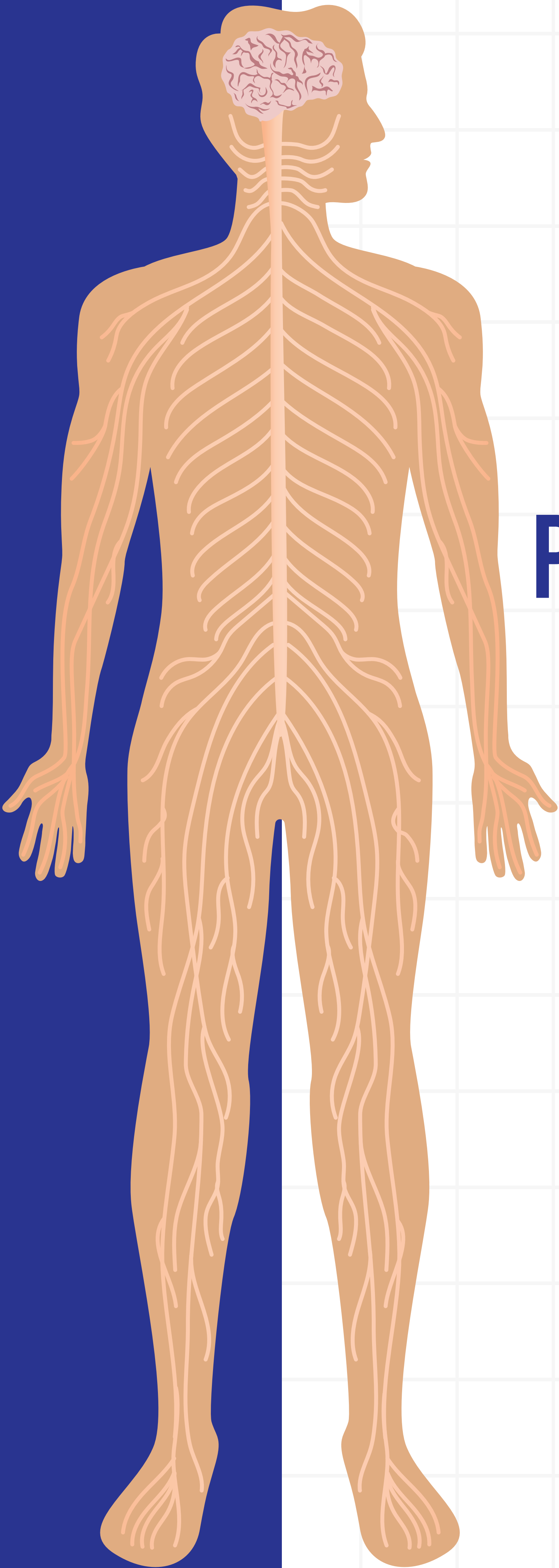
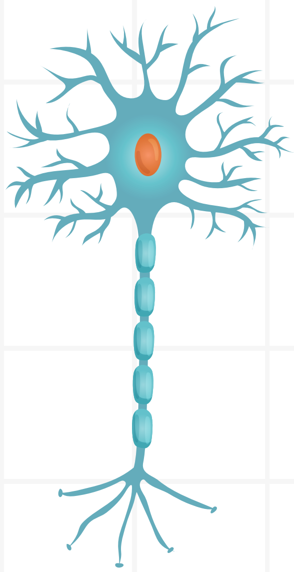
ARKAN
STUDY HOUSE



PHYSIOLOGY 2024



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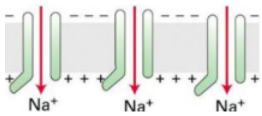
❖ Regulation of cell activities

- Cellular activities are regulated by the binding of a ligand to a receptor, leading to:
  - ➢ ***Activation of channels***
    - ✓ Binding of a ligand to its receptor, causes the activation of G protein that can activate chemical gated channels (such as Na^+, K^+ channels)
    - ✓ That causes changes in the *distribution of ions across the membrane*
  - ➢ ***Activation of second messenger system***
    - ✓ Binding of a ligand to its receptor, causes the activation of specific enzymes that can produce second messengers (such as cAMP, Ca^{++}), which can induce biochemical changes inside the cell
    - ✓ *cAMP*
      - o Produced by *adenelylyl cyclase*, which converts ATP into cAMP
      - o cAMP activates *PKA* (cAMP dependent protein kinase)
      - o This signal is mplified, where 1 cAMP can activate a large number of PKA
    - ✓ *Ca^{++}*
      - o *PLC (phospholipase C)* cleaves PIP_2 (phosphatidyl inositol biphosphate) into IP_3 (inositol triphosphate) and DAG (diacylglycerol)
      - o IP_3 induces the release of Ca^{++} from the SER
      - o Ca^{++} binds and activates *calmodulin* protein, causing cell response

❖ Membrane potential

- ***Membrane potential:*** it is the *voltage* across the membrane, caused by the *difference in the distribution of ions* between the 2 sides of the membrane
- Ions diffuses through chennels, down their **electrochemical gradeint** affected by 2 forces:
  - ➢ ***Chemical gradeint (concentration):*** ions move from higher to lower concentration
    - ✓ K^+ is highly concentrated inside the cell, but Na^+, Ca^{+2}, Cl^- are highly concentrated outside
  - ➢ ***Electrical gradeint (charges):*** caused due to the ***repulsion*** between similar charges
    - ✓ The movement down the chemical gradeint causes *charges to accumulate* on one of the side of the membrane, causing repulsion and resistance for the passage of this ion
- As the ions continue moving across the membrane, the net movement of ions becomes zero
  - ➢ ***Electrochemical equilibrium:*** ***No net movement*** of ions across the membrane because the chemical and electrical gradeints (forces) became **equal and opposite** to each other
  - ➢ During electochemical equilibrium, electrochemical gradeint become zero but electrical gradeint and chemical gradeint are not zero



- Membrane potential is calculated by:

  1. Nernest equeation

$$E = \frac{RT}{zF} ln \frac{[C]out}{[C]in}$$

- Calculates the membrane potential when it is pemeable for ***only 1 ion***
- The calculates value is called *nernest potential* or *equilibrium potential of ions*
- Positive or negative values are related to the **inner** surface charge
  - ➢ E_{eqNa^+} = + 60, which means that the inside is positive compared (relatively) to the outside by a magnitude of 60 mV
  - ➢ E_{eqK^+} = - 95, which means that the inside is negative compared (relatively) to the outside by a magnitude of 95 mV

Ion	Extracellular (mM)	Intracellular (mM)	Nernst Potential (mV)
Na^+	145	15	60
Cl^-	100	5	−80
K^+	4.5	160	−95
Ca^{2+}	1.8	10^{-4}	130

2. *Goldman-Hodgkin-Katz equation*

- Calculates the membrane potential when it is pemeable for ***more than 1 ion***

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

- It calculates membrane potential in considration of ***permeability*** to an ion
  - Membrane permeability of ions is determined by the *number of activated (opened) ion channels*

3. *The cord conductance equation*

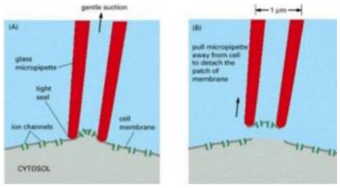
- It is somewhat similar to Goldman-Hodgkin-Katz equation but it calculates potential in consedrations of **conductance** instead of permeability

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

  - According to Ohm's law ($I = \Delta V / R$), conductance is *inversely related to the resistance*
  - Conductance of an ion is directly related to the number of activated (opened) channels

> ***Permeability:*** the ability of any substance to pass through the membrane
> ***Conductance:*** the ability of charged substances (ions) to pass through the membrane

- The **current** across the membrane which is the movement of ions (charged particales) across the membrane using chennels is measured using a technique called patch clamp



❖ Resting membrane potential

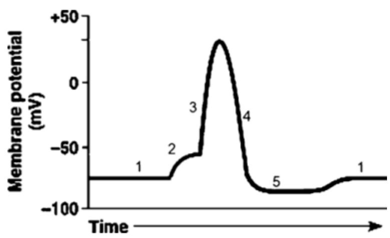
- The voltage (potential) across the membrane when it is ***not stimulated***
- The resting membrane potential of most excitable cells (such as neurons) is bout -90 mV, caused by:
  - ***Contribution of K^+ ions***
    - ✓ At resting, the membrane is *highly permeable to K^+* due to the large number of leaky K^+ channels
    - ✓ The resting membrane potential is *very close* to the equilibrium potential of K^+ due to its very high permeability
  - ***Contribution of Na^+ ions***
    - ✓ At resting, the membrane has *low permeability to Na^+* (less leaky Na^+ channels)

> Na^+ and K^+ contributes together by -86 mV

  - ***Contribution of Na^+/K^+ pump***
    - ✓ It pumps 3 Na^+ outward, and 2 K^+ inward which represents *1 positive charge outward* as a net
    - ✓ So it contributes for making the membrane potential more negative by -4 mV
    - ✓ It is called an ***electrogenic pump*** because it generates a membrane potential (voltage)

❖ Action potential

- At **resting**, cells are also considered to be **polarized** which means *seperation* of charges between the 2 sides of the membrane where the inner surface is negative and the outer is positive
- When a stimulus arrives, that causes changes in the membrane permeability to ions leading to changing membrane potential
- If this change brought the potential to a speific value called ***threshold***, that causes the ***generation of action potential*** which represents nerve impulses that transfer signals between body parts
- If this change was *not strong enough* to bring the potential to threshold, membrane potential returns to resting and that is called a ***graded potential***

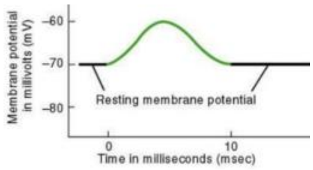


- Steps of action potential generation:

1. Resting (Polarization)

- Membrane potential is about -90 (for most cells)
- All voltage <u>gated</u> Na$^+$ and K$^+$ channels are **<u>closed</u>**

2. Depolarization



- The arrival of a stimulus causes *some voltage gated Na$^+$* channels to open making the membrane potential <u>more positive</u>

3. Rising phase (Firing stage)

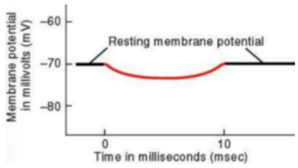
- If the depolarization brought the potential to **<u>threshold</u>**, action potential is generated and *all voltage gated Na$^+$* channels are ***<u>activated rapidly</u>***
- Membrane potential becomes more positive (less negative) until reaching the peak (about +30 mV)
- **Overshoot:** The phase where membrane potential is <u>between zero and the peak</u> (+30 mV)

Voltage gated K$^+$ channels also starts to be activated ***gradually (slowly, delayed)*** at threshold

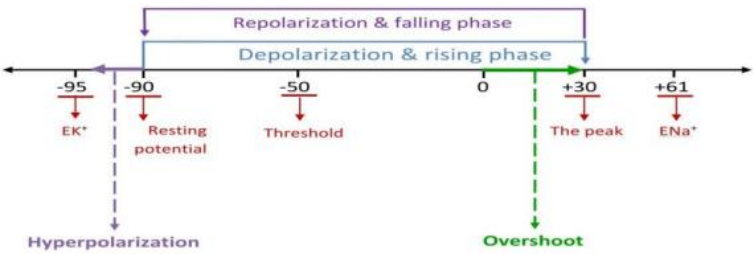
4. Repolarization (falling phase)

- At the peak *all voltage gated Na$^+$ channels closes very fast (rapidly)*, but *K$^+$ channels continue opening gradually (slowly)*
- Membrane potential becomes more negative (less positive) until reaching the resting potential where K$^+$ channels start closing (gradually also)

5. Hyperpolarization (undershoot, positive afterpotential, after hyperpolarization)



- Some voltage gated K$^+$ channels are still open, which causes membrane potential to become ***more negative than resting***
- It will **<u>never reach the E_{K+}</u>** due to the contribution of Na$^+$ ions
- Membrane potential is then <u>returned</u> to resting by ***Na$^+$/K$^+$ pump***

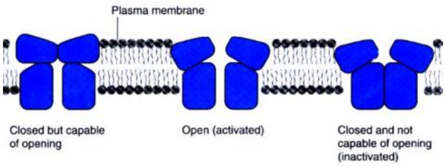


- ***Notes:***
  - Action potential follows **none or all principle** which means that it either occurs when threshold is reached or not if it is not reahed (there is no weaker or stronger action potential)
  - *Graded potential:* Any change in the membrane resting potential that <u>doesn't reach threshold</u>
  - **<u>Both</u>** voltage gated Na$^+$ and K$^+$ channels ***start openning at threshold***
  - *Na$^+$/K$^+$ pump* has <u>no role</u> in the electrical activity that are taking place during action potential but it plays an important role in ***maintaining the ionic composition*** of the intra- and extra-cellular fluids
  - The highest permeability (conductance) of an ion is reached in the phase where the highest number of gated <u>channels are activated</u> (opened)
    - ✓ Highest permeability of Na$^+$ at the rising phase (overshoot, peak)
    - ✓ Highest Permeability of K$^+$ at the falling phase

- ➢ ***Driving force:*** it is the difference between the membrane potential and the equilibrium potential of an ion (**df = Em – Eeq**) where the resultant charge is meaning less

- Channels can be:
  - ➢ **Leaky** which are responsible for the *resting* membrane potential and they are *always opened*
  - ➢ **Gated** which can be acivated or inactivated according to microenvironmental changes, such as:
    - ✓ *Voltage gated:* which change its conformation according to changes in **ions** distribution
    - ✓ *Chemical gated:* which change its conformation via **binding** of a specific ligand (molecule)
      - ▪ All gated channels are closed during resting, and start activation by the arrival of stimuli

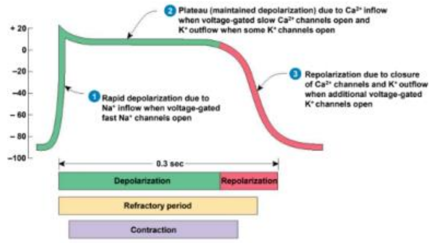
- Voltage gated Na^+ channels have 3 conformations:
  - ➢ *Open:* at the ***firing stage*** (rising phase)
  - ➢ *Closed and capable for openning:* at the ***resting*** stage, where an ordinary stimulus can activate them
    - ✓ Activation gate is closed



  - ➢ *Closed and not cabaple for openning:* at the ***falling phase*** (repolarization), where they can't be activated by an ordinary stimulus, but a superthreshold stimulus can activate them
    - ✓ Inactivation gate is closed
- The *more negative potential during hyperpolarization* causes Na^+ channels to be ***converted*** from closed and not capable for openning into closed and capable for openning

- **Refractory period:** a period where no new action potential can be generated
  - ➢ Absolute refractory period: During the *rising phase* because Na^+ channels are absolutely *opened* so neither ordinary stimulus nor suprathreshold stimulus can generate a new action potential (it is **impossible** to generate a new action potential during this phase)
  - ➢ Relative refractory period: During the *falling phase* because Na^+ are *closed and not capable* for openning, so an ordinary stimulus will not generate action potential but a suprathreshold (very strong) stimulus can generate a new action potential
- Importance of refractory periods is that they ensure the one-way (unidirectional) propagation of action potential from the axon hillock toward the terminals only

- ***Cardiac action potential***
  - ➢ It depends on other types of channels including slow channels of Na^+ and Ca^{+2}
  - ➢ It is called the action potential of ***plateau*** due to the phase of constant membrane potential caused by activated Ca^{+2} channels
  - ➢ This plateau ***prolongs*** the duration of action potential, where the refractory period is prolonged which aids in the prevention of tetanus in cadiac muscles



- Also *uterine muscles* acion potential involves ions such as Ca^{+2}