



physiology

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Sheet

Slides

Number

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In this sheet we will talk about:

- *Resting membrane potential: origin and determinants.*
 - *Electrochemical equilibrium (Nernst equation) and chord conductance equation.*
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- There are two types of cells in our bodies:
 1. Excitable cells: cells that can't perform their function unless they are excited, such as nerve and muscle cells.
 2. Non-excitable cells: cells that can perform their function without the need for excitation, such as endocrine cells (they secrete hormone without being excited).
- Excitation means reversing the membrane potential, which is negative at rest, making it positive on the inside, or making it zero (the cell at rest is polarized and by excitation we remove polarization).

This excitation happens by introducing of Ca^{+2} , or Na^+ , or both.

For example, when there is high conductance for Na^+ ions (Na^+ leakage channels are open), and since there is high concentration of Na^+ ions outside the cell (140 mM) and low concentration inside (14 mM), Na^+ ions enter the cell and cause it to depolarize.

Note: Na^+ is smaller in size than Ca^{2+} . However, Na^+ can't enter through Ca^{2+} channels, it must influx through its own channels. Na^+ will enter through sodium channels, Ca^{2+} will enter through calcium channels.

❖ Resting membrane potential

- All our cells have resting membrane potential (there is separation of charges across the cell membrane).
- In neurons, RMP ranges from -40 to -90 mV (average -65 mV).

In RBC (red blood cells), which are non-excitable cells, RMP is -7 mV and in smooth muscles -30 mV. In large nerve axon it is -90 mV. In spinal cord motor neurons, it is -65 mV. In sinoatrial cells -65 mV, and ventricular cells -90 mV.

Note: the cells of the heart are excitable cells.

➤ Therefore, most of our cells are polarized (RMP range from **+5 to -100 mV**).

➤ In almost all our cells we have:

[Na⁺] out= 140 mM, in= 14 mM

[k⁺] out= 4 mM, in= 150 mM

[Ca²⁺] out= 10⁻³ mM, in= 10⁻⁸ mM

➡ Although our cells have the same distribution of ions across the cell membrane, they have different resting membrane potentials, as we saw previously.

➤ So, what determines the RMP of different cells?

It's the **conductance** (permeability) of the membrane to different ions.

➤ NOW, let's see what the effect of different ions on the resting membrane potential is.

- Every ion tries to bring the RMP toward its own equilibrium potential.
- To know what equilibrium potential means, we should know that there are two forces acting on each ion: **chemical force** and **electrical force**.
- Let's consider K⁺ ions as an example: the chemical force (concentration gradient) pushes K⁺ ions to the outside. While the electrical force pushes them to the inside (negative potential inside attracts the positive K⁺ ions).
- When these two forces are equal then we reach the equilibrium potential for K (Eq_k), and the net movement of K⁺ ions is zero even if K⁺ channels are still open.
- So, here the equilibrium potential means how much negative inside is needed to counterbalance the chemical force.

➤ How can we measure the magnitude of equilibrium potential?

By using **Nernst equation**:

$$E_x = \frac{RT}{ZF} \times \ln \left[\frac{C_{in}}{C_{out}} \right]$$

E_x = equilibrium potential for x

R = gas constant

T = Absolute temp

Z = valance

F = Faraday's number (number of coulombs per mole of charge)

$$E_x = \pm 61 \times \log \left[\frac{C_{in}}{C_{out}} \right]$$

NOTE: The sign (±) depends inversely on the charge of ions so that positive ions get - and negative ions get +

Note: Nernst equation considers that the membrane is permeable only to one ion.

Examples: $E_K = -94 \text{ mV} = (-61 \times \log [\frac{140}{4}]) = -61 \times \log 35 = -61 \times 1.54 = -94 \text{ mV}$.

In Spinal cord motor neurons $[K^+]$ inside = 120 mEq/l and not 140 and thus $E_K = -86 \text{ mV}$ and not -94 mV.

$E_{Na} = +61 \text{ mV}$, $E_{Ca} = +150 \text{ mV}$, $E_{Cl} = -70 \text{ mV}$.

$E_{Cl} = -61 \times \log [\frac{X_o=107}{X_i=8}] = -70 \text{ mV}$ (because the valance is negative)

or we can rearrange the equation as follows: $E_{Cl} = +61 \times \log [\frac{Cl_i}{Cl_o}]$

- At rest, K^+ leak channels allow K^+ to leak 100 times more than Na^+ .
If the membrane is leaky to K^+ only then RMP would be -94 mV (Nernst).
Since it is also slightly permeable to Na^+ , the RMP is -86 mV.
But, because Na-Ka pump is electrogenic, the RMP is finally, -90 mV
(contribution of -4 mV)
Na-K pump consumes 45% of the body total ATP expenditure.

- **Current:** Flow of charges per unit time.

If the RMP is -90 mV, and the change in voltage per unit time is zero (equilibrium), there is outward current of k ions generating positive charge outside (**positive current**). Also, there is inward Na^+ current and inward Ca^{+2} current generating negative charge outside (we record from outside, thus we record the negative tail), and therefor their current is **negative current**.

Summation of all currents is equal to zero when the membrane potential is constant with respect to time (no depolarization or hyperpolarization).

Chord conductance equation: $I_K + I_{Na} + I_{Ca} + I_{Cl} = \text{zero}$

Note: we are not supposed to know the details.

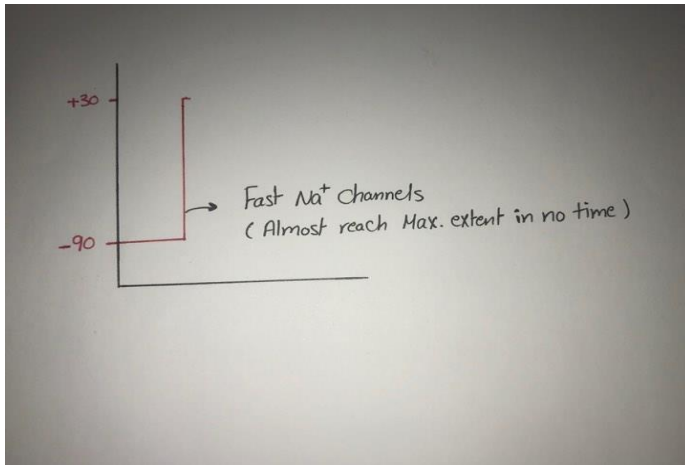
❖ Types of Na^+ channels

- There are different types of Na^+ channels and each channel opens and closes under certain condition.

➤ We are concerned with two types of Na⁺ channels:

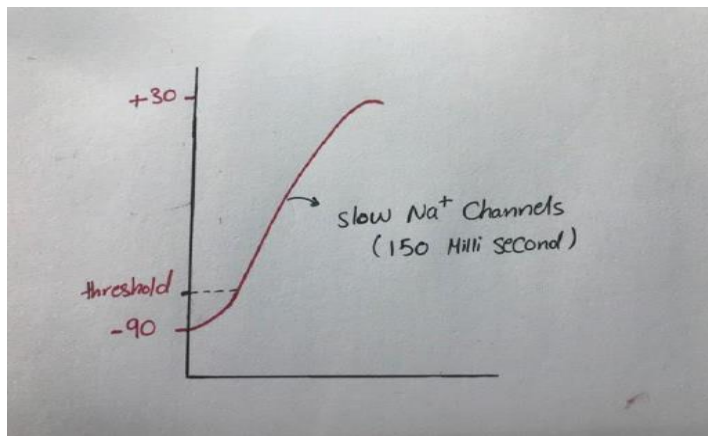
1. Fast Na⁺ channels

Na⁺ ions enter the cell and depolarize it with less than 1 mSec ($dv/dt = \infty$)

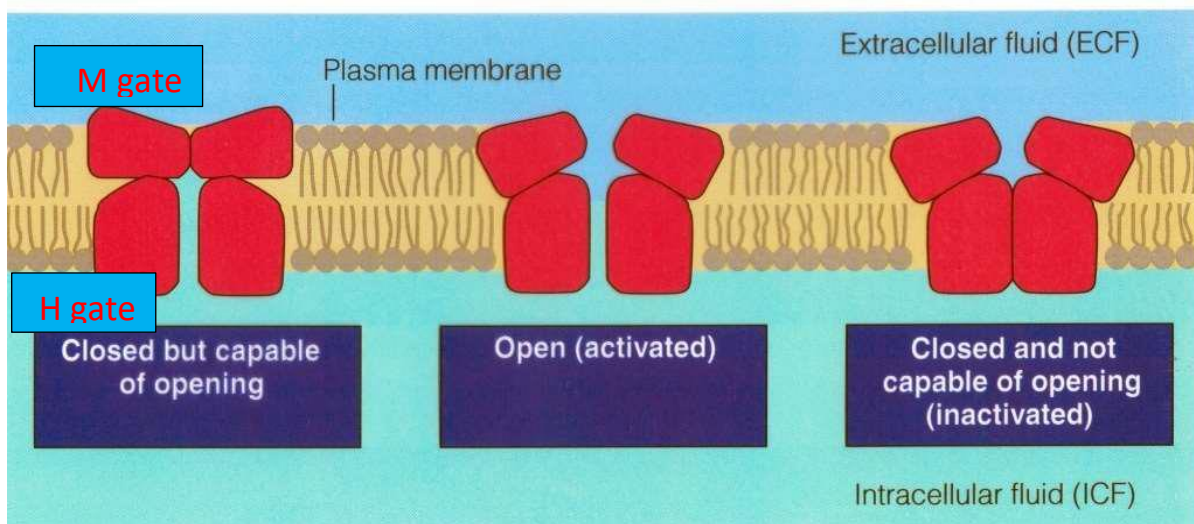


2. Slow Na⁺ channels

Na⁺ ions take several mSecs to enter the cell (dv/dt is less).

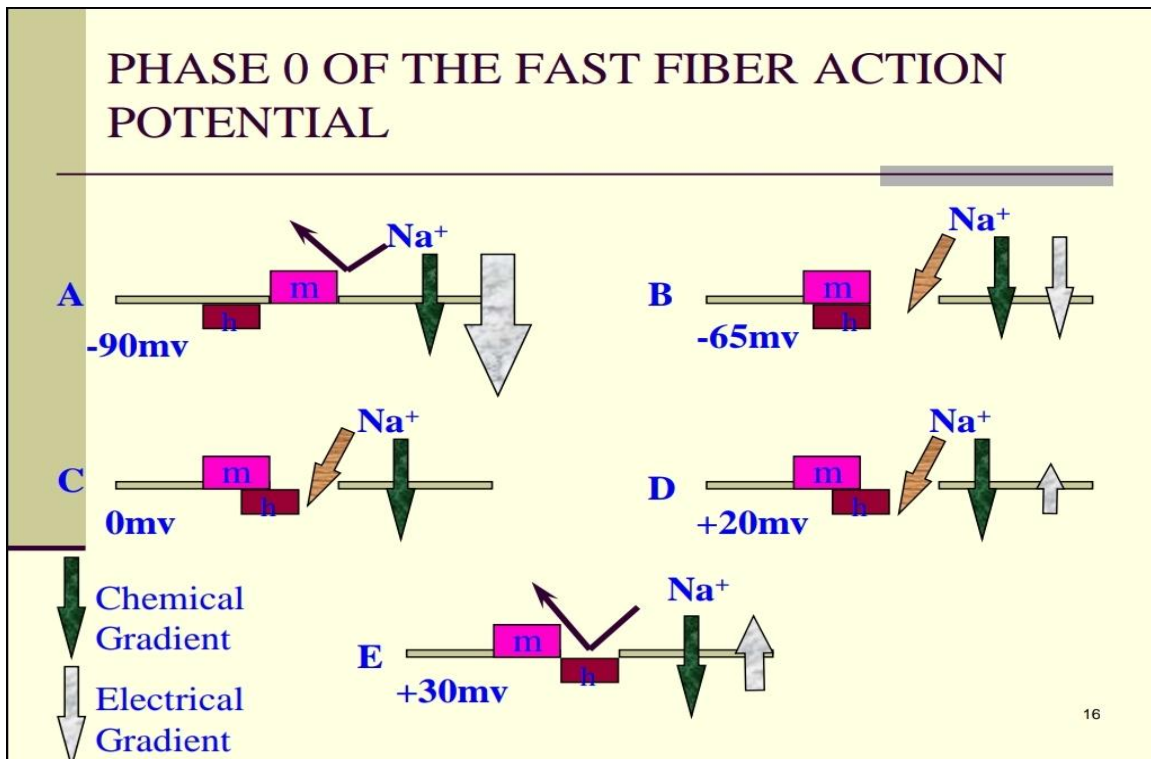


Conformations of a Voltage-Gated Na⁺ Channel



The figure above shows the Na channel with its fast gate (M gate), and slow gate (H gate).

The figure below represents the mechanism through which they act during action potential.



- At RMP external gate (m gate) closes the Na channel (A)
- Upon reaching a stimulus, there is a fast moving of m gate to open the Na⁺ channel (it takes only 0.2 mSec to move) (B), this phase is called phase 0.
- Na⁺ ions enter the cell by simple diffusion.
- When 1 Na⁺ enters the cell, it brings 2 Na⁺, and 2 Na⁺ bring 4 Na⁺ and so on (amplification). Thus, the entrance of Na⁺ ions represents a positive feedback mechanism.
- When the membrane potential becomes less negative (-75 and less negative), this causes the movement of H gate (C, D)
- h gate takes 1 mSec to close (5 times slower than m gate).
- So, at the end of depolarization, the h gate is close and m gate is open (E)
- Upon reaching second stimulus, h gate will not move no matter how strong the stimulus is.
- h gate will reopen only when the membrane restores its RMP.
- m gate is called **activation gate**, while h gate is called **deactivation gate**.

➤ So, during the action potential, the Na channels have 3 states:

1. Closed and active (when activation gate (M) is closed).
2. Open (when both gates are open).
3. Closed and inactive (when deactivation gate (H) is closed).

➤ Now let's take example about person who has hyperkalemia.

When the concentration of K^+ ions in the interstitial fluid increases from 4 to 8 mM, this causes the membrane potential to become less negative (from -90 to -78).

This potential is enough to cause the slow gate (H gate) therefore closing the Na^+ channel.

H gate remains close and not capable of opening.

This is very dangerous, **why?**

- Let's say that there are 150 ventricular cells, in order to have efficient contraction of these cells, we need all of them to contract simultaneously as a single unit.
- On the other hand, when part of these cell is contracted and another part is relaxed, we have non-efficient contraction.
- So, it's necessary for the heart to act as a single unit not as several motor units, and this is called **syncytium**.

▪ What are the factors that contributes to this feature in cardiac muscle cells?

1. There are gap junctions between these cells, they transmit the action potential from one cell to the adjacent cell.
2. Existence of fast Na^+ channels, they increase the rate of action potential (almost ∞) and depolarize the cell in less than 1 mSec. Thus, all the cells are depolarized in no time.

Remember that fast Na^+ channels are active only at RMP. Returning to the person who has hyperkalemia, since the membrane potential becomes less negative, fast Na^+ channels become inactive (we change the Na^+ channels from closed active to closed inactive state), and then action potential is slow, meaning that when the

action potential reaches the last cell, the first cell is at RMP (relaxed). This causes severe cardiac arrhythmias, and leads to cardiac arrest which might lead to death.

So again:

K⁺ ions  affect resting membrane potential  affect the availability of channels  affect

The rate of action potential (from fast to slow).

- Sometimes, changing the membrane potential might be useful.
For example, In spinal cord neurons, the RMP is -65 mV , if we want to make them less excitable (in the case of anger for instance), we should cause hyperpolarization of the membrane potential (to reach -75 mV), and now it's difficult to depolarize them, this can happen by using drug that activates Cl⁻ channels increasing the entrance of Cl⁻ ions, or a drug that deactivates Na⁺ channel reducing the entrance of Na⁺ ions.
Whereas if we want to make them more excitable (in the case of indolence), we should make the membrane potential less negative, bringing it closer to threshold.
- If the RMP is not **-65 mV** but for example like cardiac cells is around **-90 mV**, then we cannot control the neurons in term of inhibition by giving drugs (only excitation can occur since we have almost the maximum negative potential that can be reached).
- So why do we care about resting membrane potential?
It tells us what type of channels that might participate in the action potential.

SOMETIMES LATER

BECOMES NEVER

DO IT NOW.

☆ **GOOD LUCK** ☆