NERVOUS SYSTEM

It is the system that regulates the simplest & the most complex activities of the human body.

- Brain & spinal cord, contain centers which receive & process nervous signals, then formulate the response to these signals.
- Autonomic nervous system (ANS): is concerned with involuntary control of visceral activity. It include; sympathetic, parasympathetic & Enteric divisions.
- Somatic nervous system: is concerned with conscious perception of different sensations, & voluntary control of muscular activity. This system is divided into 2 divisions:
  a- sensory division: concerned with conscious perception of somatic sensations. It includes sensory (afferent) nerves, sensory (ascending) tracts inside CNS, sensory reticular formation, thalamus & sensory cerebral cortex.
  b- motor division: concerned with voluntary control of muscular activity. It includes motor cerebral cortex, basal ganglia, cerebellum, motor reticular formation, motor (descending) tracts inside CNS, & motor (efferent) nerves.

All these divisions are interconnected & their functions are integrated together & with other systems in the body.

- Reflex action is an involuntary action in response to a stimulus, e.g a painful stimulus applied to hand leads to reflex withdrawal of the arm.
- Reflex arc: is the structural unit of nervous system that is capable of conducting a reflex action; & it consist of 5 component:
  1- Receptor: a sensor which is excited by a stimulus.
  2- Afferent nerve (called sensory nerve): which conveys input signals to CNS.
  3- Center: a collection of neurons that receive sensory information & order for proper response.
  4- Efferent nerve: a nerve that conveys output signals from CNS to effector organ.
  5- Effector organ: a muscular or a glandular structure which receives the final order & executes reflex response.
Nerve cell (Neuron)

Is the basic functional & structural unit of the nervous system. It consists of the following:

- **Soma**: contain nucleus, ribosome, ER & Golgi apparatus where necessary protein synthesized.
- **Dendrites**: small 5-7 receptor membrane processes that extend outward from soma & branch extensively. They have small knobby projections called **dendritic spines**. Dendrites ↑ surface area available for synapses. Signals coming to a neuron are received at dendrites & soma.

- **Axon** (conductile structure): a long fibrous extension that originates from a thickened area of soma (**Axon Hillock**). Axon Hillock has a high density of voltage-gated channels for Na+ & K+. It is a trigger zone for first generation of action potential (AP).

- The first portion of axon is **initial segment**.

- Each axon terminates in **presynaptic terminals** (**Terminal branches**), each ends in a number of synaptic knobs (terminal buttons), they contain: Vesicles in which NT are stored, Voltage-gated ion channels of Na⁺ & K⁺, for AP, & Voltage gated ion channels of Ca²⁺ for neurosecretion.

- **Voltage-gated channels** for Na⁺ & K⁺ predominate in membranes of axons.
  - In unmyelinated axons; they are evenly distributed.
  - In myelinated axons; they are most dense at nodes of Ranvier.

- **Myelin** sheath (protein- lipid complex) is produced by schwann cells(out side CNS) & oligodendrogiocytes (inside CNS).
  - Schwann cell rotates around axon many times → multiple layers of cell membrane containing lipid substance **sphingomyelin** (excellent electrical insulator that ↓ ion flow through membrane).
  - If neurons simply surrounded by schwann cells without wrapping → unmyelinated.
  - If myelin is wrapped around axon (up to 100 times) → myelinated.
  - Myelination is interrupted along axon leaving an uncovered area **node of ranvier**

- Nerve trunk contains myelinated & unmyelinated, small & large diameter fibers.

- **Myelination speeds up the nerve conduction by**:
  1. **Prevents loss of ions**: myelin acts as insulator, reduces ion leakage except at nodes of Ranvier.
  2. **Saltatory conduction**: by making impulse jump between nodes of Ranvier.

**Synapse**

It is the junctional area between a nerve terminal & another cell. If the 2nd cell is a neuron the synapse is called **neural or neuronal** synapse. Neuron that conduct impulses to synapse called **presynaptic** neuron, & Neuron that conduct impulses away from synapse called **post synaptic** neuron. Importance: It ensures flow of impulses in nervous system in forward direction only, & more easily.
Classification of synapses:

*Histological* classification of synapses:

1. Axodendritic: between axon terminal of presynaptic neuron & dendrites of postsynaptic neuron.
2. Axosomatic: between axon terminals of presynaptic neuron & soma of the postsynaptic neuron.
3. Axoaxonic: between axon terminal of presynaptic neuron & axon of postsynaptic neuron.

*Physiological* classification of synapses:

1. Chemical: transmission of signal occurs by releasing chemical transmitters from presynaptic terminal to synaptic cleft. E.g. Ach, norepinephrine (NE), dopamine, etc.
   - (chemical synapse are the only type of synapses present in human nervous system.
2. Electrical: there is a gap junction between pre & post synaptic membrane allowing transmission of depolarization wave.
3. Conjoint synapse (electrochemical): transmission of impulses occurs by both mechanisms.
   - Both 2 & 3 are present in some fish & invertibrates.

**Mechanism of action of chemical transmitters:**

NT activates postsynaptic receptors to generate post synaptic potential (PSP) which is of 2 types:

1. Excitatory postsynaptic potentials (EPSPs): produced by depolarization of post synaptic membrane, mainly by open ligand gated Na+ channels.
2. Inhibitory postsynaptic potentials (IPSPs): produced by hyperpolarization of postsynaptic membrane due to open legand gated chloride & or K+ channels.
   - Presynaptic neuron is either excitatory or inhibitory to post synaptic neurons, because neurons can release only one type to transmitter (excitatory or inhibitory).

**The Primary Afferent Neuron** (Sensory afferent neuron)

**Stimulus-gated ion channels**, not voltage-gated, predominate in their membrane & they produce receptor or generator potentials. Receptors are analogous to dendrites & soma of a typical nerve cell. Axon immediately adjacent to such terminals (1st node of Ranvier for myelinated axons) serves as trigger zone for AP initiation & is analogous to axon hillock of a typical nerve cell. The rest is the same as for a typical nerve cell.
Resting Membrane Potential of Nerves (RMP)

- Living cells show normally a potential difference between inside -ve & outside +ve across cell membrane. RMP of nerve fibers is ~90 mV (potential inside fiber is 90 mV more -ve than outside).
- RMP is Electric charge difference inside a cell membrane, relative to outside cell membrane. 

Nernst Potential “Effect of Membrane Electrical Potential on Diffusion of Ions”

- If an electrical potential is applied across a membrane, electrical charges of ions cause these ions to move through membrane even though no concentration difference exists to cause movement.
- At normal body temperature, electrical difference that will balance a given concentration difference of univalent ions, such as (Na+) can be determined from the following formula, (Nernst equation):

\[
EMF \text{ (electromotive force) (mV)} = \pm 61 \log \frac{C_{\text{inside}}}{C_{\text{outside}}}
\]

Goldman equation (Goldman-Hodgkin-Katz equation, gives calculated membrane potential on inside of membrane when 2 univalent +ve ions, Na+ & K+, & 1 univalent -ve ion, Cl− involved.

\[
EMF \text{ (millivolts)} = -61 \cdot \log \frac{C_{Na^+} \cdot P_{Na^+} + C_{K^+} \cdot P_{K^+} + C_{Cl^-} \cdot P_{Cl^-}}{C_{Na^+} \cdot P_{Na^+} + C_{K^+} \cdot P_{K^+} + C_{Cl^-} \cdot P_{Cl^-}}
\]

C= concentration ; P= potential

Basis of resting membrane potential:

1- Selective permeability of plasma membrane. Strong permeability of K+, Weak permeability of (Na+), & Impermeability of large anions.
2- Diffusion of ions down their concentration gradients.
   K+ diffuses down its concentration gradient & out of the cell. Na+ diffuses (at slower rate) into cell.
3- Diffusion of ions down their electrical gradients; electrical attraction of cations & anions to each other. As K+ diffuses out of the cell, making the cell more -ve inside, K+ begins to move back into the cell towards -ve charge. (K+ is attracted to -vely charged cytosol.)

Threshold potential: Value of membrane potential at which AP is produced due to depolarization in response to a stimulus.
Subthreshold potential : Change in potential across cell membrane that is below level needed to produce AP.
Action potentials : Rapid change in membrane potential in an excitable tissue that acts as electric signal. It occurs due to opening & closing of voltage-gated ion channels. Stages Of AP are:
Resting state: Voltage-gated Na\(^+\) ion & K\(^+\) ion channels are closed.

Depolarization phase: Change in electric charge difference across cell membrane that causes the membrane potential moves toward zero, or becomes +ve.

- Voltage-gated Na\(^+\) ion channel open & Na\(^+\) rushes into cell, because of:
  a- concentration gradient (high to low)
  b- Electrical gradient (+ve charge to -ve charge).

- Voltage-gated K\(^+\) ion channels start to open more slowly than voltage-gated Na\(^+\) ion channels.

Repolarization phase: Phase of AP in which membrane potential moves from its maximum degree of depolarization toward value of RMP).

- Voltage-gated Na\(^+\) ion channels close.
- Voltage-gated K\(^+\) ion channels are open, & K\(^+\) ions leave the cell.

Hyperpolarization: ↑ in charge difference across cell membrane; to move away from 0 mV.

- Voltage-gated Na\(^+\) ion channels are closed.
- Voltage-gated K\(^+\) ion channels remain open longer than Na\(^+\) ion channels, thus more K\(^+\) ions leave the cell, until the voltage-gated K\(^+\) ion channels close & RMP is reestablished.
Refractory Period
Absolute refractory period: is the period when cell is completely insensitive to additional stimulation. It end during repolarization phase of AP. It is followed by a relative refractory period, when a new AP is triggered, if the stimulus is stronger than the threshold stimulus.

Effect of Na Ions on RMP
- It is least important; because nerve cell membrane at rest have a low conductance for it.

Effect of K Ions on RMP
- [K+] outside is very important; because of its high conductance of resting membrane.
  - A small ↑ in [K+]o → a considerable depolarization of RMP.
  - K+-induced depolarization of nerve & muscle fibers will produce involuntary contractions of skeletal muscles and may cause cardiac arrest (in systole).

Effect of Ca Ions on the RMP
- [Ca2+] outside is very important.
- The membranes of all cells have a Ca^{2+} pump (from interior to exterior of cell membrane).
- Voltage-gated Ca^{2+} channels (called Ca^{2+} - Na^{+} channels); when they open, both Ca & Na ions flow to interior of fiber. Ca^{2+} channels are slow activated, while Na channel is fast channels.
- [Ca2+] outside regulates number of Na^{+} channels which are open at RMP.
  - ↑ Ca^{2+} (hypercalcemia) →↑ voltage levels needed to excite Na channels→ ↓ excitability.
  - ↓ Ca^{2+} (hypocalcemia)→ Na channels can be activated by very little ↑ in membrane potential→ ↓ threshold → a highly excitable tissue.

Propagation of Action Potential: The Conduction Cycle:
AP elicited at any point on an excitable membrane usually excites adjacent portions of membrane, resulting in propagation of AP along membrane ( local circuit of current flow). That is, +ve electrical charges are carried by inward-diffusing Na^{+} ions through depolarized membrane. These +ve charges ↑ voltage for 1-3 mm inside large myelinated fiber. So, Na^{+} channels in these new areas immediately open & AP spreads. These new depolarized areas produce still more local circuits of current flow. Transmission of depolarizing process along a nerve or muscle fiber called a nerve or muscle impulse.

Direction of Propagation: An excitable membrane has no single direction of propagation, but AP travels in all directions away from stimulus, until entire membrane become depolarized.

All-or-Nothing Principle.
- It is applied to all normal excitable tissues. It states that; Once AP has been elicited at any point on membrane of a normal fiber; depolarization process will travels over entire membrane.
- Safety factor for propagation; the ratio of AP to threshold for excitation must at all time be greater than 1, for continued propagation of an impulse to occur.
NeuroMuscular Junction (myoneural junction) = NMJ

- Each skeletal muscle fiber is connected by an axon from a nerve cell called a motor neuron, which extends outward from brain or spinal cord, to muscle fiber.
- Neuromuscular junction: is functional connection between motor neuron & muscle fiber.
- Motor End Plate: is a specialized portion of muscle fiber membrane at NMJ, in which, nuclei & mitochondria are abundant, & cell membrane (sarcolemma) is extensively folded.
- The end of the motor neuron branches & projects to motor end plate. Cytoplasm at terminal ends of these motor neuron fibers is rich in mitochondria & contains tiny vesicles (synaptic vesicles) that store NT(Ach) (synthesized in cytoplasm of terminals, & absorbed rapidly into synaptic vesicles).
- As in all synapses, AP in motor nerve depolarizes presynaptic nerve ending, causing an influx of Ca+2 from synaptic space into nerve terminal bottom (through voltage-gated Ca+2 channels). Ca+2 exert an attractive influence on ACh vesicle, drawing them to fuse to presynaptic membrane & empty their ACh into synaptic space by exocytosis.
- When ACh released into synaptic space, it will activate ACh receptors (ACh-gated ion channels) in muscle fiber membrane → opening them → allow large numbers of Na+ to enter to inside muscle fiber. This creates a local +ve potential change inside muscle fiber membrane, called end plate potential → initiates AP that spreads along muscle membrane → contraction.
- In synaptic space are large quantities of enzyme acetylcholinesterase (AChE), which destroys ACh after it has been released from synaptic vesicles.

The Muscle

It is contractile tissue of the body. It is of 3 types: skeletal, smooth, & cardiac. 40% of body is skeletal muscle & 10% is smooth & cardiac muscle.

RMP of skeletal muscles: (–80) to (–90) mV, the same as large myelinated fibers.

Skeletal Muscle:

Muscle is regarded as bundle of bundles. Fascicles are the bigger bundles & each fascicle is a bundle of muscle fibers. The covering connective tissue layers are:
- Epimysium covering the muscle itself.
- Perimysium covering the fascicle.
- **Endomysium** covering the fibers.
  - **Sarcomlemma** (muscle cell membrane); contains electrically excitable channels that permit AP to be generated in response to adequate stimuli.
  - **Sarcoplasm** (cytoplasm of fiber); contains many nuclei, mitochondria, abundant myofibrils.
  - **Sarcoplasmic reticulum** (SR): surrounds each myofibril & runs parallel to it.
  - **Transverse tubules** (T-tubules) A set of membranous channels, extends into sarcoplasm as invaginations continuous with sarcolemma. Each T-tubule lie between two enlarged portions of SR called terminal cisternae.
  - **Myofibril** is parallel, threadlike structure, which play a fundamental role in muscle contraction. Myofibrils contain 2 kinds of protein filaments:
    - **Thick** filaments composed of protein myosin, each myosin molecule consists of 2 twisted protein strands with globular parts called cross-bridges.
    - **Thin** filaments composed primarily of protein actin, with 2 other types of proteins, tropomyosin & troponin. Troponin consists of 3 subunits,
      - Troponin T: anchors troponin molecule to tropomyosin.
      - Troponin I: inhibits interaction of actin & myosin.
      - Troponin C: binds Ca^{2+} & provides its sensitivity for contractile process.
  - Organization of thick & thin filaments produces alternating light & dark striations characteristic of skeletal muscle fibers (cardiac muscle fibers).
  - A sarcomere is the structure from one Z-line to the next Z-line. In center of each sarcomere is A-band. Center of A-band is H-band, with an M-line in the middle. On either side of A-band is I-band. In center of each I-band is a Z-line.

### Skeletal muscle contraction:
- AP across sarcolemma is normally initiated by stimulation of motor nerve. Voltage gated Na+ channels open first → sarcolemmal AP. Subsequently, Na+ channels close & voltage gated K+ channels open → repolarization phase.
- AP of sarcolemmal membrane also causes AP in each T-tubule as it passes by. Activation of T-tubules → release of Ca++ ions from terminal cisternae.
Ca\(^{2+}\) will diffuse rapidly throughout sarcomere & binds to troponin C → shifting of tropomyosin away from actin freeing binding site of actin to myosin head \((\text{excitation-contraction coupling})\).

- Myosin, with presence of ATP binds to actin & pulls actin filaments → shortening of muscle fibers.
- Myosin cross-bridges contain ATPase enzyme, which catalyzes breakdown of ATP → ADP & phosphate. This reaction releases energy that provides force for contraction.
- Ca\(^{2+}\) ions will be re-uptaken back to SR using ATP as energy, ending contraction phase.

**Sliding Filament Mechanism of Muscle Contraction:**
Muscle contraction occurs by a sliding filament mechanism which is caused by forces generated by interaction of cross-bridges from myosin filaments with actin filaments.

**Major events in muscle relaxation:**

- Acetylcholinesterase decomposes Ach, & muscle fiber membrane is no longer stimulated.
- Ca\(^{2+}\) ions are actively transported into SR.
- Linkage between actin & myosin filaments Break.
- Actin & myosin filaments slide apart.
- Muscle fiber relaxes.

**Muscle Tone:** (tonus)

- This result is a continuous state of partial contraction
- Even when a muscle appears to be at rest, a certain amount of sustained contraction is occurring in its fibers.
- It is a response to impulse repeatedly from spinal cord & traveling to a few muscle fibers.
- Muscle tone is important in maintaining posture.
- If tone is suddenly lost (example: loss consciousness), body will collapse.

**Rigor Mortis:** A few hrs after death, skeletal muscles partially contract, fixing joints. It may continue for 72 hours or more. It results from ↑ membrane permeability to Ca\(^{2+}\), which promotes cross-bridge
attachment, & ↓ availability of ATP in muscle fibers. Thus, actin & myosin filaments remain linked until muscles begin to decompose. **Muscle Fatigue**: inability to sustain maximal force or power. It can be divided into: physical & mental or central & peripheral. Its causes:

- Accumulation of lactic acid in muscle as a result of anaerobic ATP production.
  - ↑ Lactic acid → lowered pH which prevents muscle from response to stimulation.
- Decreased blood flow → insufficient Oxygen delivery.
- Ion imbalance across sarcolemma resulting from repeating stimulation.
- Psychological loss of the desire to continue exercise.

**Muscle cramp** is a painful condition in which a muscle undergoes a sustain involuntary contraction. It occurs when changes in ECF surrounding muscle fibers & their motor neuron, particularly ↓ electrolyte concentration, triggering uncontrolled stimulation of the muscle.

- People who regularly exercise aerobically produce less lactic acid, because aerobic training stimulate muscle to produce additional mitochondria, & new capillaries to grow within muscles, supplying more O2 & nutrients to muscle fibers.
  - Examples of aerobic exercise: bicycling, walking, & swimming.
  - Examples of Anaerobic exercise: weight lifting, basketball.

**Types of Muscle Fibers**: All muscles contain a combination of fiber types.

<table>
<thead>
<tr>
<th>Slow Fibers* (type I) red fibers</th>
<th>Fast Fibers* (type II) white fibers</th>
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<tbody>
<tr>
<td>(1) Smaller fibers.</td>
<td>(1) Large fibers, &amp; have extensive SR .</td>
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<tr>
<td>(2) More extensive blood supply.</td>
<td>(2) Less blood supply.</td>
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<tr>
<td>(3) ↑ mitochondria to support oxidative metabolism.</td>
<td>(3) ↓ mitochondria, oxidative metabolism is 2ndry.</td>
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<tr>
<td>(4) Large amounts of red myoglobin (an iron containing protein similar to Hb in RBC). - Myoglobin combines with O2 &amp; stores it until needed.</td>
<td>(4) A deficit of red myoglobin in fast muscle. ↓myoglobin =white muscle</td>
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<tr>
<td>(5) Always oxidative→ resistant to fatigue</td>
<td>(5) Large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process.</td>
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<td>(6) have 2 types:</td>
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<td></td>
<td>a- <strong>Type Ila</strong>: Fast twitch glycolytic fibers(white fibers), contract rapidly, but tend to fatigue (fatigueable) .</td>
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<td></td>
<td>b- <strong>Type Iib</strong>: Fast twitch fatigue-resistant fibers (intermediate fibers) → fast-twitch speed combined with a substantial oxidative capacity.</td>
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- When a muscle contracts weekly (swimming & running), red fibers (type I) are most activated →↑ mitochondria & ↑ capillary networks→↑ ability to resist fatigue during prolonged exercise, although their size & strengths may remain unchanged.
- Forceful exercise (weightlifting), uses muscle fast fatigable white fibers→ muscle fibers develop new actin & myosin,& as their diameters ↑, entire muscle enlarges. However, no new muscle fibers are produced during hypertrophy.

- **Motor unit** is anatomic element consisting of an anterior horn cell, its axon, neuromuscular junctions, & all muscle fibers innervated by the axon.
Summation & Tetanus: A muscle fiber exposed to a series of stimuli of ↑ing frequency reaches a point when it is unable to completely relax before next stimulus arrives. So, twitches combined & contraction becomes sustained (summation). When resulting forceful, sustained contraction lacks even partial relaxation, it is called tetanic contraction (tetanus).

Types of muscle contraction:

1- Isotonic (equal force-change in length): divided into:
   a- Concentric contraction: muscle contracts with force greater than resistance & shortens.
   b- Eccentric contraction: Muscle contracts with force less than resistance & lengthens.

3- Isometric contraction: (equal length-change in force) Muscle contracts but, does not change length. Most body actions involve both isotonic & isometric contraction.