Physiology Team Notes

Musculoskeletal Block

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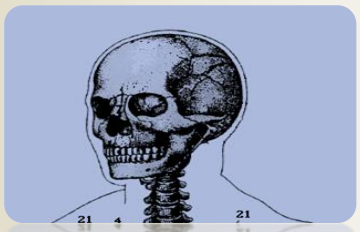

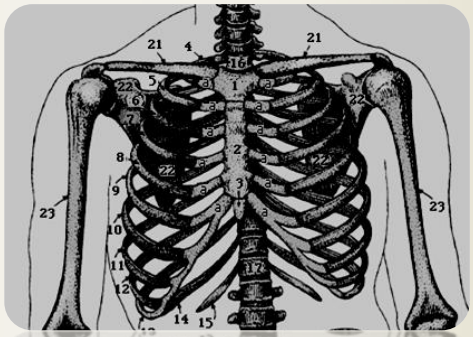

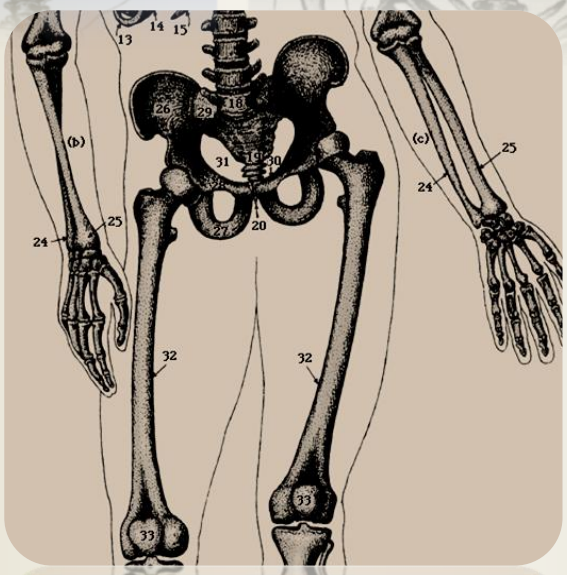

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Student Guide:

1- **The main Source of information here is the slides that was provided by the Doctors.**

2- **Anything written in brown square is an addition by the team.**

Example : Team Additions

3- **Everything written in Red is important.**

4- **Everything written in Green is from male slides.**

5- **At The end of this File . there is a summary for all numbers and values that were mentioned the lectures.**

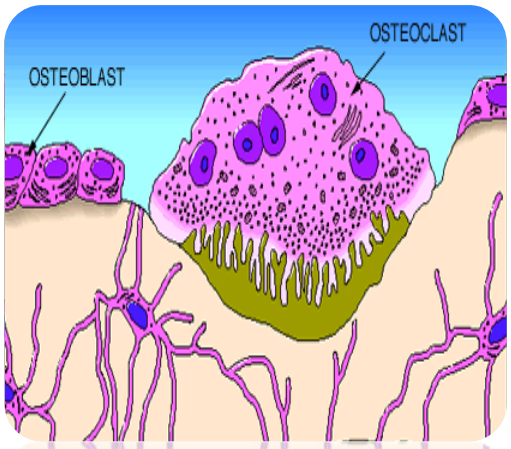
6- **These notes are for these five lectures .**

1. **Physiology Of The Bone.**
2. **Motor Unit.**
3. **RMP, Resting Membrane Potential.**
4. **Physiology Of Excitable Tissue., Prosperities Of Nerve Fibers.**
5. **Nerve Action Potential.**

Lecture 1

Physiology of the Bone

Functions of bone:



1-Supports soft tissue.
2-Protects vital organs (cranium, thoracic cavity).
3-Contains bone marrow for **blood cells synthesis.**
4-Reservoir of Ca++, PO4 to maintain constant concentrations of them in body fluids.

Calcium concentration in the blood is very closely controlled by the body. When blood calcium is low, the bones are used as a source. Calcium is added to bones when the dietary intake of it is high.

5-Allows body movement.

Structure of bone:

(Porous mineralized structure) Porous = has a pores

A-Cells.
B-Bone matrix: Calcified material, lacunae, Canaliculi
C-Periosteum & Endosteum.
D- red or yellow marrow in the center of the bone.

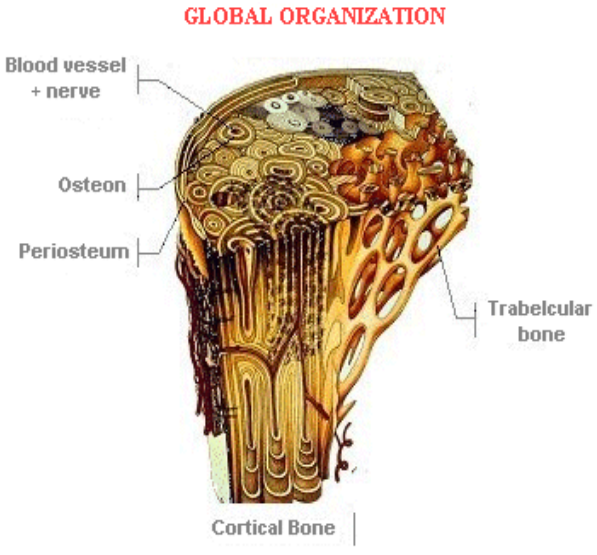
The Human Skeleton Is Actually Made Up Of 2 Types Of Bones :

(1) Cortical bone (compact bone) 80 % :

- Constitutes the dense concentric layers of long bones.
- Also outer layer surround trabecular bone at ends of long bones.

(2) Trabecular bone (spongy) 20% :

- present in the interior of skull, ribs, vertebrae, pelvis and **(in long bones present only in epipheseal and metaphysal regions.)**
- It has five time greater surface area than cortical bone (80% of the bone surface area).

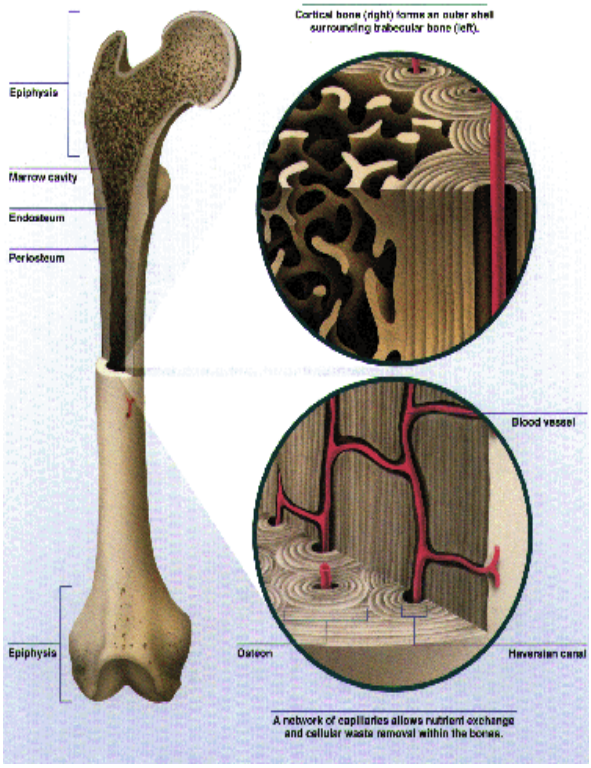


Compact Bone

- forms a protective outer shell around every bone in the body.
- has a slow ca ++ turnover rate.

Turnover Rate : Bone is constantly being remodeled throughout life, which results in the removal of old bone and its replacement by new bone. In general, turnover rate is the processes of bone resorption and formation .**[Turnover = Remodeling]**

- Has high resistance to bending where bending would be undesirable as in the middle of long bones).
- There is a series of adjacent bull's eye called osteons or **Harvesian systems**.
- **Osteon** is composed of a central vascular channel called the **Harvesian canal**,surrounded by a kind of tunnel of concentric lamellae of mineralized bone,.
- Harvesian canal can contain capillaries, aterioles, venules, nerves and possibly lymphatics.
- **Compct (Cortical) bone is The part of a bone where bone substance to bone space relationis a bigger .**



Trabecular (spongy-Cancellous) Bone

- **Rigid** but appears **spongy.**
- Forms the interior scaffolding wich helps bones to maintain their shape despite compressive forces.
- **The part of a bone where bone substance to bone space ratio is a smaller.**
- **Compared to cortical bone it is:**

  (1) less dense.
  (2) more elastic.
  (3) greater surface area.
  (4)it has high calcium turnover rate because of the greater surface area.

Calcium Homeostasis

ECF calcium:

Normal Ca2+ level in plasma ranges from 8.5-10 mg/dL

Calcuim Levels souldn't be less than 8.5-10 because , when $[Ca^{++}]_{ECF}$ is too low (**hypocalcemia**), voltage-gated ion channels start opening spontaneously, causing nerve and muscle cells to become hyperactive. The syndrome of involuntary muscle spasms called **Tetany**.

- **It exists in fractions :**

(1) Free ionized calcium 50% of total ECF calcium

(2) Protein-bound calcium 40%

- 90% bound to albumin
- Remainder bound to globulins
- Alkalosis increases calcium binding to protein and decreases ionized calcium.
- **Binding of calcium to albumin is pH-dependent.**

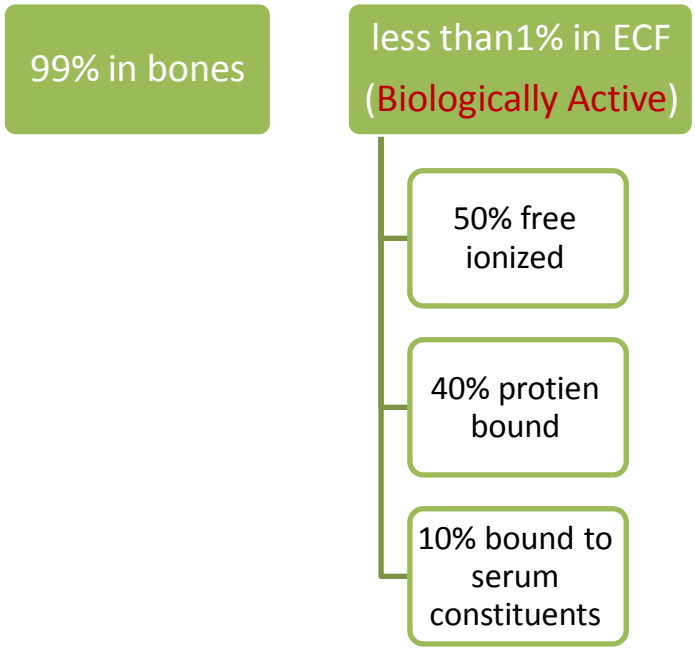
In Alkalosis, Hydrogen ions are depleted. Those ions are normally bound to plasma proteins like albumin and usually compete with Calcium ions for these proteins. Since Hydrogen ions are depleted, Calcium levels bound by the proteins will be increased.

(3) Calcium bound to serum constituents 10%

- (citrate & phosphate)

✓ **Only the free, ionized Ca^{2+} is biologically active.**

Biologically active means play important role in many biological processes in our bodies, for example: contraction of heart muscle, Coagulation.



PO_4 :

- Calcium is tightly regulated with Phosphorous in the body.
- **PO4 normal plasma concentration is 3.0-4.5 mg/dL.**

1)- **13 % Non- diffusible**: protein bound (85-90 % is found in bone.)
2)- **87 %Diffusable form:** (52% ionized & rest bound to ions)
small amount in ATP, cAMP and proteins compounds
Ca++ xPO4 =**constant** (solubility product).

If one of them(Ca or PO4) is decreased , the other one should increase to keep a **constant** amount.

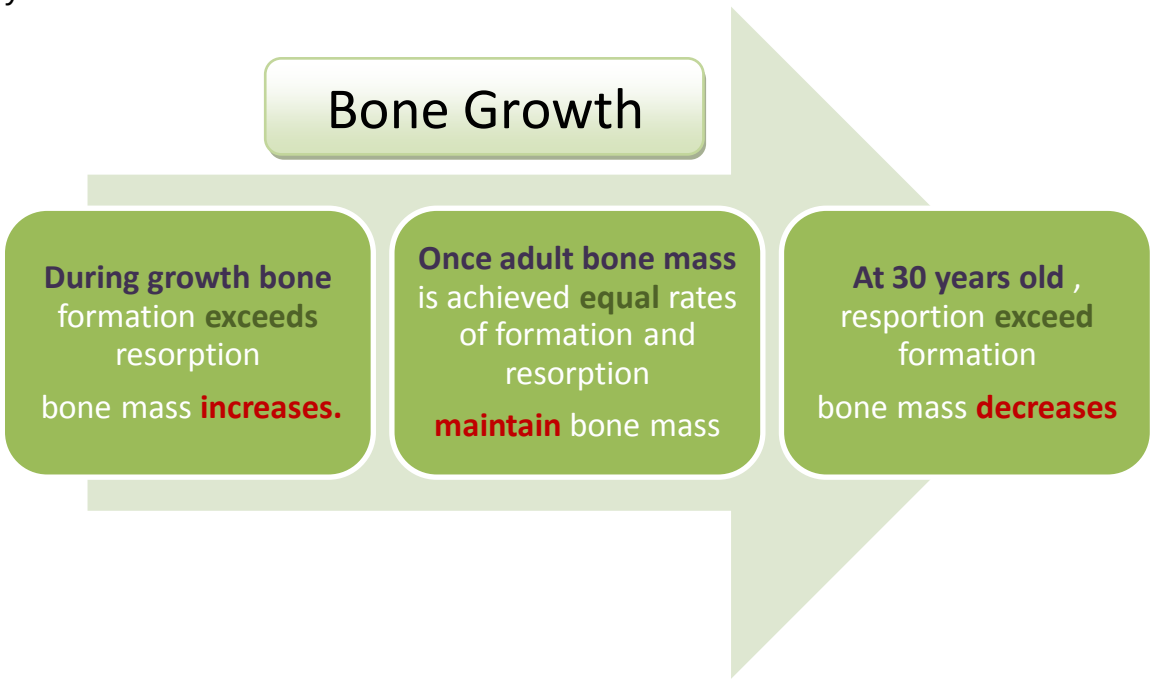
(if any one increase it should precipitate in bone)

Bone& Ca++:-

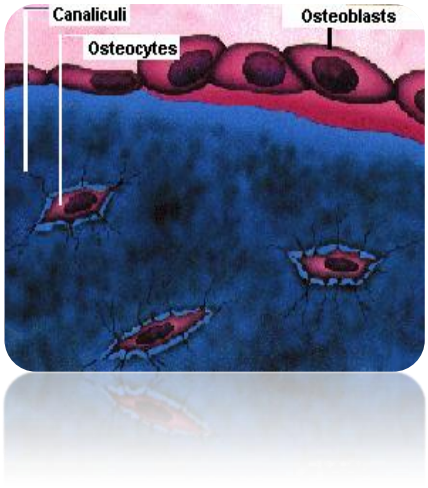
- **70% of Bone is** formed of calcium (99% of the Calcium of bone in form of hydroxyapatite crystal & phosphate salts(CaPO4 and hydroxide)
- **30% of bone is organic matrix (made mainly of collagen) It is called osteoid.**
- **Calcium salts** in bone provide structural integrity of the skeleton
- **About 99% of Ca** of our body is **in bone**, Whereas **< 1%** of Ca is **in ECF** ,if it falls below normal,Ca will move from bone into ECF.

BONE GROWTH:-

- **Linear** growth occurs at epiphyseal plates.
- Increase in **width** occurs at **periosteum.**
- During growth , rate of bone formation exceeds resorption and bone mass increases.
- 10% of total adult bone mass turns over each year during remodeling process.
- Once adult bone mass is achieved equal rates of formation and resorption to maintain bone mass.
- At about 30 years old , rate of resportion begins to exceed formation and bone mass slowly decreases.



Bone Cells: There are three types of bone cells:



(1) Osteoblast :

- bone forming cell that secretes collagen
- forming bone matrix around themselves.
- then they calcified (on which Ca++ and PO4precipitate).
- **When they become trapped in the matrix they change into osteocytes embedded into holes called“ Lacunae ”**

(2) Osteocytes :

- is the mature bone cell .
- It is **enclosed** in bone matrix.
- **Osteocyte is the most abundant cell in compact bone .**
- **Each osteocyte sends, from its cell-body , long cytoplasmic extensions that connect it to other osteocytes . These cytoplasmic extensions extend into & occupy tiny canals called canaliculi.**

Many recent studies suggest that Osteocytes:

(1) Have mechanosensory mechanisms (acts as receptors for mechanical stresses & strain).
(2) Regulate amounts of calcium & phosphate being transported in either direction (from ECF to boneor from bone to ECF).
(3) Act as regulators of osteogenesis & osteolysis by translating the degree and type of mechanical strain into biochemical signals.

Depending on the degree & type of strain , the bidchemical signals can result in:
(A) increased rate of osteogenesis (bone formation) by :
(1) stimulating osteoblasts , &
(2) increasing rate of transfer of calcium & phosphate from ECF to bone,

(B) increased rate of osteolysis (bone resorption) by :
(1) stimulating osteclasts, &
(2) increasing rate of transfer of calcium & phosphate from bone to ECF

Q - What is the function of osteocytes ?
A -Transfer of calcium from bone canaliculi to the ECF.

(3) Osteoclast :

- is a large multinucleated cell derived from monocytes
- function is to resorb the formed bone.(secrete Hcl to acidify area of bone to dissolve hydroxyapatite & acid proteases digest collagen)

they secretes HCL and Acid protease **through the ruffled border** acidifying and aiding dissolution of the mineralized bone matrix into their main components such as Ca^{+2}.

Canaliculi

- Within each bone unit is minute fluid containing channels called the canaliculi.
- Canaliculi traverse the mineralized bone.

- **Canaliculi are used for exchange of minerals (Calcium&Phosphate) nutrients and waste products through gap junctions,**

- **Interior osteocytes remain connected to surface cells (osteoblasts) via syncytial cell processes.**
- **Osteocytes transfer calcium from bone canaliculi to the ECF.**
- **These processes permits transfer of calcium from (large)surface area of the interior of canaliculi to extracellular fluid.**

Bone Formation

1-Bone formation begins when Active osteoblasts synthesize uncalcified Collagen fibrils to form arrays (raws)of an organic matrix called the **osteoid.**

2- Then **mineralization** (Deposition of Calcium &Phosphate) on the Osteoid Matrix.

Mineralization in important step in bone formation because it gives the bone its hardness and make it more dense .

Mineralization

- Requires adequate Calcium and phosphate
- **Dependent on Vitamin D**
- Alkaline phosphatase and osteocalcin play roles in bone formation(their plasma levels are indicators of osteoblast activity).

Control of bone resorption:

Bone resorption of Ca^{++} occurs by two mechanims:

(1) osteocytic osteolysis: this is **a rapid** and **transient** effect
(2) osteoclasitc resorption :is **slow** and **sustained** mechanism .
Both are stimulated by Parathyroid Hormone(PTH)

1-Osteocytic osteolysis

- Cell responsible for resorption is the osteocyte.
- Activity of osteocytes digest mineralized bone area then calcium transfer from canaliculi to extracellular f luid
- Does not decrease bone mass.
- Removes calcium from most recently formed crystals.
- Quick process

Osteoclasitc resorption

is slow and sustained mechanism .

- destroys matrix of old bone.
- diminishes bone mass.

- Cell responsible for resorption is the **osteoclast.**

(acidify area of bone to dissolve hydroxyapatite by **Hcl** then lysosomes & acid proteases digest collagen).

- **Ca from blood to bone [osteogenesis]**
- **Ca from bone to blood [osteoporosis at old age]**

- **bone resorption by osteoclasts does not merely extract calcium, but it destroys the matrix & demineralizes bone →thereby diminishes total bone mass.**

Q: Resorption involves only remove of minerals (F) (resorption involves both minerals and collagen)

Bone remodeling

- Remodeling means **continuous deposition of newbone** by osteoblasts & absorption of old bone by osteoclasts.
- Endocrine signals to resting osteoblasts generate paracrine signals to osteoclasts.
- Osteoclasts digest and resorb an area of mineralized bone.
- Local macrophages clean up debris البقايا.
- Then osteoblasts are recruited to site and deposit new matrix which will be mineralized.

Bone remodling affected by:

New bone replaces previously resorbed bone:

1-Mechanical Stress: on bone stimulates formation of stronger bone.(How?)

Mechanical Stress (Exercises for Example) stimulates Osteoblast's Activity leading to formation of Strong bone**.**

2-Pth & 1,25 Dihydroxycholecalciferol : stimulates osteoclastic activity & formation of osteoclasts.

1,25 Dihydroxycholecalciferol is the Active form of Vitamin D

3- Calcitonin :inhibits activity& formation of osteoclasts.

Osteoporosis

- The total bone mass of humans peaks at 25-35 years of age.
- Men have more bone mass than women.
- A gradual decline occurs in both genders with aging, but women undergo an accelerated loss of bone due to increased resorption during peri-menopause
- Bone resorption exceeds formation
- Reduced bone density and mass
- Susceptibility to fracture.
- Earlier in life for women than men
- The rate of osteoclastic resorption exceeds deposition of new bone.
- **The process of bone remodeling also controls the reshaping or replacement of bone following injuries such as fractures and micro-damage which occurs during normal activity. In the first year of life, almost 100% of the skeleton is replaced. In adults, remodeling proceeds at about 10% per year.**
- **An imbalance in the regulation of bone remodeling two sub-processes, bone resorption and bone formation, results in bone diseases, such as osteoporosis.**

Causes:

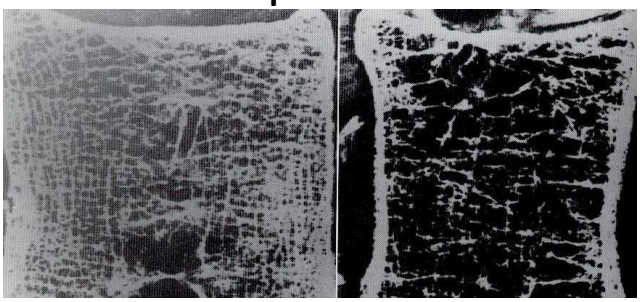
loss of anabolic steroids as estrogen & testosterone which stim osteoblastic activity . then bone becomes weak & ca++ is lost from skeleton.

Reduced risk by:

- High Calcium in the diet
- habitual exercise
- avoidance of smoking and alcohol intake
- avoid drinking carbonated soft drinks

Vertebrae of 40 vs. 92 yares old women:

Note the marked loss of trabeculae with preservation of cortex:



Hormonal Control Of Calcium:

Bone formation	*Bone resorption*
Stimulated by	**Stimulated by**
Growth hormone (constant)	Parathyroid hormone (constant)
Insulin-like growth factors	Vitamin D
Insulin	Cortisol
Estrogen	Thyroid hormone
Androgen	Prostaglandins
Vitamin D (mineralization)	Interleukin-1
Transforming growth factor-β	Interleukin-6
Skeletal growth factor	Tumor necrosis factor α
Bone-derived growth factor	Tumor necrosis factor β
Platelet-derived growth factor	
Calcitonin	
Parathyroid hormone (intermittent)	
Inhibited by	**Inhibited by**
Cortisol	Estrogen
	Androgen
	Calcitonin
	Transforming growth factor-β
	γ-Interferon
	Nitric oxide

Three Principal Hormones Regulate Ca^{++}:

1-Parathyroid hormone (PTH)

2- 1,25-dihydroxycholicalcefirol (active form of Vitamin D3) (cholicalcefirol=Vitamin D3)

3-Calcitonin.

They regulate Ca++ resorption, absorption and excretion from the **three organs** that function in Ca++homeostasis : **(bone, kidney and intestine**)

1-Vitamin D

Humans acquire vitamin D from two sources.

(1)produced in the skin by ultraviolet radiation on cholesterol to form Vit D3.
(2)ingested in the diet

In liver ⟶ Vit D3 converted to 25 hydroxycholecalciferol .
In kidney⟶ PTH convert 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol **(active form).**

The main action of active Vitamin D (1,25dihydroxycholecalciferol):

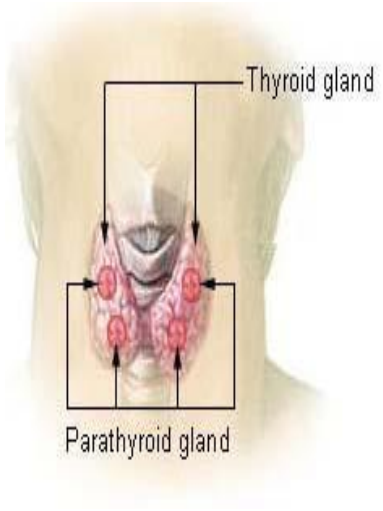
- **stimulate** absorption of Ca2+ from the intestine
- **stimulate** Ca reabsorption in kidneys
- **help** in bone formation
- **mobilize** ca++ from bone into plasma by increasing number of osteoclasts to increase plasma Ca++ levels (only when it drops)

2-Parathyroid Hormone (PTH) Action:

Parathormone from parathyroid gland.

Functions:-

- **To increase** plasma Ca^{++} levels when it drops and decrease plasma phosphate levels.



- **Acts directly** on the bones to stimulate Ca++ resorption by activating osteoclasts
- **on kidney** to stimulate Ca++ reabsorption in the distal tubule & to inhibit its reabosorptioin of phosphate (thereby stimulating excretion).
- PTH also **acts indirectly** on **kidney** by activation of 25-(OH) –D)into 1,25-(OH)2- D(active vit D).

3-Calcitonin :synthesized and secreted by the parafollicular cells of the thyroid gland (C cells).

C Cells : are the Thyroid Secreting cells.

- Calcitonin acts to decrease plasma Ca++ levels.
- The major stimulus of calcitonin secretion is: a rise in plasma Ca++ levels.

When the Calcuim levels in Plasma increased , this is the stimulus for producing Calcitonin, . Calcitonin then play an important role in decreasing Calcium Levels in Plasma. **The result is to maintain a constant levels of Calcuim in plasma**.

1. **it suppresses** osteoclastic activity and number in bone.
2. **it increases** osteoblastic activity to mineralize bone.

Osteogenesis imperfecta (brittle disease):

genetic disorder where there is defective osteoid formation .→ weak bones susceptible to fractures. Patients have short stature, blue sclera(بياض العين) ,bowed legs ,kyphosos or scolipsis.

Lecture 2

Organization of Nervous system and Motor Unit

They are 3 ways of Classify the Nervous System:

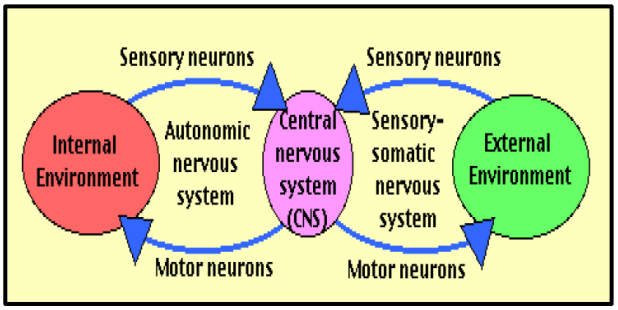
- Central &Peripheral
- Somatic & Autonomic
- Sensory & Motor

The nervous system is divided into :

1- central nervous system (CNS)
2-peripheral nervous system (PNS)

1-Central nervous system (CNS):

It is the part of the nervous system that integrates the sensory information that it receives from diff parts of body , and coordinates the activity of all parts of the body .



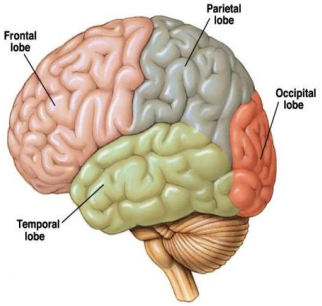
It consists of:-

1-The Brain.

2-The Spinal Cord.

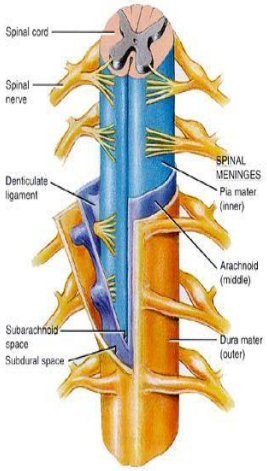
-the brain is protected by the **skull**, while the spinal cord is protected by the **vertebrae,** and <u>both</u> are enclosed in the **meninges.**

Brain:

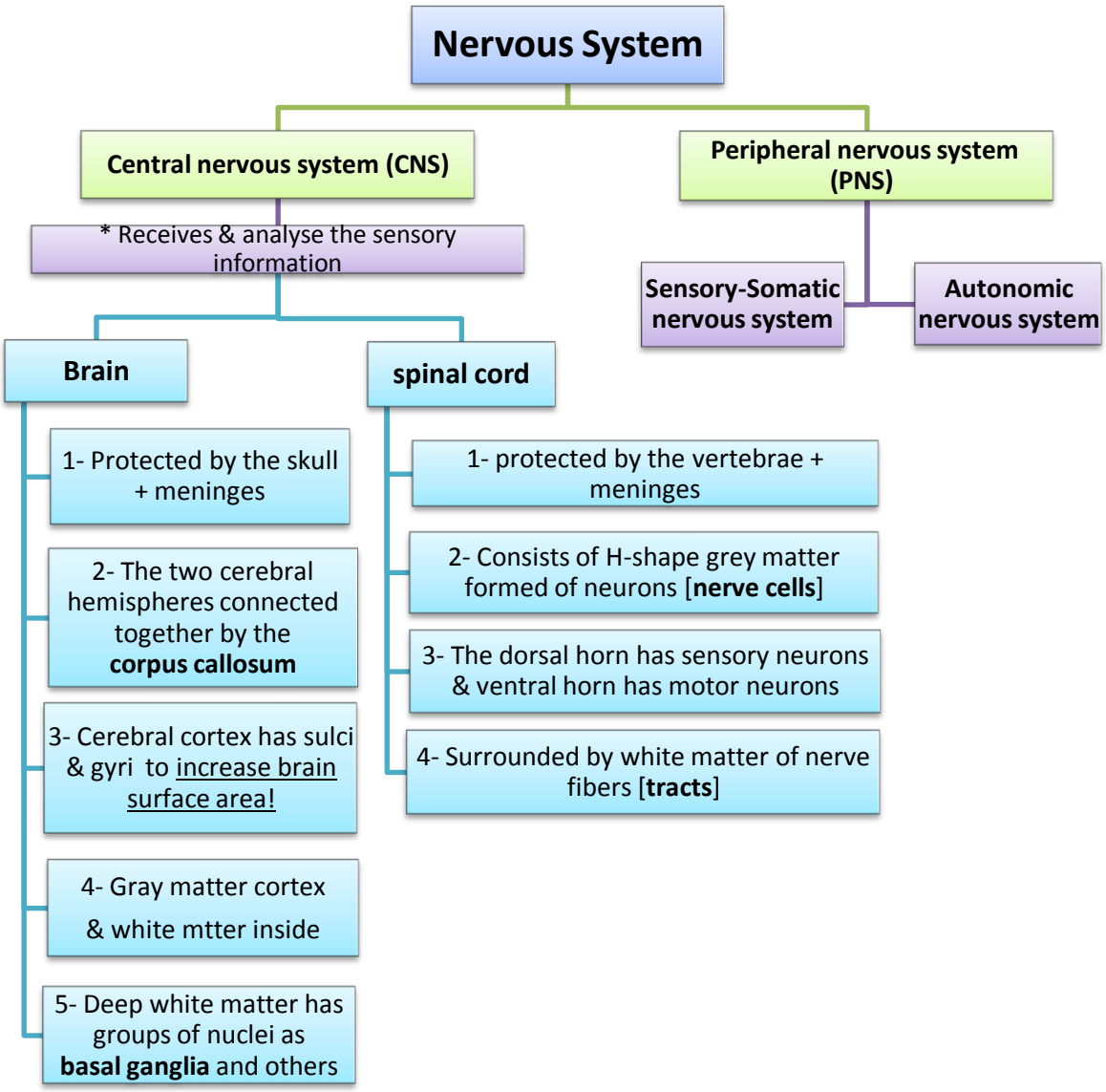


- Two cerebral hemispheres connected together.
- Each hemisphere consists of frontal,parietal, temporal & occipital lobes.
- Cerebral cortex has sulci &gyri to increase brain surface area.
- Deep white matter has groups of nuclei as basal ganglia and others
- Brain stem
- cerebellum

Spinal Cord:



- Consists of H- shape grey matter formed of neurons(nerve cells)
(dorsal horn has sensory neurons& ventral horn has motor neurons).
- Surrounded by white matter of nerve fibers(tracts).



The peripheral nervous system is subdivided into the :-

1-sensory-somatic nervous system.

2- autonomic nervous system.

Sensory-Somatic Nervous System:

- **The action** of this system is voluntary .
- **concerned with** our conscious awareness of the external environment stimulus and our motor activities toward it .
- **Operate** through the sensory-somatic division of the PNS.

The sensory-somatic system consists of :

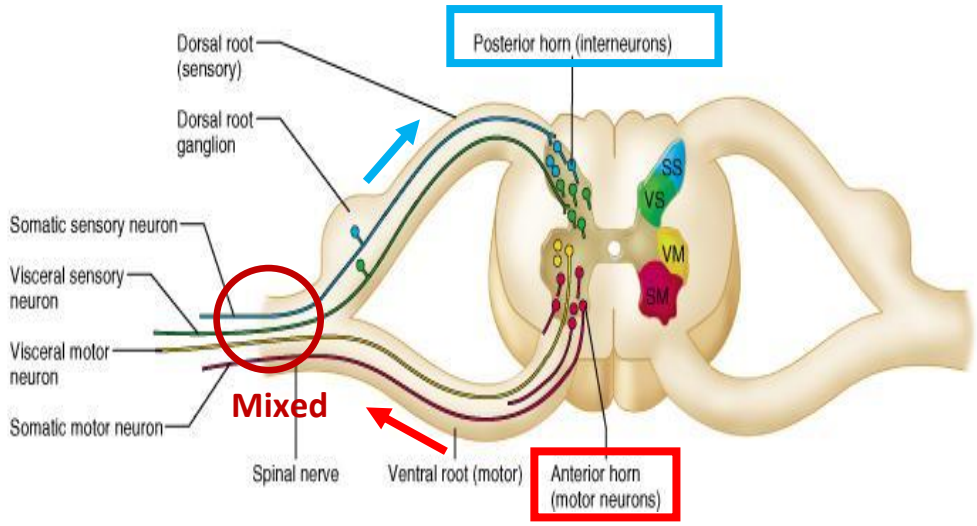
A. 12 pairs of cranial nerves (control function of head & neck)

B. 31 pairs of spinal nerves.

A) Spinal nerves in the sensory-somatic system :

1. Spinal nerves take their origins from the spinal cord.
(8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal)
They control the functions of all parts of body **except** head & neck.

2. All of the spinal nerves are "mixed" :
they contain both sensory and motor neurons.
(which came from the dorsal & ventral roots)

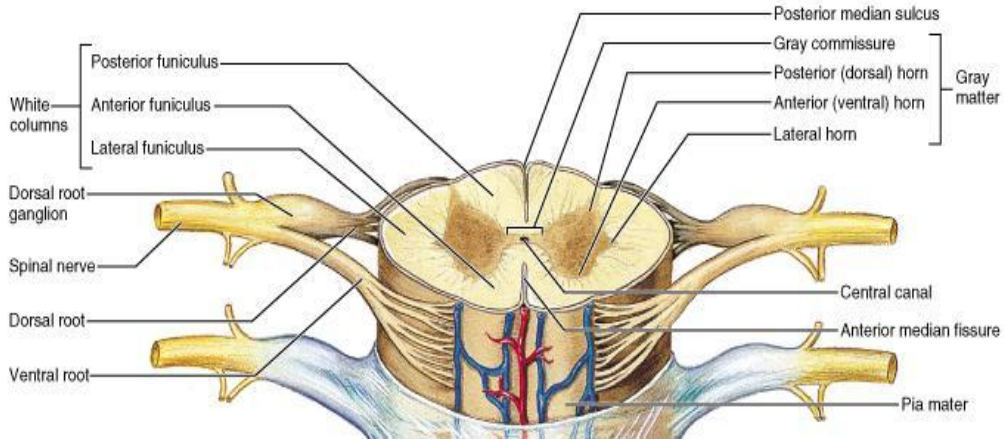


1- The Sensory Neurons:

- **Afferent** neurons which relay nerve impulses toward the central nervous system.
- Sensory neurons running from stimulus receptors that inform the CNS about all types of sensations.
- (They pass in the **dorsal root**)

2-The Motor Neurons:

- **Efferent** neurons which relay nerve impulses away from the central nervous system to periphery (skeletal muscles , or gland) to take action.
- (They pass in the **ventral root**)



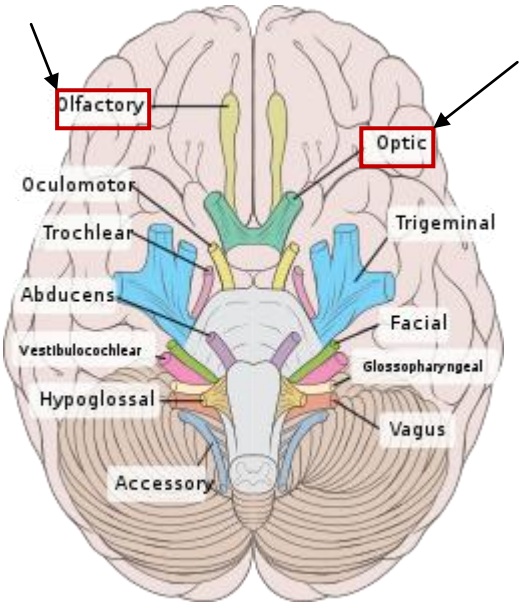
B) Cranial nerves in the sensory-somatic system :

- 12 pairs cranial : 10 originate from brain stem nucei..

While the left 2 from other parts of the brain it self.

The Nuclei of cranial nerves **I** and **II** located on **forebrain & thalamus.**
The cranial nerves mainly control the functions of all structures of the head with some exceptions.

Cranial Nerve 1 called Olfactory Cranial Nerve 2 called Optic

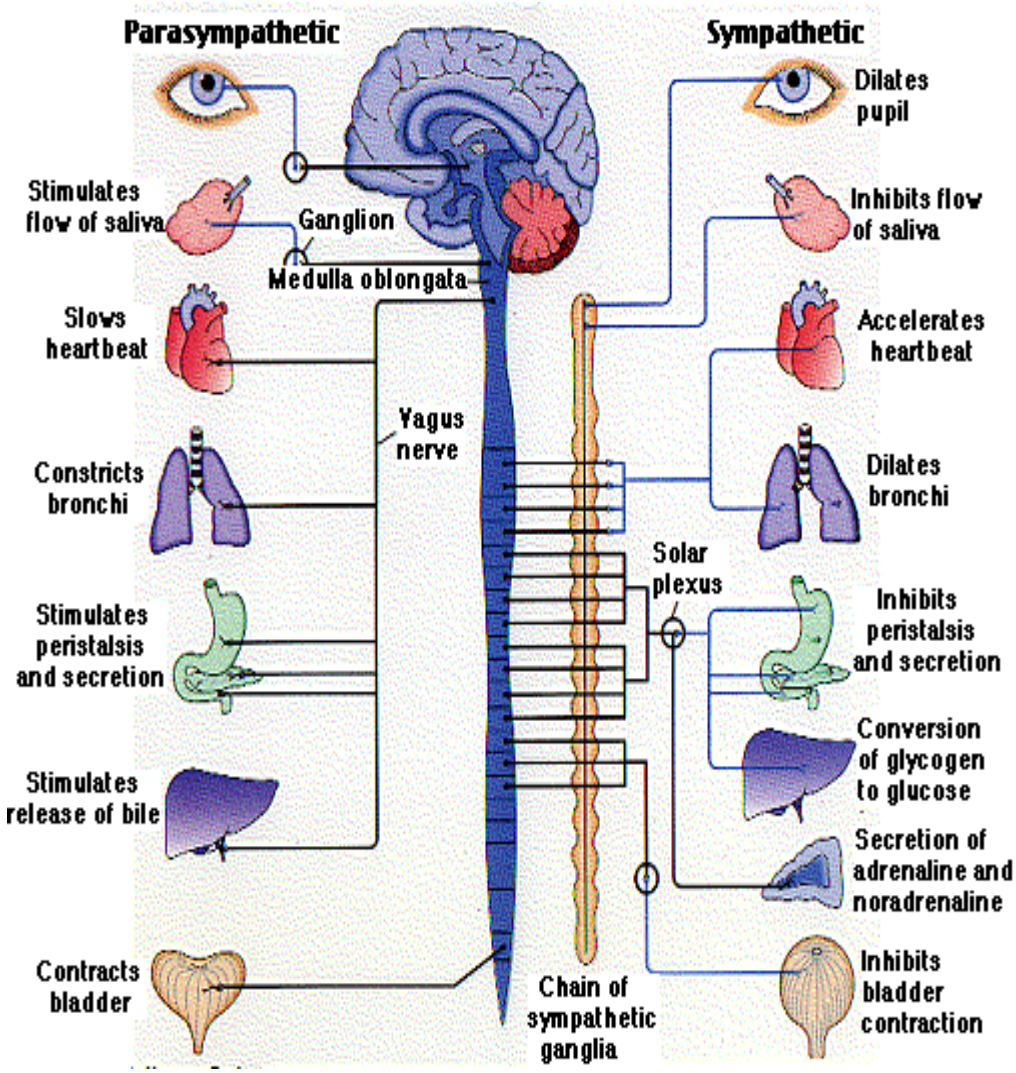


Autonomic nervous system:

- **Type of system:** Autonomic nerves
- **Origin and fate:** From hypothalamus or medulla oblongata in CNS
- **To:** the heart, lungs, viscera, and glands (both exocrine and endocrine) .
- **Action:** , movement involuntary
- **Number of fibers:** Pre and post ganglionic fibers. i.e. two fibers.
- **Function**: responsible for monitoring conditions in the internal environment and bringing about appropriate changes in them.
- **Controlling:** the contraction of both smooth and cardiac muscles.

The ANS has two subdivisions :

1-Sympathetic Nervous System And The
2-Parasympathetic Nervous System.



• The **pre**ganglionic neurons, arise in the **CNS** .
They run to another ganglion in the body "**post**ganglionic neurons",
which run to the **effector organ** (cardiac muscle, smooth muscle, or a gland).

Neuron:

- **Unit of function** of the central nervous system.
- Either **sensory** or **motor.**
- Motor neuron is **mostly antrior horn cell in the spinal cord** supply skeletal muscle.

Parts of motor neuron & function of each part:

1- Soma (cell body).
2-Dendrites :
carry nerve impulses from surroundings to the soma.
3 -Axon hillock:
at which nerve **impulses begin &pass in one direction** from soma to the axon(nerve fiber) then to axon terminal.

4-Axon and axon terminal end on skeletal muscle via neuromuscular junction
Nerve cell axons are very thin, about 1 micrometer. However, they are extraordinarily long. For many motor neurons the axon is over a meter long, extending from the spinal column to a muscle cell.

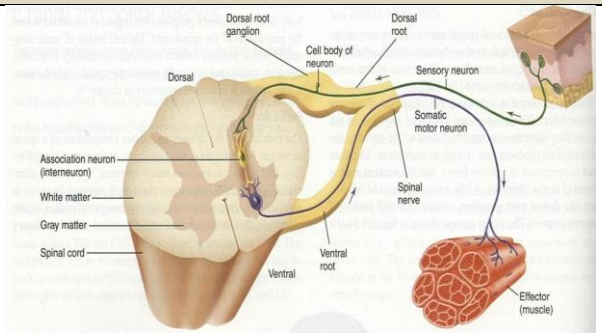
Motor unit:

- A motor unit is a single **α-motor neuron** and all of the corresponding muscle fibers it innervates (supplied with it).
- All of these muscle fibers will be of the same type (either fast twitch or slow twitch).
- When a motor unit is activated, all of its muscle fibers contract.
- Groups of motor units often work together to coordinate the contractions of a single muscle.
- all of the motor units that subserve a single muscle are considered a **motor unit pool**.
- When the axon of the motor nerve enters the muscle, it divides into many branches inside it.

• The terminal of each of these branches is enlarged, contains vesicles of ACH and it supplies only one muscle cell (muscle fiber).

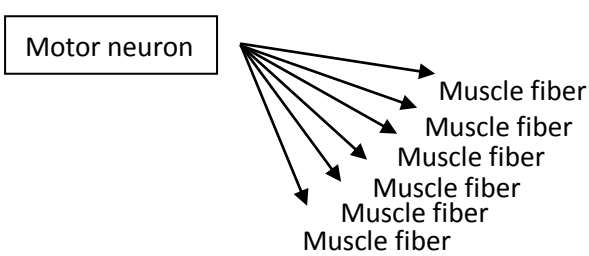
• Thus each muscle cell is supplied by only one AHC .On the other hand, one AHC through the branches of its axon, supplies several muscle cells.

One Nerve is supplies group of muscle fibers , but Each branch of the nerve is supply only one Muscle fiber.
AHC = Anterior horn cell.

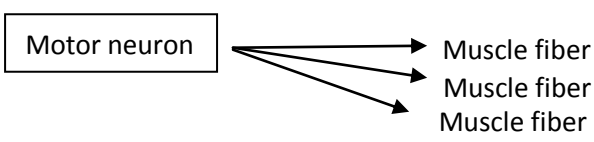


The number of muscle fibers within each motor unit can vary:

- **Fine movements:** need motor units have **small** number of muscle fibers.
- **Gross movements:** need motor units have large number of muscle fibers.



Gross movement



Fine movements

Examples:

1. **Thigh muscles** can have a thousand fibers in each motor unit. [Gross Movement]
2. A single motor unit for a muscle like the **gastrocnemius** (calf) muscle (for gross movements) may include 1000-2000 muscle fibers. [Gross Movement]
3. A single motor unit for **eye muscle** controlling eye movements (fine movements) may trigger fewer than 10 muscle fibers.

-In General: the number of muscle fibers innervated by a motor unit is a function of a muscle's need for refined motion.

- The **smaller** the motor unit, the more **precise** the action of the muscle.
- Muscles requiring more refined motion are innervated by motor units that synapse with fewer muscle fibers.

·In medical electrodiagnostic testing **(EMG , electromyography)** for a patient with muscle weakness, careful analysis of the motor unit action potential (MUAP) size, shape, and recruitment pattern can help in distinguishing a **myopathy** (مرض عضلي) from a **neuropathy** (مرض عصبي) .

Motor unit recruitment :

It is the progressive activation of a muscle by successive recruitment إمدادات متعاقبة of contractile units (motor units) to accomplish increasing gradations of **contractile strength**.

- All muscles consist of a number of motor units each one has its own muscle fibers belonging to it.
- When a motor neuron is **activated**, all of the muscle fibers innervated by this motor neuron are **stimulated** and **contract** .

  ✓ The activation of **one motor neuron** will result in a weak muscle contraction.
  ✓ The activation of **more motor neurons** will result in more muscle fibers being activated, and therefore a stronger muscle contraction

- Motor unit recruitment is a measure of how many motor neurons are activated in a particular muscle, and therefore is a measure of how many muscle fibers of that muscle are activated.
  The higher the recruitment the stronger the muscle contraction will be !

Rate coding of muscle force:

- The force of muscle contraction produced by a single motor unit is determined in part by :
  1. The **number** of muscle fibers in the unit .
  2. The **frequency** of nerve impulses نبضات عصبية with which the muscle fibers are stimulated by their innervating axon.

Motor unit firing rate معدل الاشتعال للنبضات العصبية :

The rate at which the nerve impulses arrive to the muscle .

It varies from frequencies :

- Frequencies are **low** enough to produce a series of single twitch contractions.

"**slow weak contraction**" .

- Frequencies **high** enough to produce a fused titanic contraction .

"**fast contraction without relaxation"**

- **In general,** the motor unit firing rate (firing of nerve impulses) of each individual motor unit increases with increasing muscular effort until a maximum rate is reached.

  • If AHCs fire at very fast rate >fast MUPs> strong contraction at maximum effort > we get in the EMG interference pattern.

MUP: Motor unit Potential

Lecture 3

Resting Membrane Potential

What are Excitable tissues?
A: They are nerve and muscle.

Action potential is also called Nerve Impulse

Q: what property do excitable tissues have that makes them different from other body tissues ?
A: Their membrane acts as an electric capacitor(مكثف) storing opposite charges on the opposite sides of the membrane.
this **creates**:

-Resting membrane potential(RMP) of high value (-70 to -90 mV) compared to other body cells (in RBC , for Example MP= -5 mV).

In case of **Non-stimulated** (**Resting**)neurons:
The Neuron Membrane stores a Negative charge Inside the cell and Positive charge outside the cell. Depending on the difference between these opposite charges we can decide if the tissue is Excitable or not .

Nerve and muscle have Resting membrane potential (potential means difference between opposite charges in both sides of the Neuron membrane) which is **high** (-70 to -90 mV) so they considered a Excitable tissue. Whereas RBC have a very **low** potential(-5mV) so they are **not** an Excitable tissue .

This high RMP makes the nerve or muscle membrane function as a **capacitor** , that can "discharge" producing large voltage changes (**action potentials**).

"Discharge" means the negative charges can leave from inside to outside of the cell , then these negative charge outside the cell could make an Action .

Neuron:
unit of function of the central nervous system, mostly anterior horn cell inthe spinal cord supply skeletal muscle.

Parts of motor neuron & function of each part:
1- **Soma** (cell body)
2-**Dendrites:** carry nerve impulses from surroundings to the soma

3-**Axon hillock** : at which nerve impulses begin &pass in one direction from soma to the axon(nerve fiber) then to axon terminal.
4-**Axon** and axon terminal end on skeletal muscle

The impulses reach the muscle from nerve as **electrical impulses**.

Simply , It called **Electrical** impulses because it results from **imbalance** in Charges in both sides of the membrane , this imbalance is done by **Electrolytes** (mainly Na and K)

Q : What is the membrane potential (MP) ?

It is the difference in potential (voltage) between the Inner side & outer side of the nerve membrane.

Q : What are the states of MP ?

(1)Resting Membrane Potential (RMP) :

value of MP in a " resting " state) unstimulated excitable nerve membrane(. It ranges between -70 and -90 mV in different excitable tissue cells,

in large myelinated nerves = -90 mV.

(2) Graded Potential (Local Response) :

MP in a stimulated cell (nerve) that is producing a local , non- propagated potential (an electrical change which is measurable only in the immediate vicinity of the cell but not far from it) .

- The stimulus is **weak**→ leads to a just a slight difference in charge across the membrane of a cell.
- Not propagated (غير منتشر), that's why is called **localized**, thus permit communication over a few mm, not far and cannot reach the axon terminals.

(3)Action potential (AP) :

MP in case of a nerve that is generating a propagated electrical potential after stimulation by effective stimulus (an electrical potential which can be measured even at long distances far from the cell-body of the nerve)

- The stimulus is strong→ Leads to a big difference in charges across the membrane → strong enough to spread to the axon terminal.

Q: What are the types of membrane ionic channels?

(1) Leak (Diffusion , Passive) channels :

- Pores in the cell-membrane which are open **all the time** , therefore ions diffuse through them according to the ion Concentration Gradient .

(2) Voltage-gated channels :

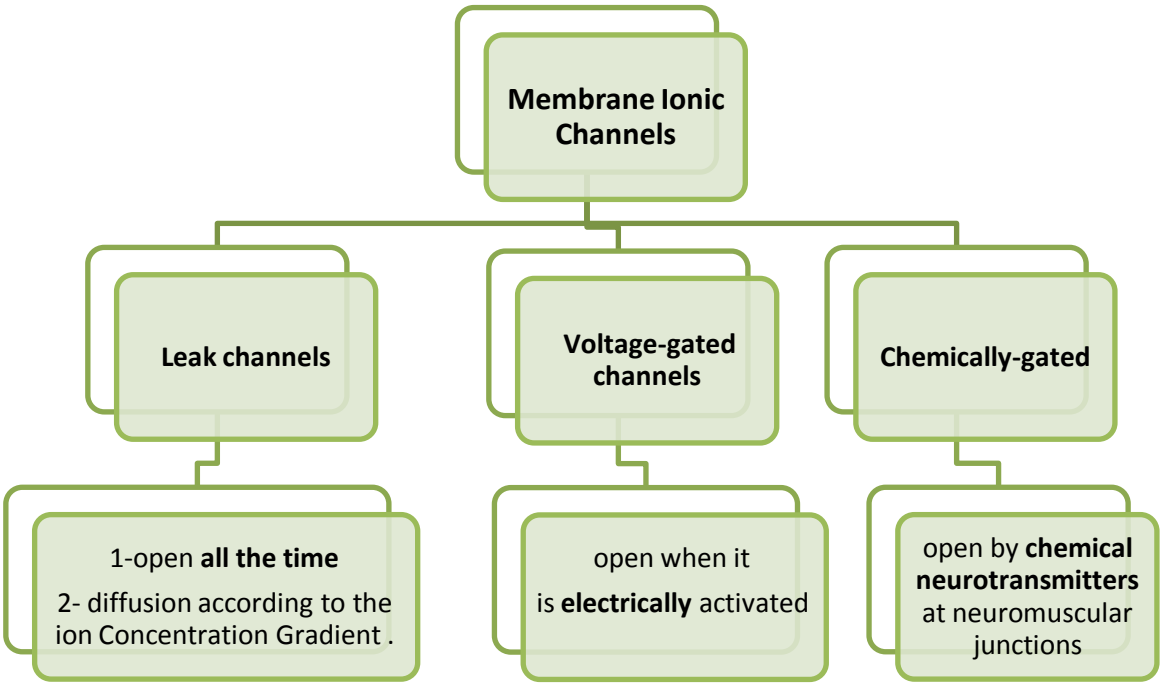
open when the cell-membrane is electrically activated .

Electrically activated= activated by changes in electrical potential difference near the channel.

(3) Chemically-gated (ligand-gated) channels :

open by chemical neurotransmitters at neuromuscular junctions & synapses (connections between neurons).

A Neuromuscular junction : the synapse or junction of the axon terminal of a motor neuron with muscle



Basic physics of membrane potential:

- Nerve has **semipermeable membrane** separating the ECF from the ICF .

1- K is high inside the nerve membrane & low outside:

- therefore potassium continuously diffuses through the K+ **leak** channels from inside the cell to outside .**Why?**

-because diffusion of k ions through membrane occurs from **high conc. inside** to outside carrying +ve charge with it→build up of <u>electropositivity outside</u> & <u>electronegativity inside.</u>

2- Na is high outside membrane & very low inside membrane

so the direction of the Na+ chemical (concentration gradient) gradient is **inward** and sodium continuously diffuses through the Na**+ leak** channels from outside (the extracellular fluid , ECF) to inside the cell (the intracellular fluid , ICF).

→build up of electronegativity outside & electropositivity inside.

NERNST EQUATION

Ions are continuously across the membrane until certain point where it stop moving through the cell membrane, Nernst Equation is used to **calculate** at wich point the ions will hane **no net movement.**

<u>We can devide the Nerst Eguation into Two Part :</u>

1-The Potassium Nernst (Equilibrium) potential: (to Know at which point there will be no net movement for Potassium ions across membrane).

2-The Soduim Nernst (Equilibrium) potential: (to Know at which point there will be no net movement for Sodium ions across the membrane).

(A) The Potassium Nernst (Equilibrium) potential.

Nersnt calculate the level of concentration potential of ions across the membrane that prevent net diffusion of ions to inside or outside.

Nernst made a hypothesis which said that if we suppose that

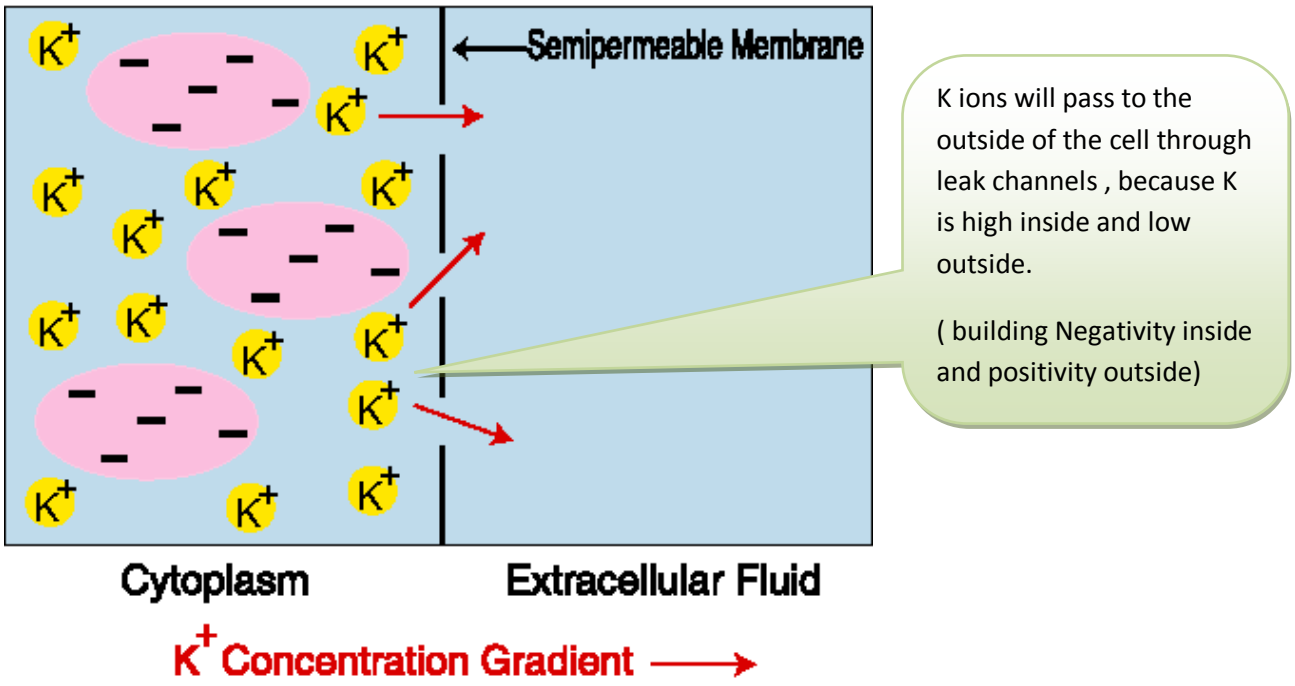
(1) the ECF and ICF contained **ONLY** potassium ion .

(2) and that the cell-membrane was freely permeable to K.

• Then K+ will diffuse down its concentration (chemical) gradient (via the K+ leak channels) from inside the cell to outside , carrying with it +ve charges to the outside .

-This progressively increasing the negativity on the inner side of the membrane because we are losing +ve charges from inside).

•At this goes on and on , negative charges build inside an opposing negative electrical potential , tending to prevent the exit of the +ve potassium ions (force tends to keep K inside) .



This negative electrical potential will grow INSIDE until it becomes strong enough to balance and counteract the concentration gradient which tends to push K+ OUTSIDE.

When this electrical gradient (electrical force) , which tends to keep K+ inside equals(=) the concentration gradient (which tends to push K+ outside) ⍰ there will be no net K+ movement across the membrane .

Electrical gradient : (imbalance in **charges** in both sides of Cell membrane)
Concentration gradient :(imbalance in Number of **molecules** in both sides of cell membrane).

No Net Movement For K when :

The **Electrical** gradient force keeps K inside **=** The **concentration** Gradient force pushes K out side . **(No K Net Movement**).

The membrane potential (MP) in that case is called:-

Nernst Potential for K+ (or K+Equilibrium or Diffusion Potential)
It equals = -94 mV (The -ve charge always refers to the inside of the cell relative to the outside)

(This value was calculated by Nernst equation)

E.M.F (mV) = + 61 log (K+ conc. Inside/ K+ Conc outside)= =**-94MV**

(B)-The SODIUM Nernst (Equilibrium) potential.

Nernst made a hypothesis which said that if we suppose that:-

(1) the ECF and ICF contained **ONLY** sodium ions ,
(2) and that the nerve-membrane was freely permeable to Na+.

Then Na+ will diffuse **down its concentration gradient** to the **Inside** of the cell, carrying with it +ve charges , and progressively decreasing the negativity on the inner side of the membrane.

Na will go inside the cell because it **is higher out side** .

As this goes on and on , and as the **positive charges build inside** , an opposing Electrical Potential begins to develop , tending to prevent the +ve Na+ ions from entering.

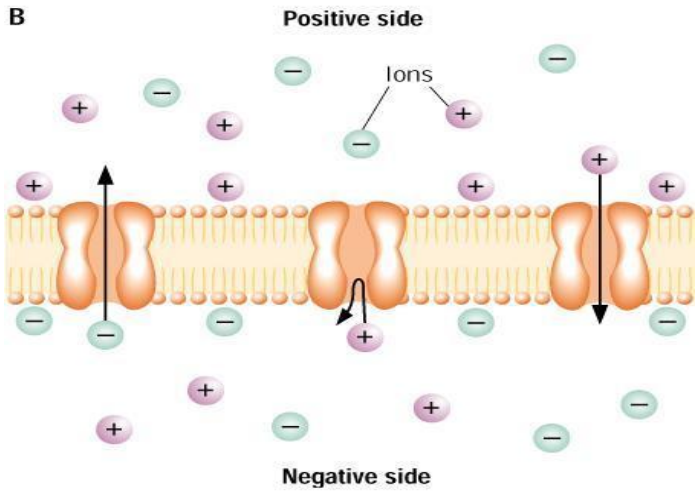
This electrical potential will grow until it becomes strong enough to balance and counteract the concentration gradient which tends to push Na+ inside .

When this electrical gradient (force) , which tends to drive (PUSH) Na+ outside **equals =** the concentration gradient (which tends to push Na+ in) ⍰ there will be no Na+ movement across the membrane .

The MP potential in that case is called:-

Nernst Potential for Na+ (or Na+ Equilibrium or Diffusion Potential) = +61 mV .

(The charge always refers to the inside of the cell)



What determines the magnitude (value) of the Equilibrium (Nernst) Potential ?

The ratio of the ion concentration on the two sides of the membrane (inside &outside).

The value of this potential EMF can be determined by :

Nernst potential = electromotive force (EMF)

Nernst potential= **Electromotive Force** = membrane potential at which there is no net (overall) flow of that particular ion from one side of the membrane to the other.

E.M.F (mV) = + 61 x log Ion conc. Inside /Ion Conc outside.

-The greater the ratio(it means ion conc inside is higher than outside) the greater the force for ions to diffuse in one direction (from inside to outside)

-for K = - 94 mv & for Na = + 61 mv

((it is –ve for K & + ve for Na (K diffuses out so ↓ the ratio & Na diffuses inside so ↑ the ratio))

RESTING MEMBRANE POTENTIAL OF NERVE:

it is **potential difference** across nerve membrane during rest (**without stimulation**).

Value:- -90 mv in large nerve fibers (-ve inside) (range-70 mv TO -90 mv)

(the -ve or +ve sign referes to the inside of the membrane)

-The membrane is **polarized**

Two questions should be asked :

Q1: What are the factors that make the inside of the cell negative ?

Q2: and give the RMP of large myelinated nerves the value of - 90 mVolts(or -70 to -90 mV)?

Depend mainly on transport properties of resting membrane , the **factors** that make the inside of the cell negative are :

1- Contribution of K & Na diffusion potential through Na & K leak channels of nerve membrane.

2-Active transport of Na & K ions (Na/K pump).

3- Negative ions inside membrane as phosphate sulphate & proteins.

How this value -90 was calculated (Resting Membrane Potential for large nerve)?

(Summary)

1

- **1- Contribution of K diffusion potential:**
- -K inside is 35 times higher than outside(35/1)
- - Nernst potential = - 61mv x log 35/1 (1.54) =-94 mv

2

- **2- Contribution of Na diffusion potential:**
- Nernst potential = + 61 x log 0.1= + 61 mv

3

- These values are calculated when there is only one ion is considered (hypothesis). In reality , there are several ions go across membrain.

4

- Using this values(-94 and +61) in Goldman equation.(to calculate diffusion potential when membrane permeable for several ions)
- =**-86** mv

5

- **3- contribution of Na/K PUMP:**
- Pumps 3Na to outside & 2 K to inside, causing
- net loss of +ve ions ,loss of + ve charge from inside , create negativity about **- 4**mv inside

6

- -so net membrane potential will be :-
- (-86 mv) + (- 4mv) = **-90 mv**

Origin of RMP:

1- Contribution of K diffusion potential:-

N.B: K diffusion contributes far more to membrane potential than Na diffusion .

(1)At rest , K inside is 35 times **higher** than outside.

K+ leak channels more K+ diffuses to outside than Na+ to inside

because K leak channels are far **more permeable** to K than Na about 50- 100 time due to **small size** of K molecules.

➔ more potassium lost than sodium gained.

net loss of +ve ions from inside the cell → more negative inside

(**net K OUTFLUX TO OUTSIDE causing –ve inside**)

Applying Nernst Equation:-

-K inside is 35 times higher than outside(35/1)

- Nernst potential = - 61mv x log 35/1 (1.54) **=-94 mv**

(if K is the only ion act on membrane) →RMP = -94 mv with negativity **inside** the nerve.

2- Contribution of Na diffusion potential:-

Na leak channels :

have Slight permeability to Na ions from outside to inside.(why slight?)

Nernst potential = + 61 x log (Na inside/ Na outside = 0.1)= + 61 xlog 0.1= + 61 mv

Nernst potential for Na inside membrane = **+ 61mv**.

(if Na is the only ion act on membrane →RMP =+ 61mv with positivity **inside** the nerve

- Na diffusion potential = + 61mv & that of K = - 94 mv

- These values are calculated when there is only one ion is considered (hypothesis). In reality , there are several ions go across membrane . So we should use a Goldman Equation.

-using this values in **Goldman equation**

(to calculate diffusion potential when membrane permeable for several ions)

net value of the internal membrane potential of about -86 mv

N.B:almost all of this determined by K diffusion

(because membrane is 50- 100 times permeable to K than to Na)

- **i.e potassium potential has the upper hand** .

3- contribution of Na/K PUMP:-

Pumps 3Na to outside & 2 K to inside, causing

net loss of +ve ions ,loss of + ve charge from inside , create negativity about - 4mv inside

-so net membrane potential will be :-

(-86 mv) + (- 4mv) **= -90 mv**

4-Effect of Large intracellular anions(negative ions)

(proteins , sulphates & phosphates)

very **low** effect.

- In a resting cell , the RMP is **closer** to the potassium equilibrium potential than to sodium equilibrium potential i.e., potassium has the upper hand .
- Therefore , we can say that the RMP depencds **mainly** on difference in concentration of potassium inside & ouside the cell
- Whereas , the value of the MP during the AP depends mainly on difference in concentration of sodium inside & ouside the cell i.e., during the AP sodium has the upper hand.

Measuring membrane potential

VOLTMETER:

To measure **very small** membrane **potential difference** between inside & outside as resting membrane potential . **How?**

a small filled pipette containing electrolyte solution put inside the nerve fiber & another electrode is placed in the outside . Membrane potential difference between inside & outside measured.

Lecture 4 and 5

The Action Potential and Properties of Nerve Fibers

Types of Nerve Fibers

Classification According to Myelination:

A- Myelinated : have myelin sheath (diameter more than 1um)

1-type A fibers:

(as somatic (motor) nerves to skeletal muscles)

2-type B fibers:

(as preganglionic autonomic nerves).

B- Unmyelinated: have **no** myelin sheath
(diameter less than 1um)

3-type C : (postganglionic autonomic & pain fibers)

Pain fibers belong to The unmyelinated class of afferent (Sensory) fibers called the **C fibers.** They do not belong to the Autonomic nervous system.

Classification According to Diameter:

A, **B** & **C** fibers

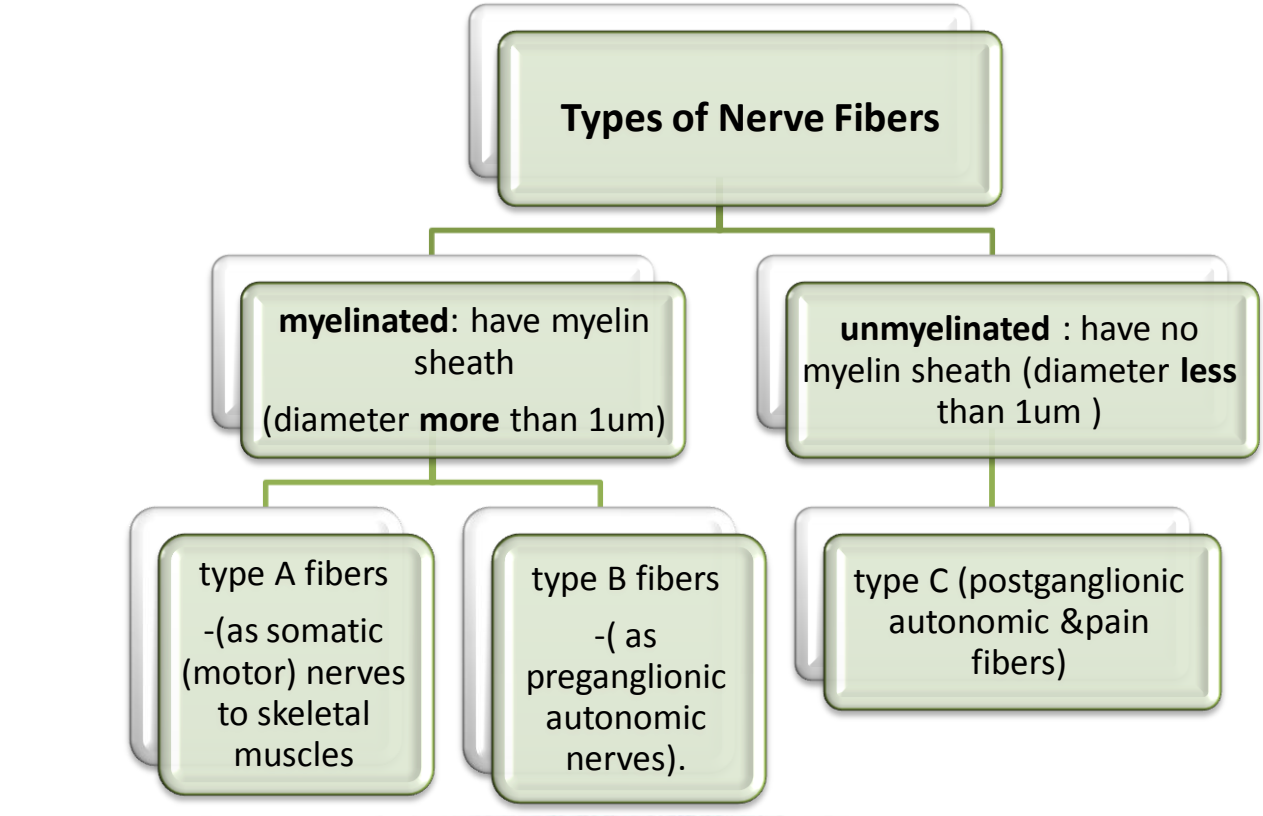
Diameter : **A** > B > **C**

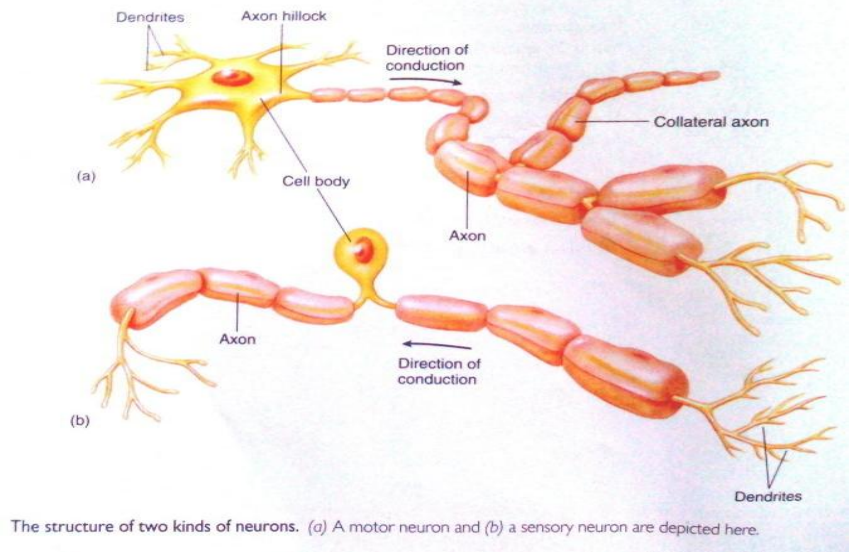
Because conduction velocity depends upon Diameter , **A are fastest and C are slowest.**

Myelin sheath:

is formed **by schwann cell** which deposit lipid substance called **sphingomyelin** around the nerve fiber.

-Interrupted at **nodes of Ranvier** (2-3 micron) at the junction between 2 cells.





The structure of two kinds of neurons. *(a)* A motor neuron and *(b)* a sensory neuron are depicted here.

Functions of myelin sheath:

1-insulator عازلة : makes ion flow across the membrane much more harder & decrease ion flow through the membrane (decreases ion leakage).

2-increase conduction velocity

(because ionic currents need to " jump " from one node of Ranvier to the next)

3-protection

4-conserve energy during transmission of AP.

How myelin sheath saves energy ? Myelin sheath is an insulator sheath , when it covers the nerve it makes ion flow harder (only few ions can across the covered nerve membrane) + (there is a flow between nodes)→ less ions flow → less energy is consumed .

Changes that occur in the nerve after stimulation by an effective stimulus are:-

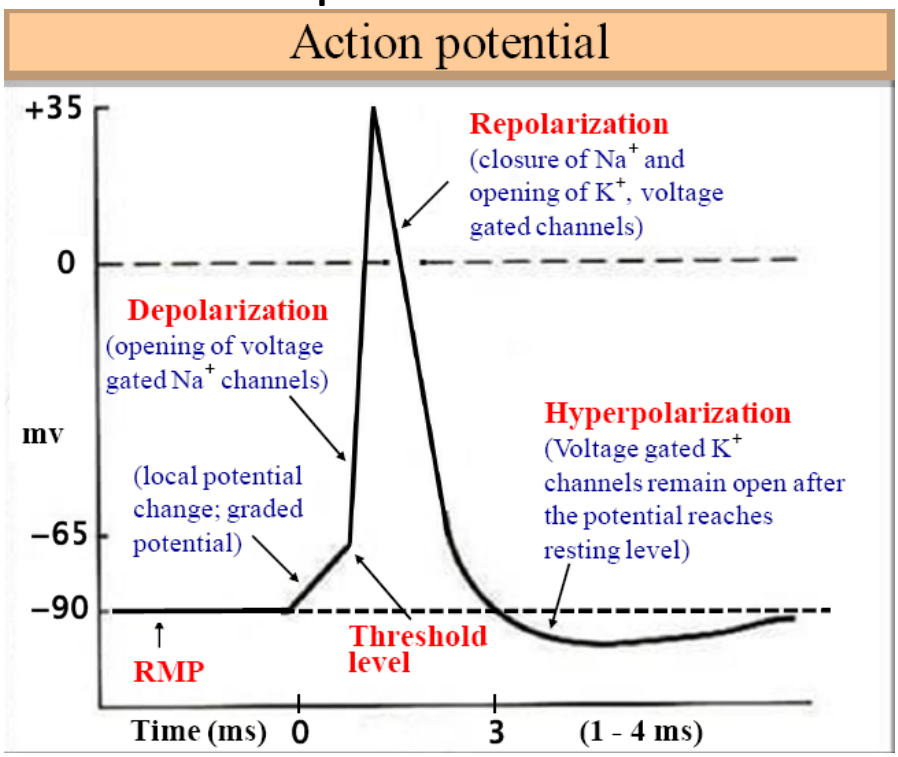
1-Electrical changes 2- Excitability changes

3-Thermal changes 4-Chemical changes

These changes can**not** occur if the stimulus is not effective.

1- Electrical changes:

The nerve action potential



It is potential difference along nerve membrane after stimulation by (Threshold = effective) stimulus.

Types of Stimuli :

1-Threshold stimulus: is the value of the membrane voltage **needed** to result in the generation of an action potential.

2-sub-threshold stimuli: weaker than a Threshold stimulus .**Do not** lead to action potentials

3-supra-threshold: Stronger than Threshold **,lead** to action potentials.

-Nerve signals (impulses) are transmitted as nerve action potentials conducted along the nerve fiber as a wave of depolarization to its end.

-The channels necessary for nerve action potential are:-

Voltage gated Na+ & k+ channels.

During action potential we use oscilloscope to measure **rapid changes** in membrane potential.

Summary of stages of acion potential are:

1-RMP:

At the resting state(no stimulation) the membrane is polarized (-ve inside = -90 mv).

2-Depolarization:

Sudden Na inflow (influx)→ polarizesd state is lost & potential rises to positive values (reach zero & overshoot to +ve values).

At Depolarization state (happens **after** stimulus) the cell loses its negativity as the Na positive ions inters the cell through the Voltage-gated channels.
Gradually the inside of the cell is becoming more positive . -90 >> -70 >> -65 >> -30 >> 0
And then it continues to become more positive 0>> +10 >> +35 and so on.
Starting from zero and reaching Positive values is called **Overshooting.**

3-Repolarization:

Na channels close & K channels open & K outflow (outflux) to outside → restoration of the normal –ve RMP.

When the Depolarization stage end, the cell starts to become negative inside again , regaining the negativity is called **Repolarization**. Gradually the inside of the cell become more and more negative +35>> +10 >> 0 >> -30 >>-65 >> -90 (until it reaches the normal Resting Potential which is -90)
The reason of regaining the negativity inside is because of the closure of Na Voltage-gated channels and the opening of K voltage-gated channels which allow K positive ions to go out, creating positivity outside and **negativity inside.**

Summary of events that causes AP (spike potential):

1-Initiation of Action Potential (AP)& +ve feedback

vicious circle that opens Na channels CAUSING DEPOLARIZATION STAGE.

Positive Feedback : when Na channels open , Na ions enters the cell , the entry of Na cause more Na Channels to open , more Na ions to enter, this is the meaning of Positive feedback.

Vicious circle: continuous events that reinforces itself through a **Positive feedback** (when Na enters the cell, cause more Na channels to open , more Na to Enter and so on)

2- Gradual depolarization stage:-

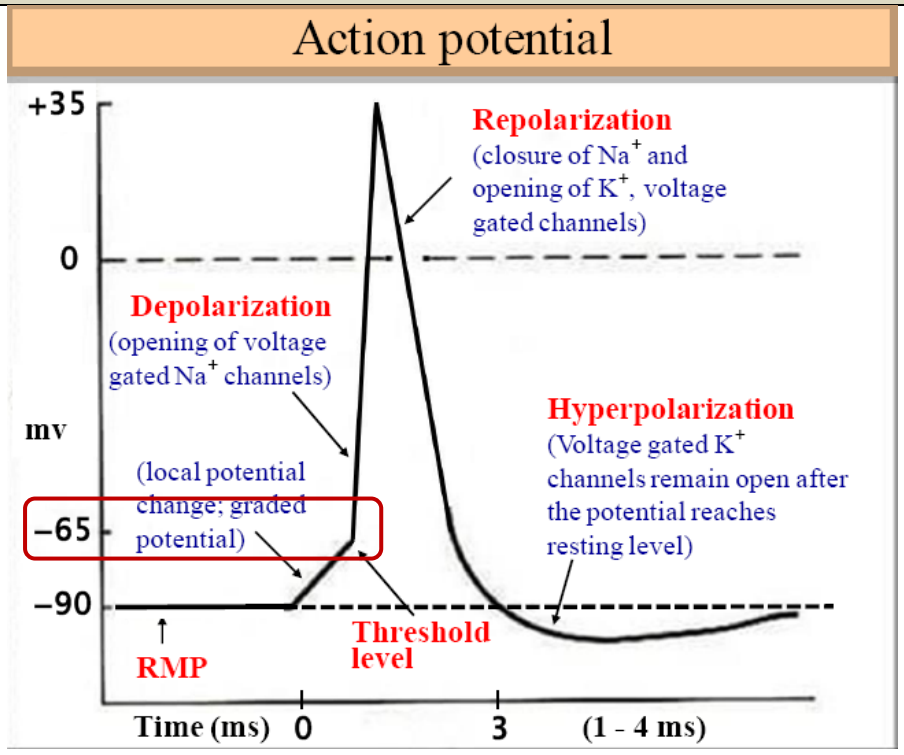
-**Threshold stimulus** (An effective stimulus strong enough)-> to cause voltage gated Na channels to open & Na influx to inside nerve membrane >rises resting potential from-90 towards zero.

- **Rise of membrane potential**-->open more Na channels & more Na influx (+ve feedback vicious circle) until all voltage gated Na channels open.

- The increase in membrane potential from -90 to -65 mv cause explosive opening of all Na channels & Na conductance is 5000 times great → massive Na+ influx

so -65mv is called firing level.

During Depolarization stage , and as the negativity inside is lost gradually -90 >> -65 >> 0 ,Na voltage channels opens gradually (Not all of them) , but when depolarization reaches **the -65** , **All Na channels open** , allow MASSIVE Na influx inside. **so -65mv is called firing level.**



3-Depolarization stage:-

- **Sharp & rapid** depolarization occurs & membrane potential reach **zero value** & then **over-shoot to reach + 35 mv** (reversal of polarity) occurs & the inside of the cell becomes +ve.
- The **peak** of AP is reached at **(+35 to +40 mV).**
- At this value all Na + channels become refractory.

(begin to close suddenly & no more Na+ entry) & Depolarization ends.

Refractory Period : The amount of time it takes for an excitable membrane to be ready for a second stimulus.(during this time it incapable of repeating a second Action) . All Na channels are closed.

4-Repolarization (return to polarized state):-

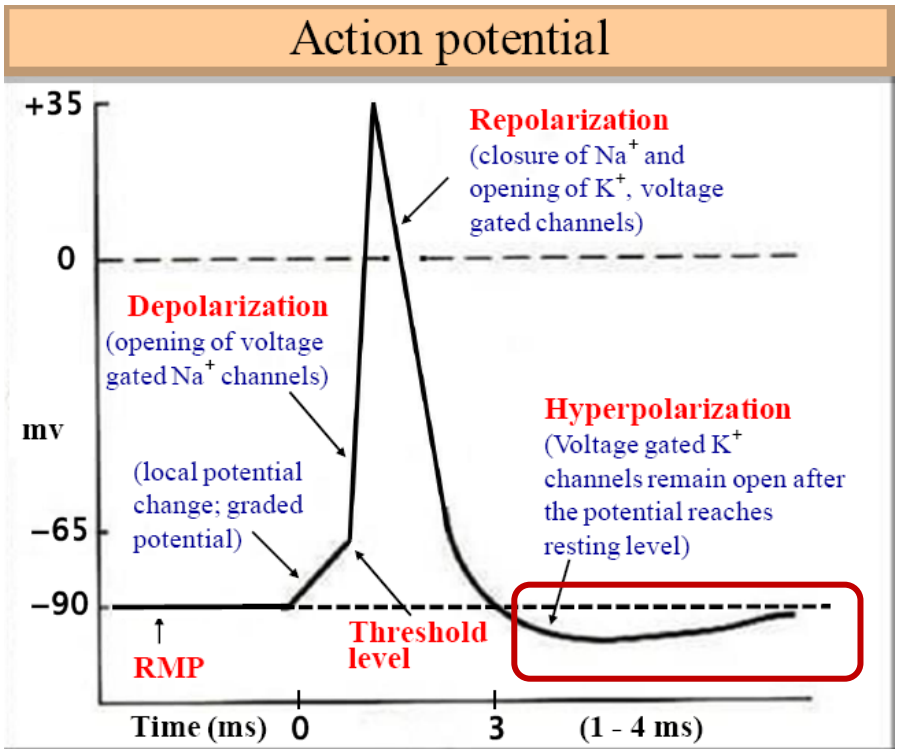
Cause:

due to high K conductance(flow) to outside of nerve membrane **by openning of all K channels** > (K outflux carrying **positivity to outside** & **raising negativity inside**)
(Also zero flow of Na to inside as all Na channels close) Causes negativity inside.

- Membrane returns to resting potential (**drop from +35**mv towards zero then to negative resting potential-**90** mv)

5- Positive after potential (In some nerves)

membrane potential becomes more negative
than resting level (because many K channels remain open & K outflux continue- causing more – ve inside = **hyperpolarized state**)
-(**positive after potential is wrong terminology it is historical one**)



6- Re-establishment of Na & K ionic gradients & return to resting membrane potential:-

a- Na that had influxed in & K that had oufluxed out returned to originalstate by Na-K pump

(active process- need ATP & ATPase)

b- Closure of some K channels so keepsome K+ inside(raise positivity inside)

-Gain of these two processses is:-

K remain inside causing some positivity to raise potential towards -90 mv

-Duration of nerve action potential is 1-1.5 ms.

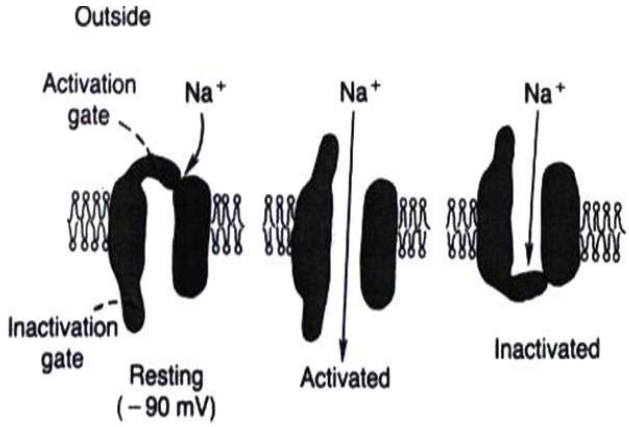
If the nerve takes more than 1-5 ms to produce an Action Potential the nerve here is weak.

The factors necessary for depolarization & repolarization are :-

1-Na voltage –gated channels important for both depolarization & repolarization

2- K voltage –gated channels important for repolarization.

A- Voltage –gated Na channels:-



Outer activation gates & inner inactivation gates.

1-Resting state:-at RMP -90 mv activation gates close & inactivation gates open

No Na entry.

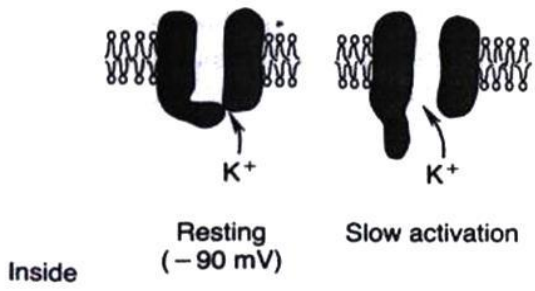
No Na Entry to maintain the -90 inside the cell (RMP)

2- Activated state:-after stimulation, the membrane potential rises at a voltage between -90 to -65mv, conformational change occur & activation gates open (now both gates are open) & Na influx causing depolarization.

3- Inactivation state:- inactivation gates close slowly while the activation gate is still open & they close completely at + 35 mv & stops Na influx & repolarization begins.

B -Voltage –gated K Channels:- 1- Only one gate,

a-at RMP (resting state) :
the gate of K is closed & no K pass to out.

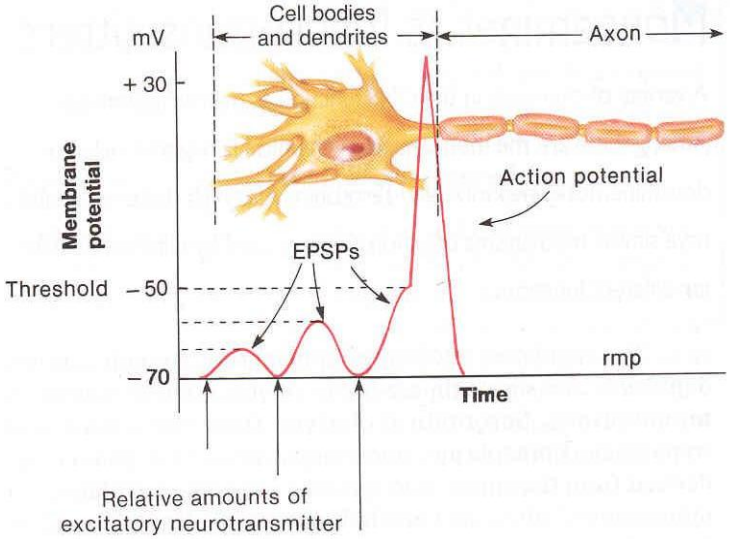


b- after stimulation & between:
-90 to zero mv, the potassium
channel opens slowly& K outflux begins slowly.

- **They open completely only when Na gates close** & when Na influx stop) causing rapid re-polarization.

-Acute local potential (acute local response):

A very weak stimulus (not threshold) can cause local change in membrane potential e.g from -90 to -85 mv which is not sufficient for generation of AP, this is acute subthreshold potential(which is graded and does not propagate). It should increase to threshold level to produce AP.



- In nerves , the AP is generated at the Axon Hillock .By contrast , a local responses can be generated at any membrane area if the stimulation is sufficient .

-The AP differs from local response in that AP is:-

(1) not graded. (2) obeys All-or None Law.
(3) propagated (conducted for long distances).

Local Response	AP
Graded (varies with the strength of the applied stimulus , does not obey All-or-None Law)	Not graded. obeys All-or None Law.
Not propagated	propagated (conducted for long distances).
Can be summated (the responses to a second , third , fourth or more stimuli can be added on top of the response to the first stimulus)	

In case of local responses :

(a) If the stimulation is **excitatory** (opening sodium or calcium channels) , it produces a **depolarizing local response** →which makes the inner side of the membrane **less negative** (i.e., reduces the numerical value of the RMP).

- It is called Excitatory Postsynaptic Potential (EPSP)

Reduce numerical value -90 , -65 , -10 and so on , more positive inside because of the entry of Na ions.

(b) If the stimulation is **inhibitory** (opening potassium or chloride channels) , it produces a **hyperpolarizing local** response →which makes the inner side of the membrane **more negative** (increases the numerical value of the RMP)

- is called Inhibitory Postsynaptic Potential (IPSP)

Increases numerical value -90 , -100 and so on .

All or nothing principle:

-The nerve respond to a threshold stimulus maximally or does not respond at all (there are no half solutions)

-Once threshold stimulus applied, it gives AP spread all over the nerve fiber.

-its intensity (peak amplitude) can not increase by increasing stimulus intensity(or by suprathreshold)

-**sub**threshold stimulus can not elicit action potential (but produce a local response which does not obey this law).

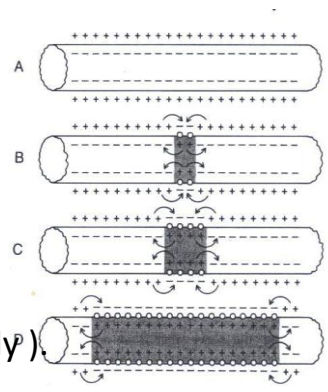
Direction of propagation of AP:

- In one direction from axon hillock to nerve terminal.

- (**experimentally**) if nerve stimulated at its midportion ,

AP pass in both directions

Under Artificial condition of electrical stimulationin the laboratory(only).



Na & K conductance (flow) during action potential:-

1-At resting state , before AP:-

K conductance through K leak channels is 50-100 times as Na.

2- At onset of action potential:-

Voltage gated Na channels activated & Na conductance is 5000 folds , at the same time voltage gated K channels begin to open slowly.

3- During depolarization :- Na conductance / K conductance >1000 fold.

4- At peak of AP :

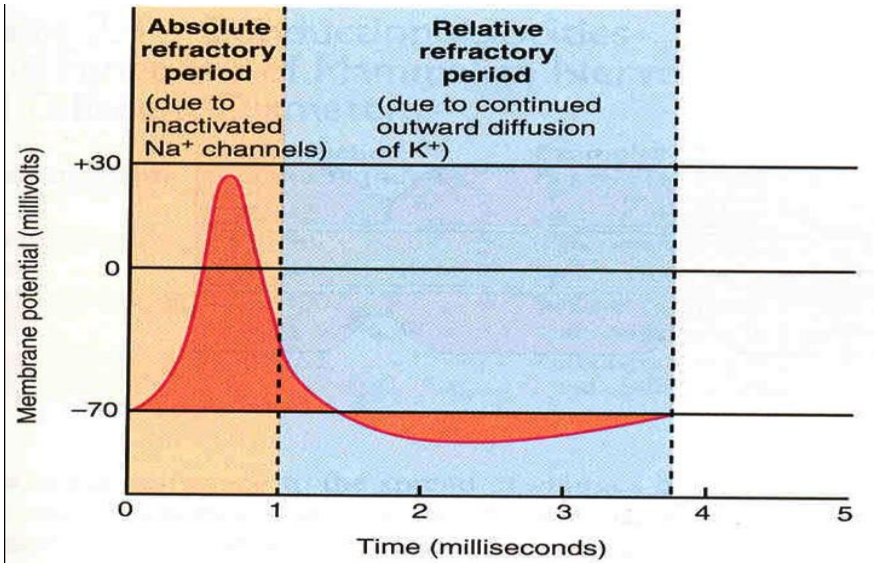
Na channels close & voltage gated K channels open & K conductance increase

5- At repolarization: the ratio Na conductance/ K conductance decreases.

6-At end of AP :-return to –ve potential , close voltage gated K channels & no K+ conductance.

2-Excitability changes

the ability to respond to a second stimulus



1-Latent period.

2-absolute refractory

(period During depolarization & early repolarization).

During it the nerve **can not excited by a a second stimulus** & a second spike action potential **can not be elicited** whatever strength of the stimulus (**even suprathreshold**)

Why??

(because all Na channels are **already opened** & Na influx occurred & a new stimulus can not open further Na channels)

3- Relative refractory period:-

-It is during the late third of repolarization (½ to ¼ absolute refractory period in its duration)

-it is the period during which a second action potential of low amplitude **can be elicited by stimulus stronger than normal suprathreshold**)

Why suprathreshol stimulus?

because :

1- Na channels still inactive so need stronger stim to open

2- rapid flow of K to outside during repolarization oppose any stimulation to occur (so need stronger stim to cause a new AP.)

Propagation of action potential

Transmission of depolarization process along a nerve= spread of nerve impulse:

1- in myelinated nerve fibers by:-

Saltatory conduction **(jumping)**

AP occurs at nods of Ranvier & directed from node to node, through axoplasm inside & ECF outside.By jumping.

APs can develop only at the Nodes of Ranvier Where

(1) ions can relatively easily flow in & out

(2) there are voltage-gated channels

Value:-

1-↑velocity of conduction (100 m/sec in large myelinated nerve fibers in comparison to 0.25 m/sec in small unmyelinated nerve fibers).

2-Conserve energy for axon because only nodes depolarize (need little energy for re- establishment of Na&K ions).

3-Insulation by myelin sheath allow repolarization to occur rapidly (with many K channls have not open)

2- Non- myelinated nerves by :-

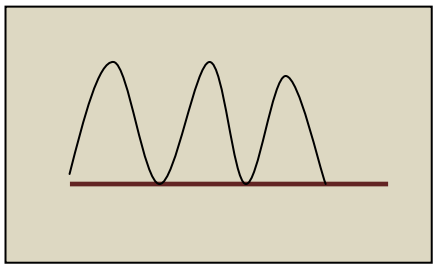
local circuits=Continuous Conduction =point to point

-depolarization pass by local circuits.

-depolarization in an area, + ve charge carried inward by Na ions flow for several 1-3 mm in the axon core & increases the voltage inside the nerve to threshold value to cause depolarization in a new area & Nachannals open & depolarization spread to new areas.

Recording of AP:-by cathode ray oscilloscope:

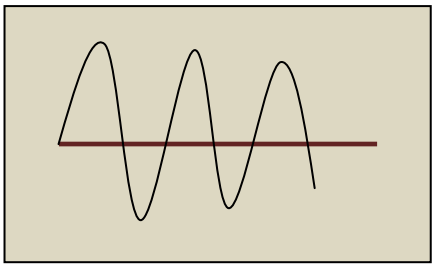
1-Monophasic AP:



one microelectrode outside & one inserted into nerve fiber.

2-Biphasic AP:

tow microelectodes placed on outside of nerve fibers(biphasic means one in one direction then second in second direction.



Questions From Dr. Taha :

Q: if you stimulate any nerve at any place or point ,the AP will go in both direction (**True**)

Q: if you stimulate normal nerve from its origin to terminal, the AP will go also in both direction (**false**) **AP will go in one direction**

- **Stimulation of nerve cells will increase frequency of signals not duration or length**.

Summery For All Values

- 80% Of bones are compact bone.
- 20% of bones are tubercular bone, (with 80% of bone surface area)
- 70% of bone is Calcium , 30% of bone is organic matrix (collagen)
- 99% of Calcium in bones , less than 1% in ECF.
- 99% calcium is in form of hydroxyapatite crystal and phosphate salts .
- Calcium plasma levels (8.5 -10 mg/dl).[ECF]
  - ➔50% of ECF calcium is free.
  - ➔40% of ECF calcium is protein bound. (90% bound to albumin, rest to globulin)
  - ➔10% ECF calcium is bound to serum constituents(citrate and phosphate).
- PO4 plasma levels (3.0-4.5 mg/dl)
  - ➔ 13% non-difusable (protein bound .85% -90% in bone)
  - ➔ 87% diffusible (52 ionized , rest bound to ions).

- 10% of abult bone is remodeled each year.
- 100% of the skeleton is remodeled in the first year of life.

- 12 pairs of cranial nerves , 10 orignate from brainstem , 2 orignate from fore-brain and thalamus.
- 31 pairs of spinal nerves (8 cervical, 12 thoracic, 5 lumar. 5 sacral . 1 coccygeal)
- Resting Membrane potential (-70 to -90) but for large myelinated nerves is -90 .
- Nernst Equilibrium potential for K -94.
- Nernst Equilibrium potential for Na is + 61.
- Peak of action potential is(+ 35 to +40)
- -65 is the firing level .
- Velocity of transduction is 100m/s for myelinated nerves and 0,25m/s for un-myelinated nerve.