Physiology of the nerve
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Neuron:

It consists of

1- Soma (body): ---- processing center for the nerve fiber

2- Dendrites:

- short branching processes, arise from the cell body
- carry impulses from periphery to cell body

3- Axon (nerve fiber):

- single, elongated process.
- arises from a thickened area on the cell body ; axon hillock.
- ends with a number of branches (nerve terminals) which end with synaptic knobs (terminal buttons that contain vesicles which store neurotransmitters).

Classification of Nerve Fibers:

(I) Histological classification:

Myelinated	Non-myelinated
Axon is surrounded by **Schwann cells**	
Which form the myelin sheath: - protein-lipid complex act as insulating layer = decrease ion flow through the membrane - The area between two successive schwann cells is called **node of Raniver** where: myelin sheath is absent (uninsulated area) ----- ions can flow easily.	without formation of myelin sheath
e.g: most nerve fibers except ⟶	- Postganglionic autonomic NF - NF less than 1 u in diameter

(II) According to their thickness:

	A fibers (α, β, γ and δ)	**B fiber**	**C fiber**
ϕ (microns)	2-20	1-5	Less than 1
Rate of conduction	20-120 meter/sec	5-15 m/sec	0.5-3 m/sec
Duration of spike	0.5 msec	1.0 msec	2.0 msec
eg	Myelinated somatic	Myelinated preganglionic autonomic NF	Unmyelin postganglionic autonomic NF.
Very sensitive to	pressure	Hypoxia	Local anaesthetics and cocaine.

N.B: Very sensitive to hpoxia= hypoxia → decrease or block conduction through the NF.

Changes that accompany nerve impulse propagation:

1- Electrical changes (action potential)
2- Excitability changes
3- Metabolic changes
4- Thermal changes

Electrical changes

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Resting membrane potenial (polarized state):

Measured by : voltmeter

Procedure:

- one electrode is placed on the outer surface of the fiber and the other is inserted inside the fiber.
- both electrodes are connected to a voltmeter

Observation:

Defeletion of the pointer (R.M.P)=

-90 mV (large nerve fiber and large skeletal muscle fiber)
-70 mV (medium-sized neuron)
-20 to -40 mV (nonexcitable cells eg red blood cells and epith cells)

Causes:

Unequal distribution of ions on both sides of the cell membrane, with relatively excess:

- cations (eg Na^+)→ outside.
- anions (eg proteins)→ inside

Distribution of ions under resting conditions:

	Extracellular	Intracellular
Principle cations	Na^+	K^+, Mg^{++}
Principle anions	Cl^-, $HCO3^-$	$PO4^{--}$, $SO4^{--}$ and proteins

Factors which induce RMP:

(1) Selective permeability of the membrane:

The resting cell membrane is:

Permeable to	Impermeable to
K^+ ions (about 20-100 times more than Na^+ or Ca^{++}) ↓ K^+ outflow is much greater than Na^+ inflow	Intracellular proteins and other organic anions

↓

net effect = more

positive ions (outer surface) Negative ions (inside)

* Each ion try to reach an equilibrium potential ie:

the flow of ions by concentration (chemical) force is balanced by the flow in the opposite direction by electric force.

* At equilibrium:

$$\frac{K^+ \text{ inside}}{K^+ \text{ outside}} = \frac{35}{1} = 35.0$$

$$\frac{Na^+ \text{ inside}}{Na^+ \text{ outside}} = \frac{1}{10} = 0.1$$

(2) Sodium-Potassium pump:

= active transport mechanism (required energy derived from ATP), responsible for pumping:

3 Na^+ to exterior
& of the cell/ each revolution of the pump
2 K^+ to interior

Significance:

Electrogenic nature:

Since:

* Na^+-K^+ pump → moves 3 Na^+ to exterior for every 2 K^+ to the interior

↓

one positive charge is moved from the interior to exterior
for each revolution of the pump

↓causes

negativity on the inside (elecrogenic pump)

The voltage-gated sodium and potassium channels:

A) Voltage-gated sodium channel:

has two gates

Activation gate	Inactivation gate
(near the outside)	(near the inside)
↓	↓
Close during rest	Opened during rest

N.B: Inactivation gate does not constitute any barrier to Na^+ movement

B) Voltage-gated potassium channel:

has single gate
(located near the inside)

↓

close during rest

↓

prevent pass of K^+ to exterior

Action potential

= changes in membrane potential following stimulation of the nerve by adequate stimulus

Types of action potential:

(I) Monophasic AP: (I) Biphasic AP: (III) Compound AP:

(I) Monophasic AP:

recorded if one electrode is placed on the outer surface of the fiber and the other is inserted inside the fiber, and connected to cathod ray osilloscope CRO, then the neve is stimulated

Component of monophasic AP:

1- Stimulus artifact:

= brief, irregular deflection (oscillation) of the baseline following application of the stimulus.

2- Latent period (polarised interval):

= Time between application of stimulus and appearance of the response.

depends on:

- distance between the stimulus and recording electrode.
- velocity of nerve impulse

3- Spike (2 msec)

a) Depolarization (ascending limb).

b) Repolarization (descending limb).

4- Hyper-polarisation (undershoot):

Lasts 35-40 msec ie long duration

5- Re-establishing Na^+ and K^+ gradient (Na^+-K^+ pump):

Lasts 50 msec to many seconds

Action potential wave (Spike): (lasts about 2 msec)

a) Depolarization phase (ascending limb):

Membrane potential:

- rises rapidly from -90 mV (polarized) to → -65 mV (firing level) → isopotential (zero potential) line→ **overshoots** to approximately +35 mV (depolarization)

Ionic basis:

(i) Na^+ channels:

1- rising the membrane potential (from -90 to -65 mV):

outer gate (activation gate):

undergo sudden and rapid confirmatory changes→ open → Na^+ influx→ stimulate more outer gates to open→ more streaming of of Na^+ to inward and so on till all Na^+ channels are active (open) at firing level (-65 mV). This process is **called positive feedback = regenerative process:**

2- at firing level (-65 mV)

inner gate (inactivation gate):

undergo slow confirmatory change→ start to close→ Na^+ channel start inactivation → limits Na^+ inflow

N.B: The closure of inner gate of sodium channels is slow.

3- at the top of spike (+35mV):

- all Na^+ channels return to resting state → outer gate→ close ——
  → inner gate → open ——

↓

stop inward flow of Na^+

-inner surface becomes +ve in relation to outer surface (depolarization)

∴ *Na^+ channels gates move in a sequential manner.*

(ii) K^+ channels:

- Just at the time where Na^+ channels start to be inactivated:

  K^+ gates undergo slow confirmatory changes→ slow outward diffusion of K^+

Na^+ conductance:

high

b) Repolarization phase (descending limb)**:**

Membrane potential:

- returns rapidly towards its resting potential.
- when repolarization is about 70% completed , the rate of repolarization decreases and RMP level is reached slowely.

Ionic basis:

(i) K^+ channels:

more K^+ gates open→ activation of K^+ channels → rapid outflow of K^+ to the exterior (K^+ outflux)

(ii) Na^+ channels:

return to resting state

K^+ conductance:

higher than that of Na^+ conductance

N.B:

The opening of K+ channels:

- is slower and more prolonged than the opening of Na^+ channels.

- occurs within a fraction of millisecond after sodium channels open.

Hyperpolarization "Undershoot" (+ve after potential):

long duration = lasts 40 msec

Membrane potential:

- overshoots slightly in the hyperpolarized direction to form the small but prolonged hyperpolarization.

Ionic basis:

slow closing of K^+ channels high K^+ conductance

↓

at the end of action potential (rest)

↓

potassium ions still diffuse out the NF
membrane becomes hyperpolarized
(more negative than resting state)

Re-establishing Na^+ and K^+ gradient:

Lasts 50 msec to many seconds

Mechanism:

Na^+-K^+ pump→ re-establish sodium and potassium membrane concentration difference which is disturbed during action potential.

All or Non law:

Action potential once generated it occurs and propagates with a maximal amplitude, constant duration and form, regardless of the intensity of the adequate stimulus (threshold or above threshold)

Electronic potentials:

= Passive changes in the membrane polarization caused by ***subthreshold galvanic (constant) current*** *ie*. addition of charges at the particular electrode

1) Catelectronus	**2) Anelectronus**
= state of partial depolarisation (= less than 7 mV) at the region of cathode	= state of hyperpolarisation
Cause: Cathode (negative electrode) ↓ add negative charges to the outer surface of the membrane ↓ ↓membrane potential ↓ ↑nerve excitability	Anode (positive electrode) ↓ add positive charges to the outer surface of the membrane ↓ ↑membrane potential ↓ ↓nerve excitability

(II) Biphasic AP:

recorded if both electrode are placed on the outer surface of the fiber and connected to CRO, then the neve is stimulated

<u>Component of biphasic AP:</u>

- During rest:
    no potential difference between the two electrodes.
- During depolarisation where the impulse (wave of depolarisation):
    - reach the 1st electrode (nearest to stimulator)→ becomes negative (relative to 2nd electrode)
    - pass through the nerve between the two electrode→ potential returns to zero.
    - reach the 2nd electrode (away from the stimulator) → becomes negative (relative to 1st electrode).
- When the impulse leaves the 2nd electrode:
    no potential difference between the two electrodes.

N.B:

Crushing or destroying the:

- portion of the nerve between the two electrodes
- region under the 2nd electrode.

↓

monophasic deflection is obtained

(III) Compound AP (AP in nerve trunk):

= AP in nerve trunk (many nerve fibers) characterized by:

1- having **many peaks,** as each NF vary in its:

- *threshold for stimulation*.
- *speed of conduction* (the thicker the nerve, the more rapid will be the conduction, and vise versa)
- distance from stimulating electrode.

2- graded response:

a- subthreshold stimuli→ electronic potential and local response

b- Increasing the strength of stimuli to threshold stimuli→ maximal stimuli

Increasing the strength of stimuli→ small AP appears (due to response of NF of low threshold). Further increase in the intensity→ AP grow in amplitude till all NFs respond (maximum response) at maximal stimulation.

c- Supramaximal stimuli→ maximal response.

Propagation of action potential (*Nerve conduction*)

(A) Mechanism of nerve impulse conduction:

(1) In Unmyelinated nerve fibre:

AP generated at any one point on the axon act as a stimulus for the adjacent resting regions (local circuit) → and the entire process is repeated→ propagation of AP along the axon.

- Polarized portion (rest) → outer surface → +ve
→ inner surface →-ve
- Depolarized portion (active) → outer surface → -ve
→ inner surface → +ve (due to Na^+ influx)

↓

flow passively to the adjacent negative area

↓

↑ voltage (act as a stimulus) at this new area

↓

depolarization of this new area
(= activation of Na^+ channels → open → Na^+ influx)

↓

& so on till the AP travel along the NF.
This process is called ***local circuit*** of current flow

N.B: Speed of propagation is proportional to the square root of the fiber diameter

(2) In myelinated nerve fibre:

Propagation in myelinated axons is the same as in unmyelinated axons. However, depolarization jumps from one depolarised node of Ranvier to the next as the myelin sheath act as insulator. This is called saltatory conduction

Importance of saltatory conduction:

1- increases the velocity of conduction along the NF (by the process of jumping) up to 50 folds.

2- Conserve energy:

depolarisation is limited to the node of Ranvier, so leakage of Na^+ to the inside of NF is minimum. Consequently, energy required by Na^+-K^+ pump (to expell Na^+ to outside) is low

(B) Types of nerve impulse conduction:

1) Orthodromic conduction:	**2) Antidromic conduction:**
= pass of impulses in the normal direction ie from receptor or synapse along the axons to their termination	= pass of impulses in the opposite direction ie along the axon to the synapse.

N.B: Synapse, unlike axon, permit conduction only in one direction. Therefore, any antidromic impulses fail to pass the 1st synapse and die out at that point.

Excitability changes during nerve stimulation

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= ability of living tissues to <u>respond</u> to <u>a stimulus</u>

↓

<u>depends on:</u>
1- Strength (intensity) of the stimulus:
subthreshold, threshold, overthreshold
2- Duration:
an effective current must be applied for certain period to give response
3- Rate of rise of stimulus intensity:
- rapidly increase stimulus intensity to threshold value --- active response
- slowly increased intensity--- not give response, as the nerve would accommodate (adapt to) it.

↓

<u>Types:</u>
1- Electrical (preferable)
- similar to natural stimuli.
- easily controlled
- accurately measured
- leaves the tissue undamaged.
2- Mechanical.
3- Chemical.
4- Thermal.

Strength -duration curve:

= relation between stimulus strength
&
duration of its application to an excitable membrane to produce response

Strength of stimulus	Duration of application	Response
1- Whatever strength	shorter	No response
2- Strong (within limit)	Shorter	
3- Subminimal	-----	Local (local excitatory state)
4- Threshold (minimum) = **Rheobase**	Utilization time	+ve
* Twice Rheobase	**Chronaxie**	+ve

* **Rheobase** (threshold stimulus):
= minimum strength of stimulus applied for nerve or muscle for a **<u>certain time</u>**, and produce response.
↓
Utilization time = time needed by Rheobase to produce response

* **Chronaxie (C) =** duration (length of time) needed by twice Rheobase strength to give response

Physiological significance:
within limit C is constant for certain tissue but differ among various tissues.
So, **Chronaxie** is used to → measure tissue excitability &
→ compare excitability among various tissues.
eg.: excitability of nerve is high as C is short

Phases of excitability:

	(1) Absolute Refractory period	(2) Relative Refractory period

	(ARP):	(RRP):
Extends from:	firing level till early part of repolarization.	ends of ARP till the membrane potential returns to its resting level
Excitability	= zero = Nerve fiber does not respond to any stimuli whatever its strength = a 2nd action potential cannot be generated	lower than during rest = Nerve fiber respond only to over threshold stimuli.
Cause:	Na^+ channels are inactivated as inner gates are closed	1- some of the of Na^+ channels still in inactivation state. 2- K^+ channels are opened widely→ hyperpolarization→ makes more difficult to stimulate the fiber

Factors affecting membrane potential and excitability:

(A) Factors increase excitability:	(B) Factors decrease excitability (= **membrane stabilizers**):
(1) Any condition that **increase Na^+ permeability:** - Veratrine - low Ca^{++} concentration in the extracellular fluid	(1) Any condition that **decrease Na^+ permeability (hyperkalemia):** - local anaesthetics eg cocaine - high Ca^{++} concentration in the extracellular fluid. - tetrodotoxin (TTX) block Na^+ channels.
(2) Increase extracellular K^+ concentration: RMP becomes more positive (hypopolarize)	(2) Decrease extracellular K^+concentration: RMP becomes more negative (hyperpolarize) Occurs in: hereditary disease (familial periodic paralysis)??

Familial periodic paralysis

Manifestation:

- excitability greatly reduced
- no nerve impulses are produced
- person becomes paralysed.

Treatment:

- K^+ administration (iv).

N.B: *Blockage of K^+ channels by tetraethyl amonium (TEA) will result in:*

- *AP of longer duration (due to prolonged repolarization)*
- *absence of hyperpolarisation*

Local response (local excitatory state):

Action potential	Local response
1- Produced by: Threshold or suprathreshold	Subthreshold stimuli:
2- Na^+ activation gates: Open enough → depolarization→ repolarization ie **(ie propagated)**	Does not open enough→ produce local excitatory changes→ repolarization **(ie non-propagated)**
3- Can't be **summated**	Can be **summated**
4- Not **graded**	**Graded**
5- Obey All or Non law	Doesn't obey All or Non law
6- Accompanied by ARP	No ARP
7- Excitability: ???????	Increased

N.B:

** Graded = the magnitude and duration of local response vary with the size and strength of the stimulus.*

** Summated = simultaneous subthreshold stimuli may act together → higher depolarisation which may reach the firing level.*

Accommodation of nerve fiber (failure to fire despite rising voltage**):**

= If a subthreshold stimulus is applied to the nerve and its intensity is increased very slowely (over many milliseconds instead of a fraction of second) → nerve will not respond (= accommodate).

Cause:

The gradual opening of activating gates of Na^+ channels is balanced, at the same time, by:

1- prolonged closure of the slow, Na^+ inactivation gates Consequently: opening of activation (outer) gate is not effective	2- slower opening and delayed closure of K^+ gates K^+ diffuse outward (try to restore ionic equilibrium)→ balance the effect of opened Na^+ gates

Na^+ inactivation gate:

- open→ slowly.
- remain close for long time

K^+ gates:

-open→ slowly

- close→ very slowly (ie remain open for long time).

Metabolic changes of nerve

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- During rest:

  Energy (from breakdown of ATP) is required to maintain resting membrane potential (polarized state) ie energy for Na^+-K^+ pump activity.

- During activity:

  Na^+ conc inside the nerve increases so energy expenditure increases

  If Na^+ conc increases two folds→ Na^+-K^+ pump activity increases eight folds

Thermal changes of nerve

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- During rest:

  resting heat (negligible amount when compared to muscle fiber).

- During activity:

	(1) initial heat	(2) recovery heat
- heat produced:	during action potential	after action potential
- cause:	anaerobic breakdown of ATP	aerobic reactions

N.B: recovery heat → is about 30 times as the initial heat
→ lasts for longer time

Neutrophins

Nature:

protein necessary for neuronal development, growth and survival

Source:

glial cells, muscles or other structures that the neurons innervate