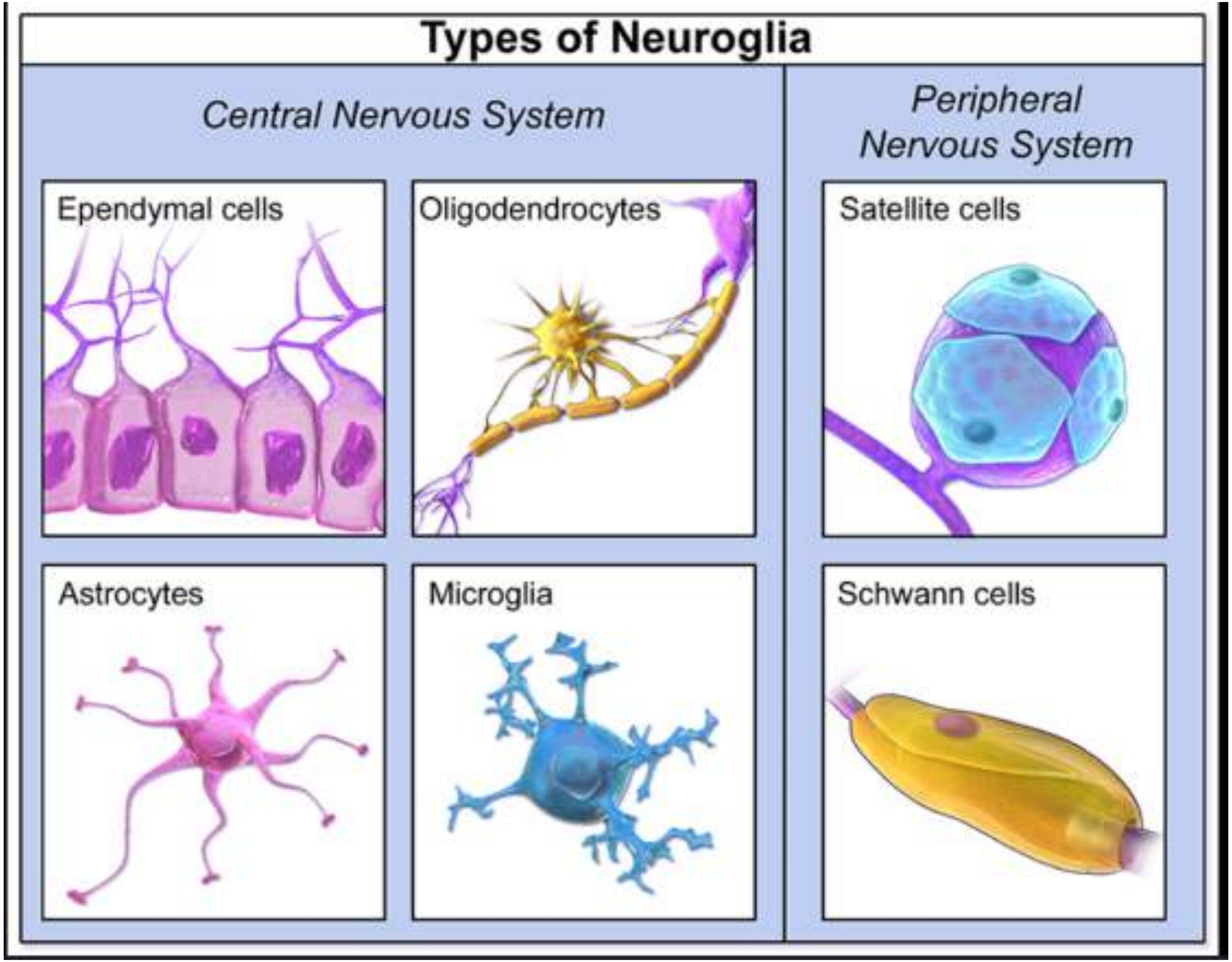
* some cells their membrane potential doesn't change, unless there is a significant change in the concentration, and they do not initiate nerve impulses or action potential, those are called non-excitable cells

* nerve cells (nuerons), muscle cells (smooth, cardiac, skeletal) they have a resting potential, but their membrane potential under certain conditions can undergo rapid change and they initiate whats known as action potential or nerve impulse

* so, when there is a cell that has a resting potential and this cell is stimulated by chemical or electrical or whatever and there's rapid change in the M.P. and an action potential is initiated or a nerve impulse is initiated those cells are called excitable cells

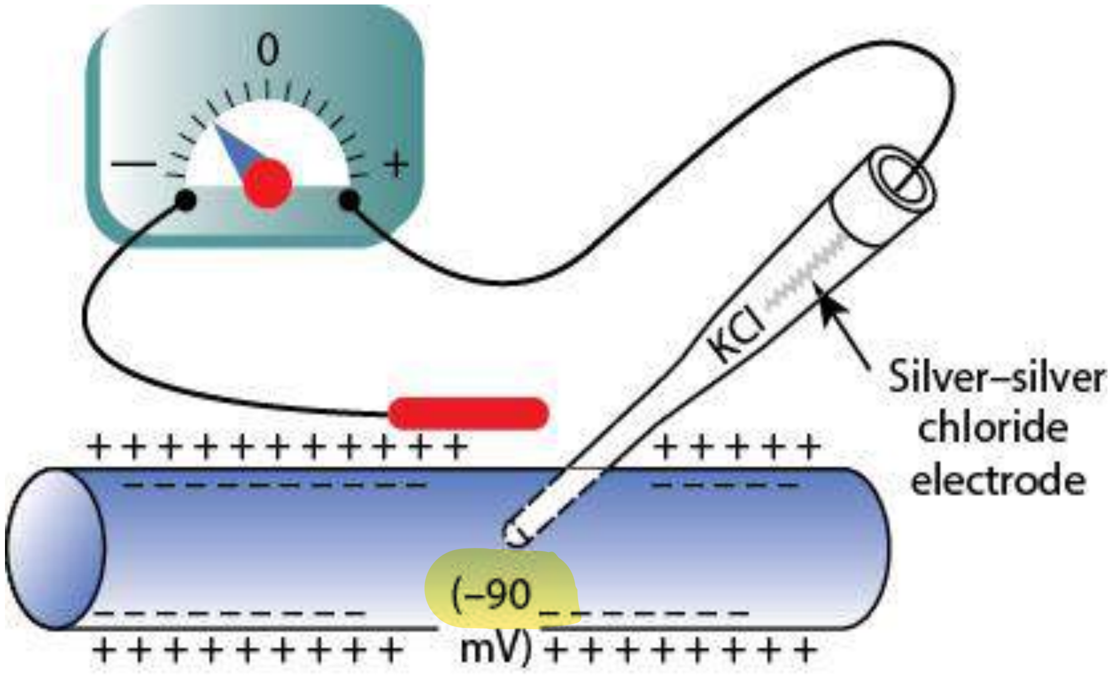
Schematic diagram of a neurons




Types of Neuroglia
Central Nervous System
Peripheral Nervous System
Ependymal cells
Oligodendrocytes
Satellite cells
Astrocytes
Microglia
Schwann cells

Measurement of Resting Membrane Potential (RMP)

RMP is a potential difference across biological membranes, and it reflects the separation of charges across the membrane.
There are a few excess negative charges (about 1 pmol/cm2) on the inner surface and the same number of excess positive charges on the outer surface
The resting membrane potential measured when the cell is at rest—that is, not active
Different cells have different resting potentials.



not all cells are –90mV some are –80, –70 dependig on their location and function

* We measure the R.M.P by inserting a fine electrode (micro electrode) and once we penetrate the cell or the axon of the cell, there will be a potential difference between the inside and outside of the cell, and our RMP is always negative, not all cells are -90mV, they vary depending on the location and their function.

* this is due to the diffusion potential and accumilation of slight negative charges across the cell membrane (not a huge amount) and the negativity is within the vacinity of the membrane.

* inside the cell membrane (nerve cell) in the cytoplasm, if you can somehow insert electrones, you won't see potential difference because there is electrical nuetrality, so we measure it (RMP) just across the cell membrane

Resting Membrane Potential of Different cell

Cardiac muscle are close (-90 mV)

Cell types	Resting potential
Skeletal muscle fibers	-85 to 95 mV
Smooth muscle fibers	-50 to -60 mV
(slide 22) ← Astrocytes	-80 to -90 mV (glial cells of the brain)
Neurons	-60 to -70 mV , -80
Erythrocytes (RBCs)	-8 to -12 mV
Photoreceptor cells	-40 mV (dark) to -70 mV (light)

a massage to take home

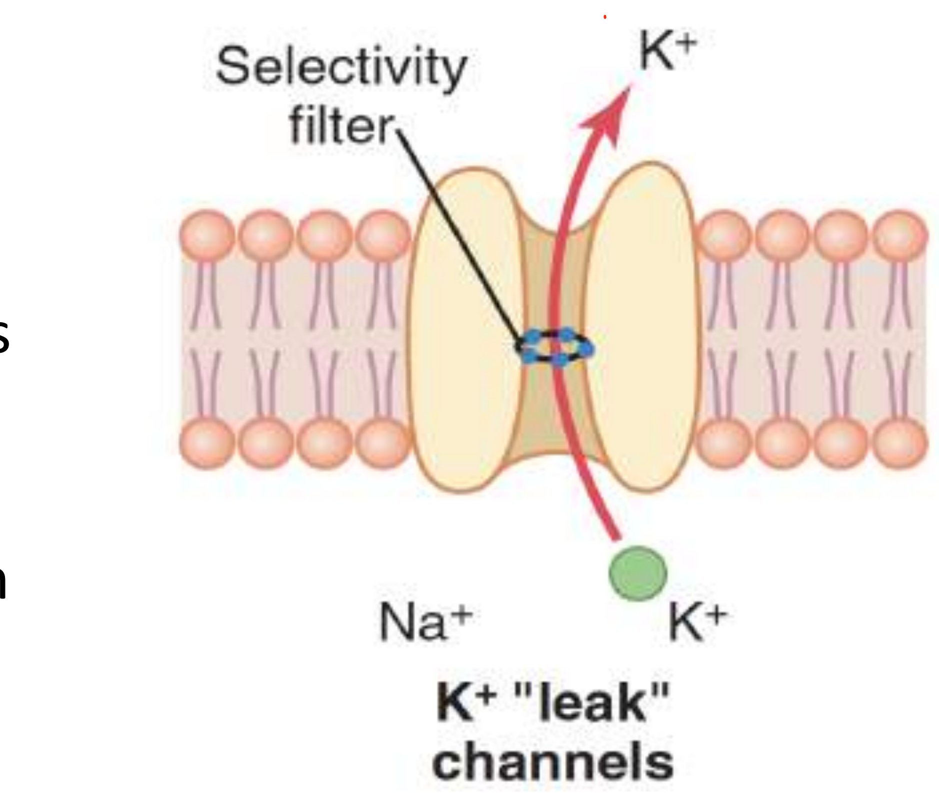
The highest permeability is for the K^+ ions and thats why our RMP is closer to the equilibrium potential of K^+ ions

Leaky Ionic channels in nerve cells

Leak Channels

- Predominately for K Ions
- Some Na Leak channels
- cell membranes of Neurons and muscle cell in resting state are highly permeable to K ions than Na Ions ((100X)

3. Thus the resting membrane potential is mainly determined by the concentration gradients of K ion



* at resting condition the membrane potential, the highest permeability is for the K^+ ions and thats why the RMP is closer to equillibrium potential of the K^+ ions, not only because there is a concentration gradient, but because the membrane potential is closer to K^+ ions (cuz of the high permeability)

A massage to take home:

* Later on, when we have an action potential, everything will be reversed, during one phase of action potential the permeability of the membrane will be the highest for Na^+ ions (momentarily) for a couple of ms

Origin of Resting Membrane Potential of Neurons

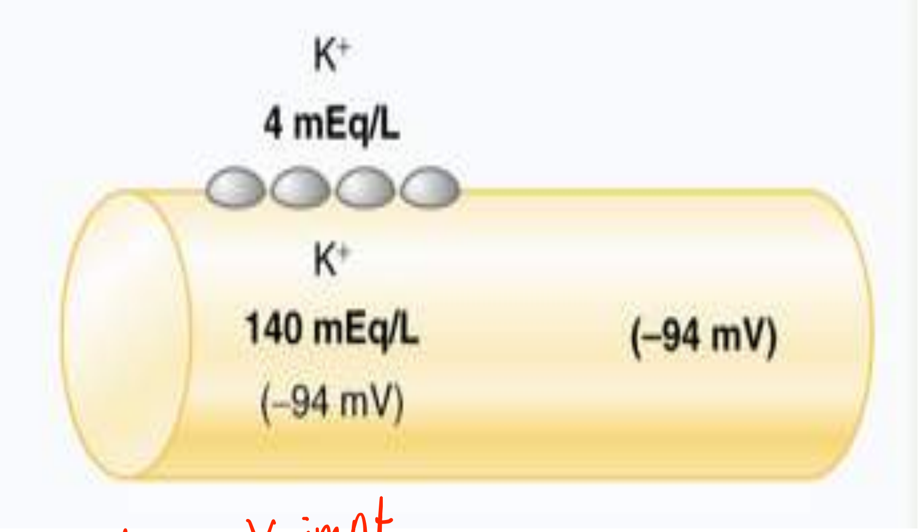
$RMP = -90\ mV$

Contribution of K Diffusion Through the Nerve Membrane

Concentration difference 35 : 1 → K+ Nernst potential =-94 mV

If K+ ion concentration and permeability were the only factors causing RMP → RMP inside the fibber would be equal to −94 millivolts and will be equal to the Nerst potential of K ions

* if the membrane is only permeable to K^+ ion, The (RMP) will be exactly equal to the equilibrium potential of K^+ ions



* note: V. impt
it is good to remember how much is the K^+ ion outside of the membrane (4 mEq/L) because in alot of cases we have electrolytes disturbance happening which affects the part activity

Effects of disturbances of ionic concentration in the ECF on RMP

A massage for today

↑ K^+ ions

- Hyperkalemia : The cell membrane depolarize, (becomes less negative) and the resting potential moves closer to the threshold for eliciting an action potential and the neuron becomes more excitable
- When the K concentration reaches 7 mEq/L can lead to significant hemodynamic and neurologic consequences; levels exceeding 8.5 mEq/L can cause respiratory paralysis or disturbance in heart rhythm and cardiac arrest and can quickly be fata.

└ ↑ of BPM (tachy)

↓ K^+ ions

- Hyporkalemia If the extracellular level of K+ is decreased (hypokalemia), the membrane potential becomes is reduced (becomes more negative) and the neuron or muscles cells are hyperpolarized Changes in ECG are also expected during hypokalemia

(disturbance in the electricity of the heart)

- Effects of hypocalcemia ↓ Ca^{2+}
- A decrease in extracellular Ca2+ concentration increases the excitability of nerve and muscle cells(membrane destabilization) and may lead to hypo calcemic tetany imprompo spasm (muscle spasms)

* normal Ca^{2+} concentration must be present to stabilize the membrane

*Q : assume that the Concentration of K^+ ions is equal inside and outside the cell, what will happen to the membrane potential ?

Ans: zero, Cuz if they are the same, ex: 10^{in} and 10^{out}, when you apply nerst equation it becomes

$$Emf = -61 \times Log\left(\frac{10}{10}\right) \Rightarrow -61 \times Log(1)$$

$$\Rightarrow -61 \times 0 \quad \Rightarrow Emf = 0$$

* we don't mention Na^+ ions a lot about the membrane permeability, but it affects the fluid balance.

Q: does hyperkalemia affect the fluid balance and plasma osmolarity?

Ans: No it doesn't. only Na^+ and maybe glucose and urea

Origin of Resting Membrane Potential of Neurons

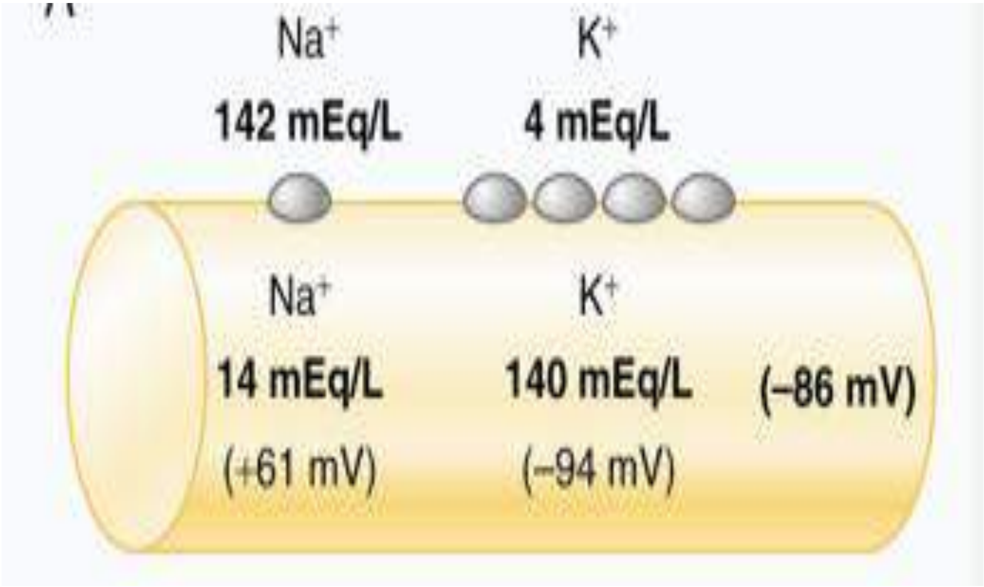
RMP =−90 mV

↓ Permeability of Na^+

Contribution of Na Diffusion Through the Nerve Membrane

Concentration difference 10 : 1 → Na+ Nernst potential =+61 mV

Slight permeability of the nerve membrane to Na+→ minute diffusion of Na Therefore , According to **Goldman equation** → RMP = −86 mV→ close to K potential but not equal to the equilibrium



*Contributes to the R.M.P. :

- mostly :

* The RMP is somwhere between Na^+ (+61mV) and K^+ (-94mV) but you'll find it closer to the K^+ ions cuz of the higher permeability Co ared to that of sodium

- Little bit:

* Na^+ ions diffusion through the membrane

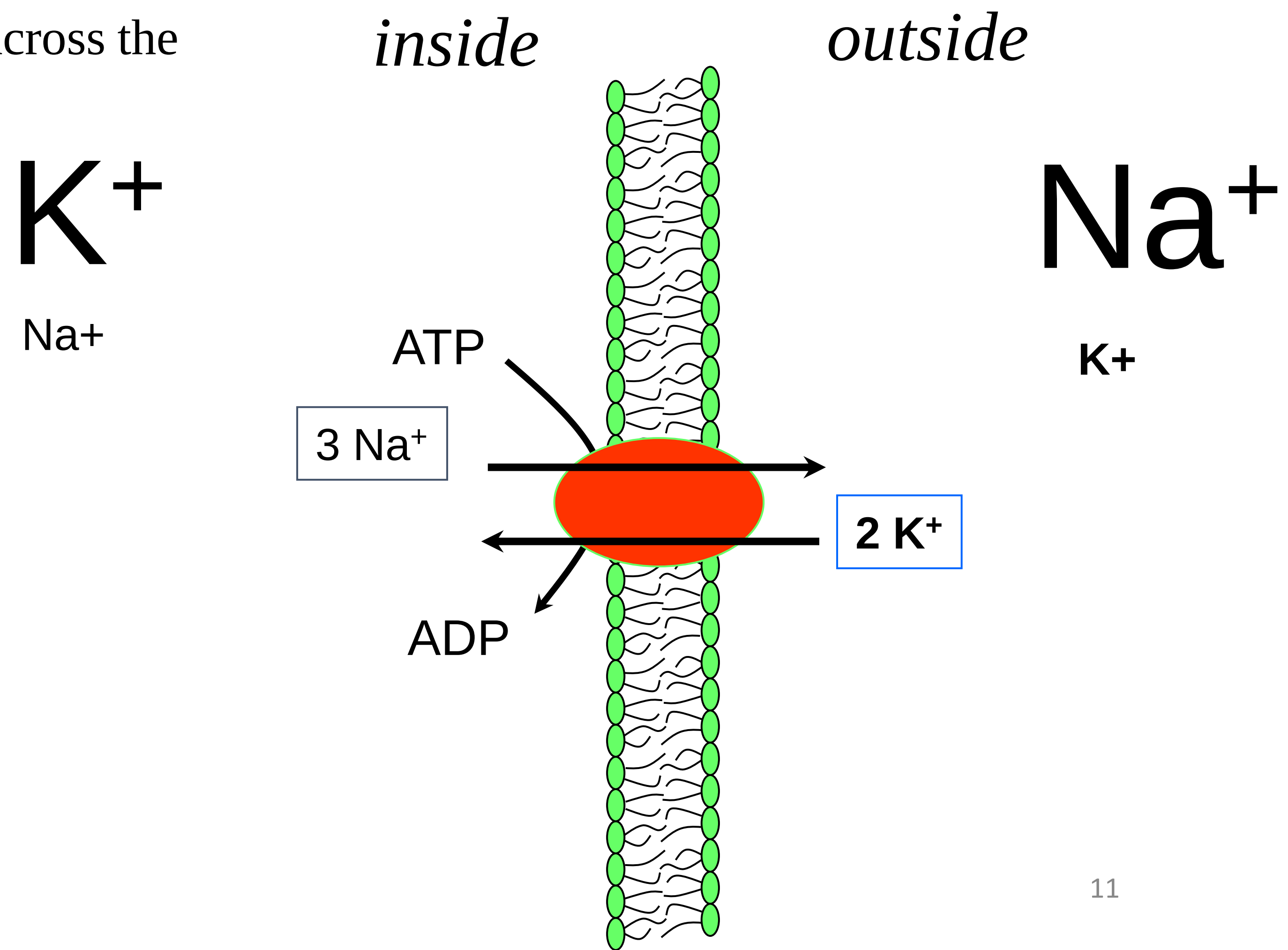
- tiny bit:

* the electrogenic Na^+, K^+ pump (-4mV)

Active Transport of Na^+ and K^+

Electrogenic pump

More positive charges are pumped to the outside than to the inside→ causing **negative** potential inside the cell membrane. Causes **large concentration gradients** for Na & K across the resting nerve membrane.



Origin of Resting Membrane Potential of Neurons

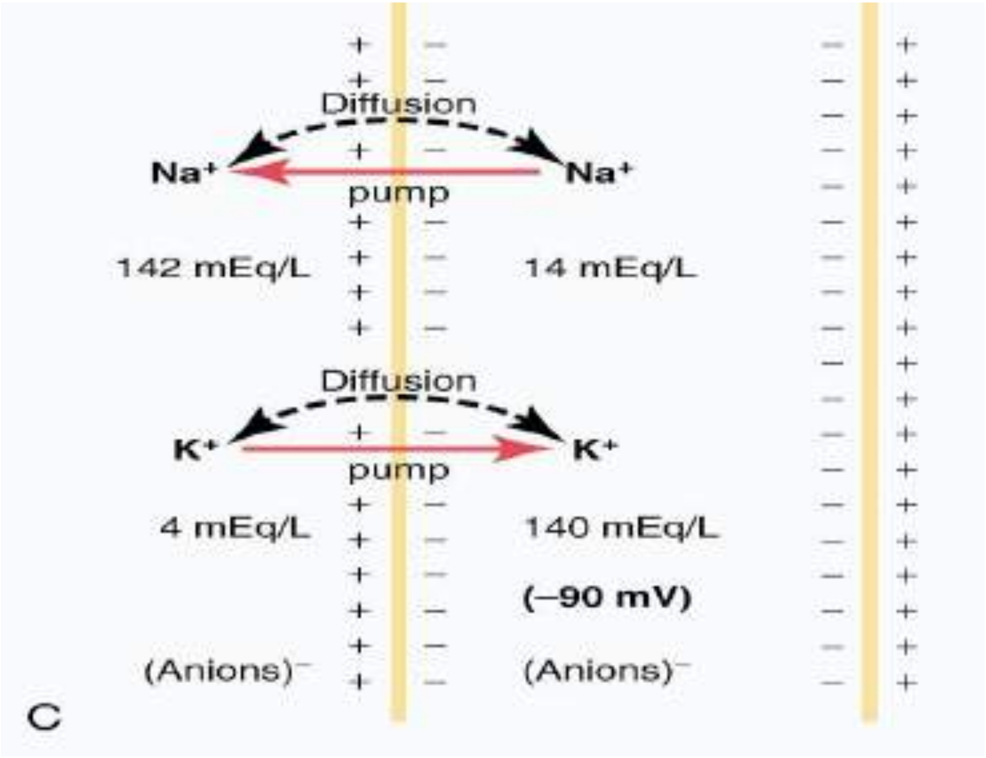
$RMP = -90\ mV$

Contribution of the Na+-K+ Pump

Creating additional degree of negativity (about −4 millivolts additional)→ -86+-4=-90 mV

Na+ K+ diffusion

from the Pump



The Resting Membrane Potential Summary

- Membrane potentials are generated mainly by diffusion of ions and are determined by
  - the ionic concentration differences across the membrane, and
  - the membrane's relative permeabilities to different ions.

Plasma-membrane Na,K-ATPase pumps maintain intracellular sodium concentration low and potassium high.

- In almost all resting cells, the plasma membrane is much more permeable to potassium than to sodium, so the membrane potential is close to the potassium equilibrium potential—that is, the inside is negative relative to the outside.
- The Na,K-ATPase pumps also contribute directly a small component of the potential because they are electrogenic.

Net Driving Force on Ions across the cell membrane

The difference between Electrical Forces (membrane potential) and equilibrium potential of Na^+

- When multiple ions contribute to membrane potential (Vm) of a cell→ membrane potential would **not** be at the equilibrium potential (Veq.) for any of the contributing ions. Thus, no ion would be at its equilibrium (i.e., Veq. ≠ Vm).

- i.e. chemical and electrical forces acting on K+, Na+, and Cl− are not equal→ electrochemical driving force (VDF) acts on the ion, causing the net movement of the ion across the membrane down its own electrochemical gradient.

- VDF = Vm − Veq.

* we take the Electrical Force and the Chemical Force, at equilibrium, the EF should be equal to the CF

* when we have a cell membrane and we have ions that diffuse back and forth, there are 2 Forces which act on an ion, one is the electrical force due to the membrane potential, and the second one is the chemical potential due to the concentration gradient

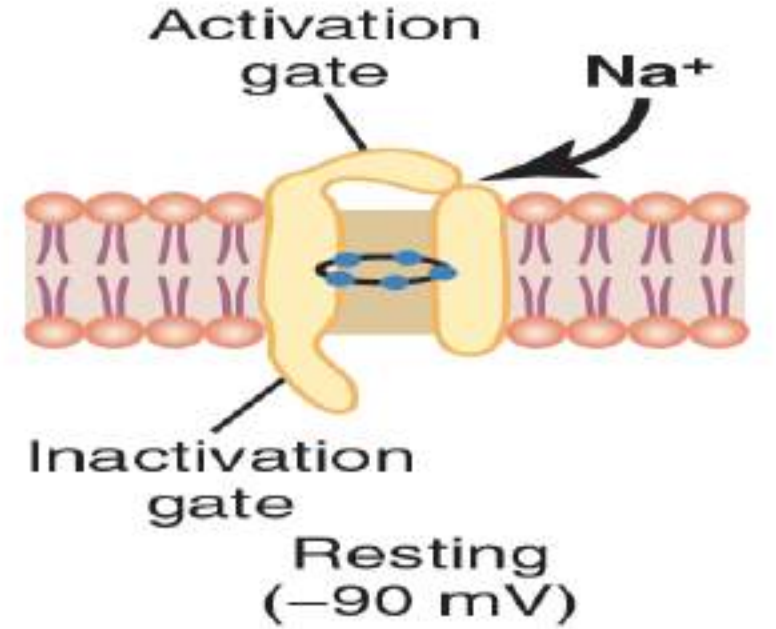
Voltage-Gated Na Channel in neuronal cell membranes
Activation and Inactivation of the Voltage-Gated Na Channel

The gate only opens when there is a change In membrane potential

This channel has two gates:

1- activation gate → near the outside of the channel

2- inactivation gate → near the inside of the channel



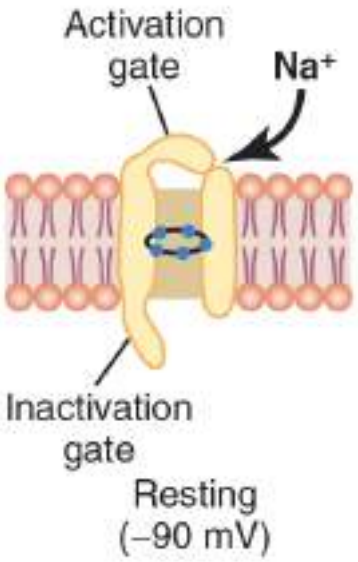
it will open during action potent

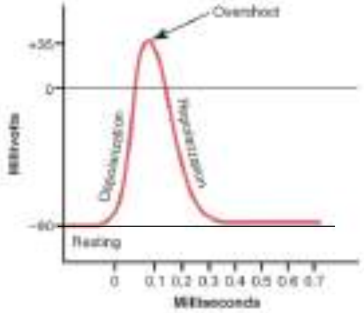
we will talk about it later

Activation and Inactivation of the Voltage-Gated Na Channel

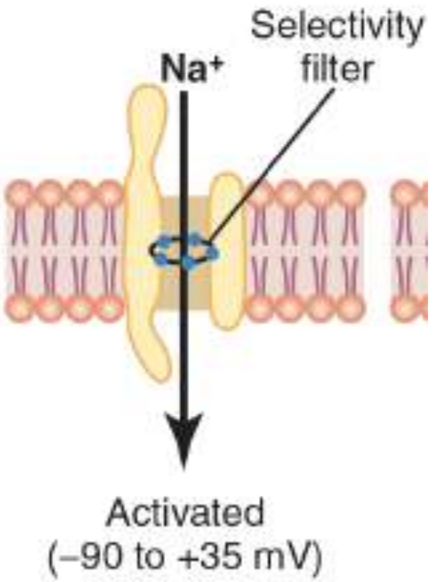
<u>state of two gates in</u>:

A- RMP=−90 mV.
activation gate is closed → prevents Na entry to the interior

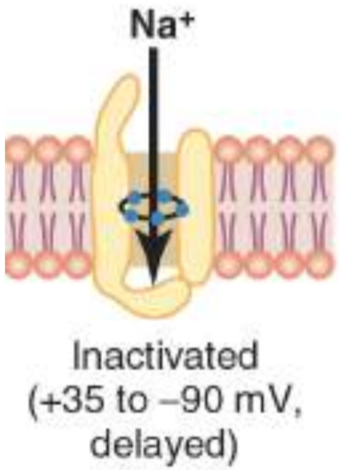




B- **Activation of the Na Channel**
activation gate → open position
inactivation gate → open→ Na pour inward, increasing Na permeability of membrane 500-5000X.



C-**Inactivation of the Na Channel.**
activation gate → open
Inactivation gate→ closed
No Na ions entry



- Occurs a few 10,000ths of a second after **activation** gate opens.
- Conformational change that closes **inactivation** gate is a **slower** process than conformational change that opens the **activation** gate.
- The inactivation gate will not reopen until the membrane potential returns to or near the original RMP

* Q: at the peak of action potential, the membrane potential is closer to the Na^+ or the K^+ ions?

Ans: the Na^+, because of the increasing Na^+ permeability.

Membrane potential

At resting state

- closer to the K^+ ions

Peak of Action potential

- closer to the Na^+ ion

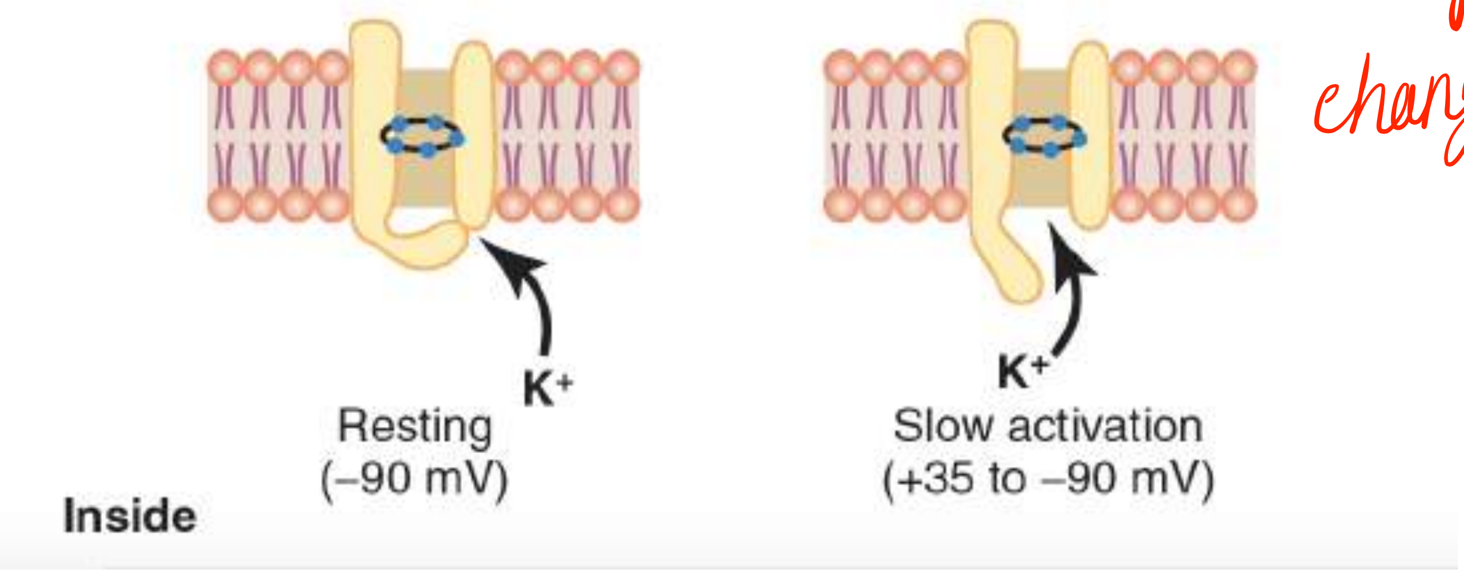
Voltage-Gated K Channel and Its Activation

when the Na+ channels close, the K+ channels open

two states:
A- during the resting state→ Closed
B-Activation state → opened→ K diffusion **outward**

Opens just at the same time that the Na channels are beginning to **close** → ↓ Na entry & ↑ K exit→ recovery of RMP within another few 10,000ths of a second.

They depend on the change of voltage



Thank you for your attention