Physiology

HOMEOSTASIS

Introduction 00:01:22

It is concept of constancy (inspite of changes in external environment, body tries to maintain all its parameters near to a constant value)

Claude Bernard said despite of changes in the external environment, the body will always try to maintain a stable internal environment (milieu interior).

Walter Cannon : Coined the term homeostasis.

To maintain constancy, body uses 3 control systems :

- Negative feedback process.
- Positive feedback process.
- Feed forward control system.

Negative feedback process :
During exercise, there is an increase in BP. Once the purpose is achieved there is an opposite effect i.e decrease in BP.

Positive feedback process :
BP is usually under the nervous control (CNS) via action potential.
During action potential, Na^+ channels open leading to Na^+ influx. This is depolarization. It opens more Na^+ channels, more Na^+ influx and further depolarization.
This cycle is known as Hodgkin's cycle.
In positive feedback, the initial stimulus is amplified further.

Feed forward control system :
No stimulus required. Anticipatory thinking produces response.
It is also called as anticipatory control system.
The process of thinking of doing exercise itself can rise heart rate and respiratory rate. Applicable to all events in life.

Active space

Negative feedback control system

00:12:26

Initiating stimulus is decreased further.

Examples :

- Blood pressure control through baroreflex (short acting).
- Majority Endocrine hormone regulation (Increase in T3, T4 ⟶ Decrease TRH & TSH)

Baroreflex :

Stimulus : Increase in BP
↓
Baroreceptor activation
↓ Via cranial nerves (9 & 10)
Centre : medulla
↓
Effectors : Symphathetic (–) & parasymphathetic (+) nervous system
↓
Decrease in BP

Integral components of negative feedback system :

- Stimulus
- Receptor
- Centre
- Effector organ/system
- Response

The degree of effectiveness is assessed by gain.

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}}$$

Example : At the start of exercise, SBP is normal. During exercise SBP increases to 180 mmHg and at the end, it decreases to 150 mmHg.

$$\text{Gain} = \frac{180-150}{150-120} = 30/30 = 1$$

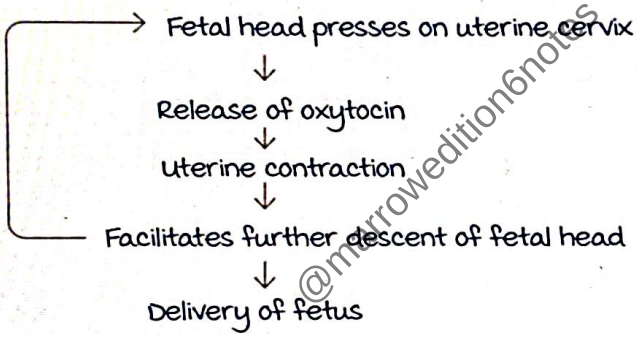
As it is a negative feedback mechanism, gain is –1 (starting and ending points are opposite to each other : ↑ in BP followed by a ↓ in BP).

Active space

Infinite feedback gain :
If error is zero, gain is infinity.
Example : Role of kidneys in the control of BP.
Kidneys bring back BP to 120mm hg by excreting urine containing water and sodium but it takes a longer time.

Positive feedback control system 00:22:41

The initiating stimulus is amplified further.
Mnemonic : CLAPS
C : Clotting is an amplification cascade, forming a stable clot.
L : LH surge (Increase in estrogen → increase in LH to bring ovulation).
A : Action potential (Hodgkin's cycle).
P : Parturition (delivery of fetus).
Ferguson's reflex :



S : Shock (decrease in BP → decreased blood flow to heart → weakening of heart muscles → decrease in contraction → decrease in BP → Shock worsens). It is a vicious cycle. So, positive feedback is not always beneficial.

Feed forward control system 00:30:57

No stimulus is required.
It is also called as anticipatory control system.
Examples :

- Thinking of performing exercise leads to anticipatory tachycardia and tachypnea.
- Body temperature regulation : When an individual is exposed to cold, skin temperature (shell temperature) falls.

Active space

Hypothalamus anticipates fall in core temperature (internal organ temperature) which leads to shivering to maintain the core temperature.

- Role of cerebellum in anticipatory motor control.
  (eg : hitting the brakes seeing a dog at distance while driving).
  Cerebellum always thinks about the future.

Properties of homeostasis :

- Dynamic equilibrium :
  Constancy of body parameters is maintained under the fluctuating limits (range). Example : Normal HR ranges between 60-100 bpm.
- Prioritization : Homeostasis prioritizes one function over another.
  PH changes and BP changes are prioritized over other functions.

MCQs :

1. Which of the following is not mediated through negative feedback mechanism?
   A. BP regulation.
   B. Growth hormone release.
   C. Thrombus formation.
   D. ACTH release.

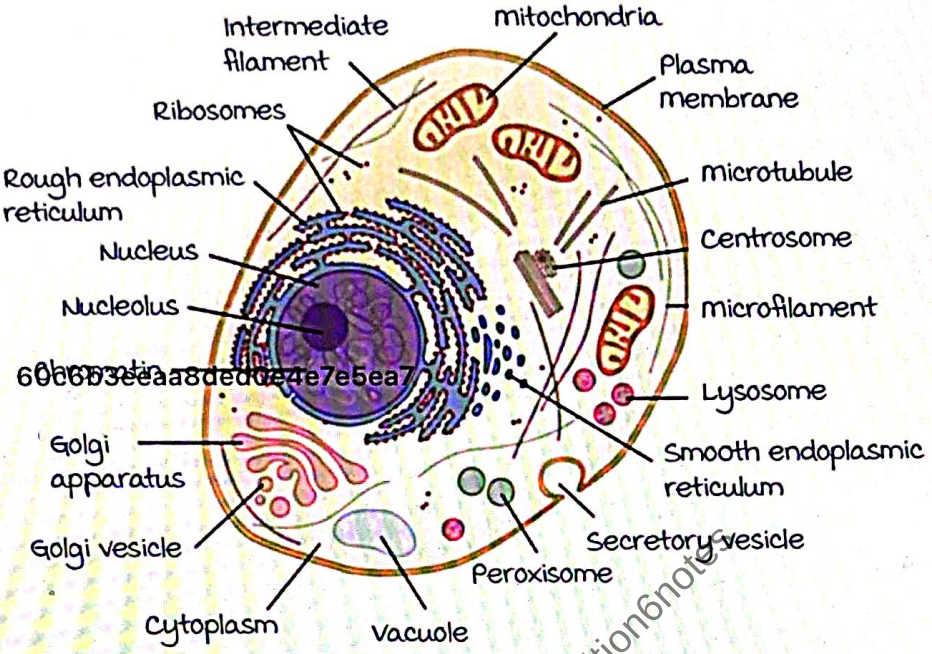
2. Positive feedback is seen in all except?
   A. LH surge.
   B. Entry of calcium into sarcoplasmic reticulum.
   C. Thrombus formation.
   D. Temperature regulation.

3. On changing position from lying down to standing position there is a drop in 10 mmHg. Immediately he recovered by 8 mmHg leaving behind 2 mmHg. The gain for baroreceptor system for the control of BP is
   A. +2
   B. −4
   C. −6
   D. +8

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}} = 8/2 = -4$$

CELL MEMBRANE

Parts of a cell :



Cell membrane components

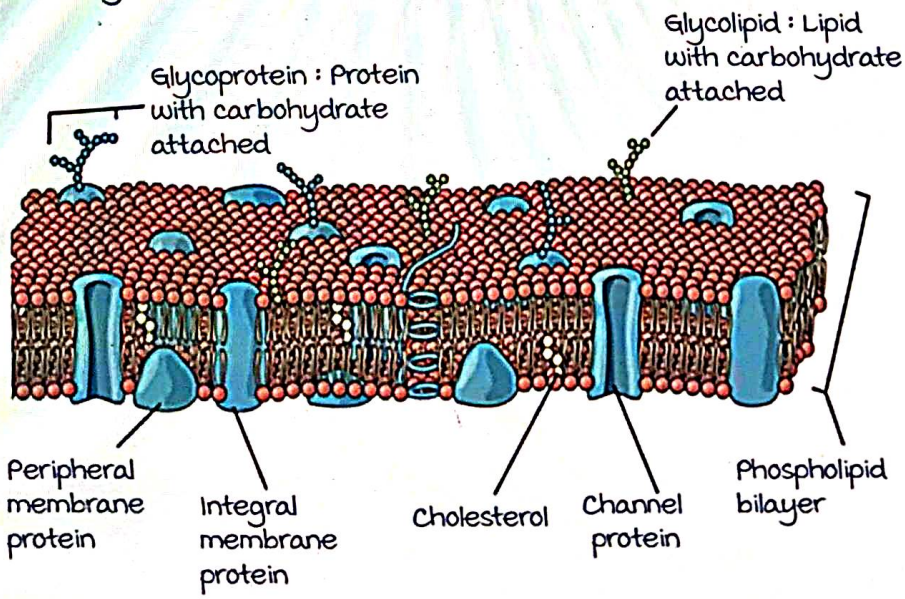
00:02:13

The 3 macromolecules present are :

Proteins (55%) : Major component of cell membrane.

Lipids : 40%.

Carbohydrates : 5%.



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Fluid mosaic model/ lipid – protein model :
Fluid component : Lipids.
Mosaic (stone like) component : Proteins.
Given by Singer and Nicholson.
Lipids are arranged in a bilayer.

Lipids 00:05:40

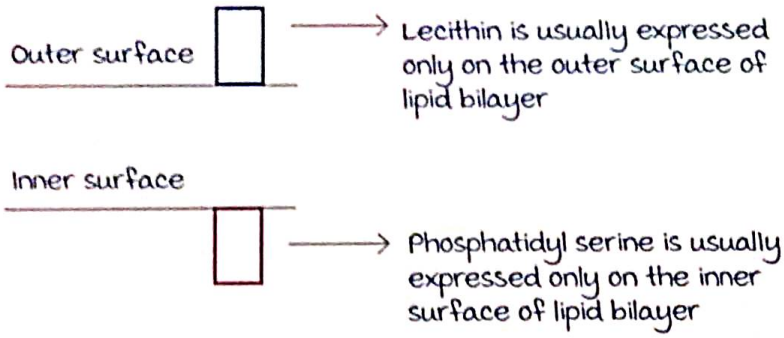
Phospholipids : Lipids attached to a phosphate moiety.
Glycolipids : Lipids attached to a carbohydrate.
Sterols : Cholesterol.

Phospholipids :

1. Phosphatidyl choline (PC)/ Lecithin (L) :
   Major surfactant lipid in the lung alveoli and prevents collapse of alveoli.
   Biochemical molecule : Dipalmitoyl phosphatidyl choline (DPPC).
   Deficiency of surfactant (DPPC) causes Hyaline membrane Disease (HMD) leading to alveolar collapse.

2. Sphingomyelin (S) :
   Also found in surfactant. Minor component.
   Used to assess fetal lung maturity.
   L /S ratio ≥ 2 indicates lung maturity.
   (L/S : Lecithin/ Sphingomyelin).
   Also found in cell membrane of nerves.

3. Phosphatidyl serine (PS) :
   Phospholipid that is present onlu on one side of lipid bilayer (outer or inner surface), never on both the surfaces. This is called as membrane asymmetry.
   If phosphatidyl serine is present on outer side of bilayer, stimulates cell for apoptosis (Eat me signal).
   Annexin V staging : Annexin V binds to PS present on outer surface of lipid bilayer and this complex can be detected, indicating cell entering apoptosis.



4. Phosphatidyl inositol :
- Also called as inositol triphosphate (IP_3).
- Acts as a second messenger. Causes influx of Ca^{a+} ion which also acts as a second messenger.
- Forms IP_3 – DAG Ca^{a+} system.

5. Cardiolipin :
- Exclusively abundant in mitochondria of cardiac cells.
- If anti cardiolipin antibodies develop in body, indicates infection by Treponema pallidum (syphilis).
- Detected on VDRL test.

Glycolipids :
Exclusively abundant in CNS and GIT.
Types of glycolipids :
1. Gangliosides :
   GM I ganglioside present in GIT, is recognised by microorganisms and used as a receptor for entry. Vibrio cholerae toxin enters through GM I ganglioside and causes diarrhoea.
2. Cerebrosides.

Cholesterol : Present in skin as a precursor form.

7 – dehydrocholesterol
↓ Sunlight
Vitamin D.

Fluidity of lipids :
- Cell membrane needs to be in a fluid like state for optimum functioning.

Active space

- Unsaturated fatty acids (UFA) increase fluidity and thus are good for heath.
- UFA are also known as essential FA. They are :
  - Linoleic acid.
  - Linolenic acid.
  - Arachidonic acid.

Fish and fish oil capsules are rich in omega 3 fatty acids, thus good for health.

- Excess saturated fatty acids decrease fluidity by making cell membrane static and thus rigid.
- Bad for health.
- Also called as trans fatty acids. Eg :
  - Stearic acid.
  - Palmitic acid.
- Abundantly present in junk food.

Fluidity buffer :

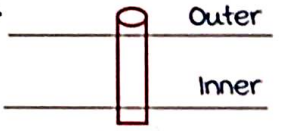
Cholesterol maintains fluidity for optimum functioning of all cell membrane functions.

Proteins

00:31:58

Mosaics : Stone like structures.

Major component of cell membrane (55%).



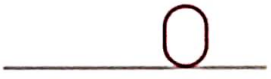
Transmembrane proteins

3 types :

1. Transmembrane proteins or Integral membrane proteins :
Present throughout the membrane.

2. Peripheral proteins :
Present on cell surface.

Peripheral proteins



3. Lipid anchored proteins :
Attached to lipids present on the outer side on cell membrane.

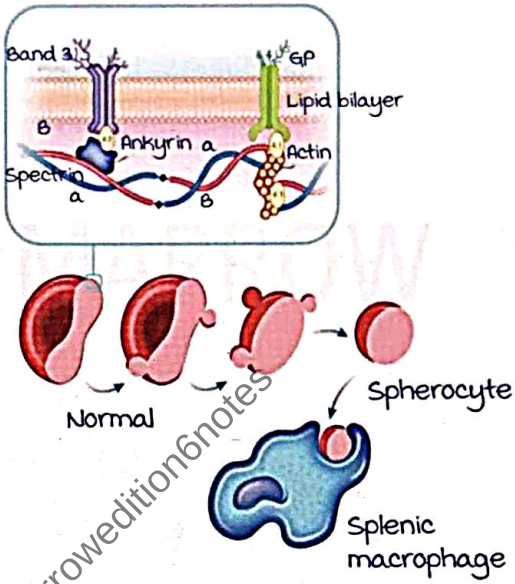
Lipid anchored proteins

Active space

Transmembrane proteins :

- Hormone receptors : GPCRs (G - protein coupled receptors), Insulin receptors etc.,
- Pumps : Na^+ - K^+ pumps.
- Ion channels : Chloride ion channel.
  CFTR (Cystic Fibrosis Transmembrane Regulator) gene regulates the opening of Cl^- channels.
  CFTR gene mutation leads to cystic fibrosis disease.

Peripheral proteins :



Function :
Supportive in nature. They support the structure of RBCs and skeletal muscle.

- RBCs (biconcaved disc shaped cells) structural proteins :
  Spectrin.
  Ankyrin.
- Skeletal muscle structural proteins :
  Dystrophin.
- Certain cell surface receptors.

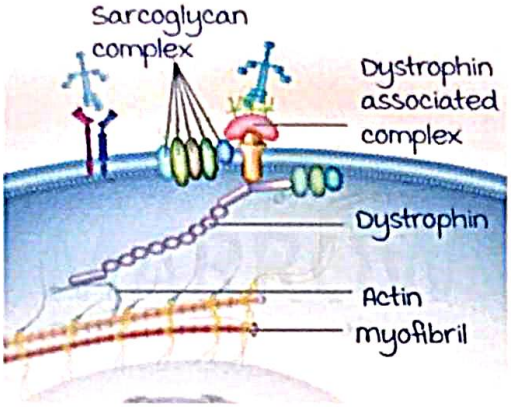
Hereditary elliptocytosis : Change in shape of RBCs to elliptical due to mutation in spectrin protein.
Hereditary spherocytosis : mutation in ankyrin protein alters shape of RBCs, causing extensive destruction by splenic macrophages leading to hemolytic anemias.

Dystrophin (anchor protein) : mutation of dystrophin leads to Duchenne Muscular Dystrophy (DMD).

- Skeletal muscle weakness.
- Gower's sign positive : Climbing on own body to stand.
- Muscle weakness progressing to diaphragm, leads to respiratory muscle paralysis and causes death.

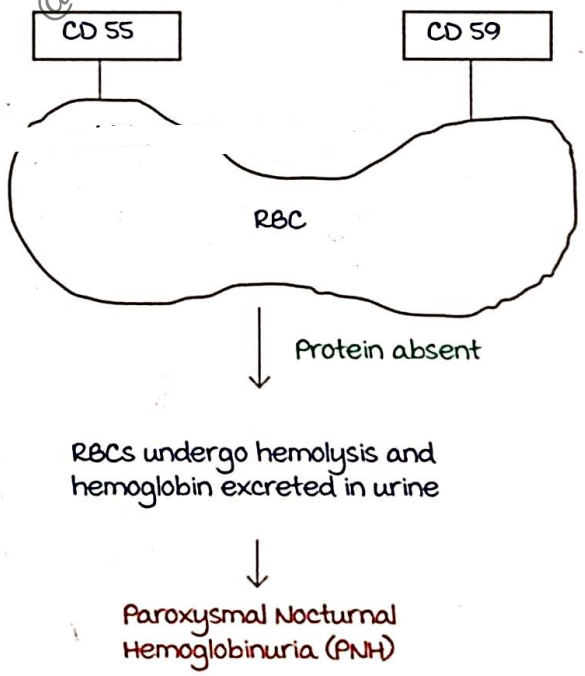
Active space

The Dystrophin – glycoprotein complex



Lipid anchored proteins :

- Phosphatidyl Inositol (IP_3) anchors these proteins.
- Aka GPI proteins.
- Expression of these proteins (CD55 and CD59) prevent hemolysis of RBCs.
- Absence of CD55, CD59 causes hemolysis of RBCs at night, leading to Paroxysmal Nocturnal Hemoglobinuria (PNH).



Active space

Membrane carbohydrates 00:50:56

Function in RBCs : For blood grouping (ABO).

- A blood group : N - acetyl galactosamine (NAG) sugar present on RBC.
- B blood group : Galactose sugar on RBC.
- AB blood group : Both sugars found on RBC.
- O blood group : No sugar on RBC.

Highest protein content is seen in inner mitochondrial membrane (70%).

Exception :
In myelin (nerve cell membrane) lipid - protein ratio is reversed. Lipids : 80% & proteins : 20%.

Q1. A cell membrane is damaged by insertion of microneedle repair shall occur by which of the following processes ?

A. Lateral movement of proteins.
B. Resealing by lipid bilayer.
C. Enzymatic reaction.
D. Hydrophobic interaction.

Small gap : Lipid bilayer resealing; Big gap : Ca^{a+} dependent processes.

Q2. Which of the following membrane has the highest protein content per gram tissue ?

A. Inner mitochondrial membrane.
B. Outer mitochondrial membrane.
C. Plasma membrane.
D. Myelin sheath.

Active space

Q3. Which of the following maintains membrane fluidity?

A. Linoleic acid.

B. Stearic acid.

C. Cholesterol.

D. Arachidonic acid.

Active space

CELL ORGANELLES

Cell organelles are parts of the cell.
Two important cell parts are Endoplasmic Reticulum (ER) and Golgi Apparatus (GA). They are similar structurally & functionally. Hence, they are called twin organelles.

Endoplasmic reticulum 00:01:54

Two types :

- Granular endoplasmic reticulum : Surface appears rough due to the presence of granules. Granules contain ribosomes. Also known as Rough Endoplasmic Reticulum (RER).
- Agranular endoplasmic reticulum : Surface appears smooth due to absence of granules/ribosomes. Also known as smooth endoplasmic reticulum.

Rough endoplasmic reticulum :

Functions :

- Synthesis of proteins called translation.
- Folding of proteins with the help of chaperones (Heat shock proteins or HSPs). For proper functioning.
- Endoplasmic Reticulum Assisted Degradation (ERAD) : Accumulation of misfolded proteins can lead to cell death. To prevent cell death, endoplasmic reticulum destroys misfolded proteins. Endoplasmic reticulum combines the misfolded protein with ubiquitin (process known as tagging) ⟶ This complex moves to proteasomes ⟶ undergoes degradation.
  Hence, rough endoplasmic reticulum is associated with quality control of proteins.

Diseases due to misfolded proteins :

1. Prion diseases :
   CNS expresses a normal protein called PrPc. Misfolding of this protein forms PrPsc. PrPsc is toxic and its accumulation leads to Creutzfeldt Jakob Disease (CJD)

2. Aβ amyloid protein :
   It is a misfolded protein. Its accumulation causes Alzheimer's disease.

Smooth endoplasmic reticulum :

Functions :

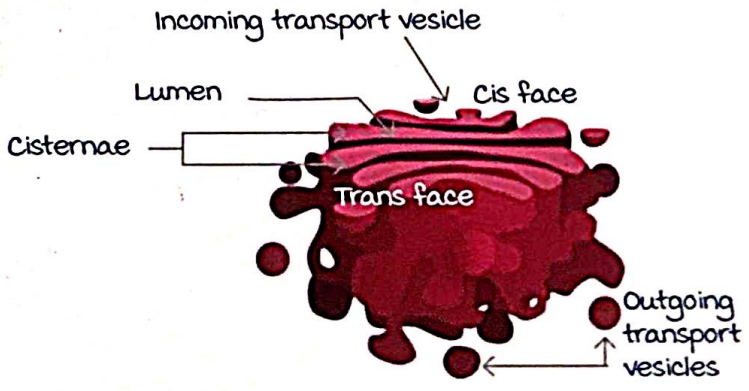
- Synthesis of steroid hormones (exclusive site).
- Sarcoplasmic reticulum (seen in skeletal muscles) is a type of smooth endoplasmic reticulum. It is concerned with storage of calcium.
- metabolism of drugs/foreign substances (detoxification) in liver cells. It occurs due to presence of cytochrome P450 enzymes in liver cells.

Golgi apparatus 00:14:48

Functions :

- Post translational modification of proteins :
  Translated proteins undergo modification in the golgi apparatus.
  Example : Glycosylation ⟶ Addition of carbohydrate side chain to a protein to enhance stability, forming glycoproteins.
- Sorting of proteins :
  Addition or tagging of mannose-6-phosphate to proteins directs them to lysosomes. Absence of mannose 6-PO_4^{3-} tagging results in I Cell disease (inclusion body disease)
  Proteins remain in SER itself.

Structure :



3 Parts :

Cis end : Close to rough endoplasmic reticulum, receiving end.

Golgi apparatus proper : Functions of golgi apparatus are performed like PTM & Sorting of proteins in the form of vescicles.

Trans end : Away from rough endoplasmic reticulum, vescicles are released from trans end.

Lysosomes 00:23:53

On a general note, it is the recycle bin of cells.

Concerned with acid mediated destruction :

- Has H^+ ATPase proton pump ⟶ Influx of H^+ ions ⟶ Acidic pH inside lysosome ⟶ Acid mediated destruction.
- Also called as suicidal bags as they are prone for acidic damage. Other names are residual bodies and recycle bins.
- Has many enzymes for destruction such as acid hydrolases, acid proteases etc.

Autophagy (self destruction) : Given nobel prize.

Starvation ⟶ Lysosomes engulf mitochondria ⟶ Mitochondria is destroyed ⟶ Release of proteins from the inner mitochondrial membrane ⟶ Proteins undergo metabolism to release energy.

This process is exclusively important for survival especially in the later stages of starvation.

Peroxisomes 00:31:21

Peroxisomes are concerned with generation and destruction of hydrogen peroxide (H_2O_2) :

- Hydrogen peroxide is a free radical. Its destruction is mediated by the enzyme catalase in peroxisomes.
- Catalase is also available in drug form : Pseudocatalase. It is useful in diseases with excessive free radicals such as Vitiligo (free radical mediated skin pigmentation).

Oxidation of long chain and very long chain fatty acids :

- Occurs in peroxisomes. Phytanic acid oxidase enzyme is involved in this process.

Active space

- Deficiency of phytanic acid oxidase enzyme causes Refsum's disease (peroxisomal storage disorder).

Mitochondria

00:36:15

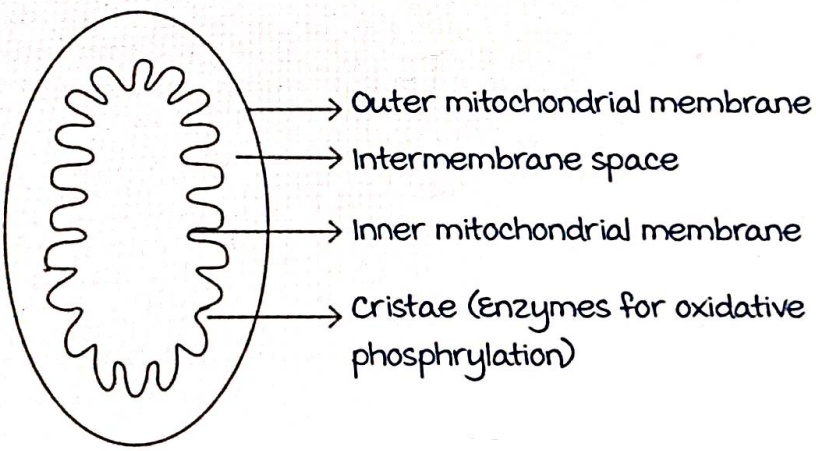
Development of mitochondria is due to an endosymbiotic relationship (mutually working) between engulfed aerobic bacteria and the eukaryotic cell (engulfment of aerobic bacteria by the eukaryotic cell happened long ago).

Functions :

- Mitochondria is exclusively concerned with ATP synthesis, hence known as the energy powerhouse of cell. ATP synthesis occurs by oxidative phosphorylation.
- Mitochondria is also implicated in apoptosis (programmed cell death).

Structure :

- Mitochondria contains an outer mitochondrial membrane and an inner mitochondrial membrane. Inner mitochondrial membrane contains high amount of proteins. Cristae in inner mitochondrial membrane contains enzymes for oxidative phosphorylation. The gap between the outer mitochondrial membrane and the inner mitochondrial membrane is the intermembrane space.



- Mitochondria contains genome of its own. It has ds DNA with 16,500 base pairs.
- Inheritance of mitochondria is maternal (derived exclusively from ovum).

- Mutations in mitochondrial genome are 10 times greater compared to nuclear genome and DNA repair is ineffective compared to nuclear genome.
- Mitochondrial genome cannot function on its own. It works with nuclear genome to produce proteins that are enzymes concerned with oxidative phosphorylation.

Mitochondrial diseases :

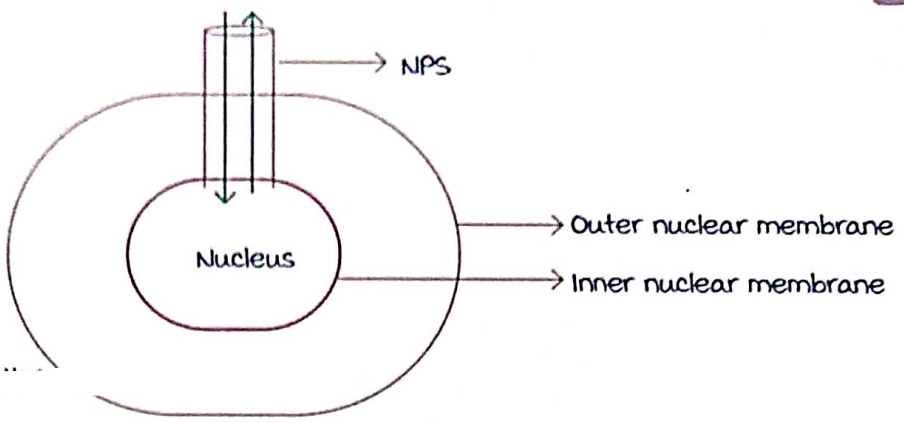
- Affects organs with high metabolic rate ⟶ defective energy production.
- Involvement of skeletal muscle ⟶ altered muscle contraction and relaxation (1st to be involved). Always accompanied by lactic acidosis.
- Involvement of GI tract ⟶ GI disturbances.
- Involvement of CNS ⟶ Seizures, developmental delays.
- Altered growth.
- High susceptibility to infections.

Nucleus

00:45:44

- Present in all dividing cells.
- Contains chromosomes which has the blueprint for all genetic expressions.
- Chromosomes are made of DNA wrapped by histones. DNA + Histones = Chromatin.
- Chromatin contains a repeating structural unit called nucleosomes.
- Nucleoli contain granules with RNA and ribosomes ⟶ Give rise to proteins.
- Part of DNA contains genes (units of heredity).
- Nucleus is surrounded by outer nuclear membrane and inner nuclear membrane. Substances can move back and forth through nuclear pore complex that spans the nuclear membrane.
- Nuclear pore complexes express two proteins : exportins (take substances outside) and importins (take substances in).
- Substances should express nuclear localization sequences (NLS) to move through nuclear pore complexes.

Active space



Central dogma of life :

DNA (undergoes replication) ⟶ Transcription ⟶ RNA ⟶ Translation (occurs in endoplasmic reticulum) ⟶ mRNA ⟶ Proteins ⟶ Golgi apparatus ⟶ Post translational modification and ⟶ sorting Stored in the form of vesicles and released whenever needed.

MCQs :

1. The abnormal cleavage of mannose residues during the post translational processing of glycoproteins results in the development of a lupus-like autoimmune disease. Which organelle is affected?
   A. Endoplasmic reticulum.
   B. Lysosomes.
   C. Peroxisomes.
   D. Golgi apparatus.

   Answer : D. Golgi apparatus.

2. Agranular endoplasmic reticulum is involved in the synthesis of :
   A. Proteins.
   B. Lipids.
   C. Ubiquitins.
   D. Carbohydrates.

   Answer : B. Lipids.

3. Catabolism of H_2O_2 is carried out by :
   A. Endoplasmic reticulum.
   B. Lysosomes.
   C. Peroxisomes.
   D. Golgi apparatus.

   Answer : C. Peroxisomes.

CYTOSKELETAL FILAMENTS AND CELLULAR JUNCTIONS

Cytoskeletal filaments 00:00:17

Considered to be the bone/skeletal structure of cells. It provides strength and support to the cell.
It also helps in cellular movements.
It is classified based on the size into 3 types :

- Microtubules : Big size filaments.
- Microfilaments : Small size filaments.
- Intermediate filaments : most abundant cytoskeletal filaments.

Microtubules 00:02:53

Three structural proteins play a role in three vital functions.
The structural proteins are :

- Kinesin.
- Dynein.
- Tubulin.

The three vital functions are :

- Axonal transport in neurons. Forward axonal (substances move from cell body to synapse) and reverse axonal (synapse to cell body) transport.
  Kinesin mediates forward axonal movement.
  Dynein mediates reverse axonal movement.
  Certain [illegible] invade the cell body via reverse axonal movement. Some examples include :
  1. Rabies virus.
  2. Herpes virus.
  3. Tetanus toxin.
- Dynein is exclusively involved in the movement of 3 structures :
  1. Cilia in lungs. It is capable of bending type of movement and is involved in collecting and

expelling debris in the form of sputum.
The movement of cilia is directed towards the nasopharynx to expel the sputum.

This type of ciliary movement is usually synchronized and has a protective function.
This nature of synchronized ciliary movement is termed metachromism.

2. Sperm movement.
3. Fallopian tubes.

If Dynein is absent, the cilia becomes immotile. It occurs as a syndromic manifestation (Immotile cilia syndrome) such as Kartagener's syndrome.

- Tubulin is exclusively involved in mitosis of cell division. During mitosis there is movement of chromosomes into the daughter cells.
  This movement is important in the survival of the cells. Microtubule inhibitors inhibit the chromosome movement leading to cell death. This is an important mechnism in treatment of cancer.

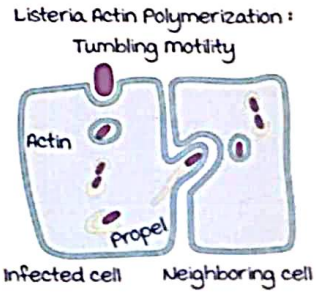
Some of the microtubule inhibitors include :

1. Vinca alkaloids : Vincristine, Vinblastine.
2. Taxanes : Paclitaxel.
3. Colchicine : Used in gout. Prevents movement of neutrophils.

Small size filaments/ Microfilaments 00:15:58

It has a important structural proteins involved in a vital functions :

- Actin.
- Myosin.



The vital functions are :

- Muscle contraction and relaxation.
  Sliding Filament theory explains how the muscle movements occur.
  The filaments slide over the other leading to movement.

Active space

- Cellular movement (actin). Actin polymerization leads to movement.
  Listeria monocytogenes is capable of inducing actin plymerization to develop a poly-A tail.
  It is involved in the characteristic tumbling motility seen in the microorganism.

Intermediate filaments 00:20:43

They are specific to each cell type and are hence considered as tumor markers. Examples are :

- Keratin : Seen exclusively in epithelial cells. It is used as tumor markers (cytokeratin) for squamous cell carcinoma.
  Cytokeratin can be accumulated in alcoholic liver disease forming the Mallory Denk bodies.
- Desmin : It is exclusively expressed in muscles and is hence considered a tumor marker for sarcomas (rhabdomyosarcoma).
- Vimentin : Commonly expressed in connective tissue cells like fibroblasts.
  Majority of these connective tissue are mesenchymal derivates and they are tumor markers for cancers of mesenchymal origin.
- Glial fibrillary acidic protein (GFAP) : They are the intermediate filaments seen in glial cells like astrocytes. They are tumor markers for gliomas like astrocytoma.
- Lamin : Exclusively expressed in cell nucleus. Mutations can cause Werner syndrome (progeria) leading to premature ageing.

Cellular junctions 00:28:22

Cell–cell junctions :

- Cell adhesive junctions (cells touch each other).
- Tight junctions.
- Gap junctions (cells communicate to each other).

Cell-basal lamina junctions :

- Hemidesmosome.
- Focal adhesions.

Cell-cell junctions :

Cell adhesive junctions use Cellular adhesion molecules (CAM) like :

- Cadherins.
- Integrins.
- Selectins.

A primary protein attaches with the help of a linker protein to a cytoskeletal filament.

Cell adhesive junctions can be of two types :

- Zonula adherens : Abundant in epithelial cells.
  E-cadherin is the primary protein which attaches to actin (cytoskeletal protein) via linker protein β-catenin.
  Molecular hijacking : Listeria monocytogenes invades the cell by hijacking this mechanism.
  Internalin-A recognizes E-cadherin and eventually invade the cell.
- Desmosomes : Important in cells undergoing mechanical stress like heart cells, skin, and cervix.
  The primary proteins are Desmoglein and Desmocolin, which attach to the intermediate filament (tonofilaments) via linker protein called Desmoplakin.
  Certain auto-antibodies can attack desmogleins in a blister forming skin disorder called Pemphigus.

Tight junctions 00:39:40

They are also called as Zonula occludens. The main proteins are Occludin and Claudin.

Substances cannot easily pass through via tight junctions.

They are :

- Blood brain barrier.
- Gastrointestinal tract.
- Kidneys.

Movement of substances through the entire cell is called transcellular pathway.

Tight junctions regulate the sideward movement of substances called paracellular pathway (sidewards).
Claudin 16 mutations exclusively affects tight junctions in the kidney. It causes familial hypomagnesemia hypercalciuria.
Affected patients are prone to develop calcium stones or nephrocalcinosis.

Gap junctions :
Cells communicate via gap of 3 – 4 nm gap called gap junctions. These are exclusively abundant in the heart, smooth muscles (vascular and GIT) and neurons.
Connexin is the protein which forms the gap junctions. They are seen in locations where rapid communications between cells are important.
In an X-linked disease called Charcot Marie tooth disease, Connexin 32 is mutated and it affects neurons and nerve fibers.
If connexin 40 (seen in heart) is mutated, it leads to idiopathic atrial fibrillation.
Connexin 37 is present in vascular smooth muscles and its mutation can lead to arteriosclerosis.

Cell–basal lamina junctions 00:48:34

When these junctions are disrupted, the cells start to move which is seen in metastasis.
They are of two types :

- Hemidesmosomes : Connects to intermediate filaments.
- Focal adhesions : Connects to actin.

Identifications of cell parts :
Each part can be identified by certain enzymes specific to that cell part called marker enzymes.

Cell part	marker enzyme
Cell membrane	Na^+K^+ ATPase and Adenylyl cyclase.
Endoplasmic reticulum	Glucose 6 phosphatase.
Golgi apparatus	Galactosyl transferase.
Lysosomes	Acid phosphatase and cathepsins.

Peroxisomes	Catalase and uric acid oxidase.
Mitochondria	ATP synthase and creatine kinase.
Nucleus	RNA polymerase and Histone deacetylase.

Q. A 24 year old man presented with recurrent episodes of nasal congestion with itching and paranasal discomfort, and productive cough for more than a decade. Clinical and imaging findings revealed chronic sinusitis and bronchiectasis. These clinical features are because of.

A. Defective migration of neural crest cells
B. Defective development of foregut
C. Mutation in endothelin receptor.
D. Impaired ciliary motility.

Answer : D. (Kartagener's syndrome)

Q. Force generating proteins are?

A. Myosin and myoglobin.
B. Dynein and Kinesin.
C. Calmodulin and G-protein.
D. Troponin.

Answer : B. (microtubule proteins)

Q. A 50-year-old man presents with blisters and erosions of oral mucosa and flaccid blisters on the skin. This disease is because of autoantibodies directed against?

A. Claudin.
B. Occludin.
C. Connexin.
D. Desmoglein.

Answer : D. (Pemphigus)

Active space

CELL MESSENGERS AND RECEPTORS

Hormones

00:01:03

There are 4 classes of hormones :

1. Single amino acid derivatives :
   - Tyrosine : Thyroid hormones (T3 and T4) and catecholamines.
     (Epinephrine, norepinephrine, and dopamine).
   - Tryptophan : Serotonin.
   - Arginine : Nitric oxide.
2. Protein hormones (multiple amino acid) :
   - Insulin : 51 amino acids.
   - Parathormone : 84 amino acids.

Any hormone with a protein structure cannot cross the cell membrane and hence, act on the membrane receptors.

3. Cholesterol derivatives :
   - Steroids :

   Sex steroids like estrogen, progesterone and testosterone, adrenal cortex steroids like aldosterone and cortisol.
   Steroid hormones can cross cell membrane and act via intracellular receptors.
4. Vitamins : A and D.
   They are fat soluble vitamins and can cross the cell membrane. They have intracellular receptors as well.

Receptors

00:07:22

membrane receptors or extracellular receptors can be of different types :

- G-protein coupled receptor (GPCR).
- Tyrosine kinase receptor.
- Janus kinase receptor/JAK.
- Serine kinase receptor.

Intracellular receptors : Exclusively for steroid hormones and vitamin derivatives.

- Cytoplasmic receptor.
- Nuclear receptor.

Cell membrane receptors :

1. GPCRs :

Transmembrane protein.

Revolves around the cell membrane 7 times and are hence called 7-transmembrane receptor.

It is also called serpentine receptor.

GPCRs have 3 subunits : α, β, and γ.

Hormones are the ligands which binds to the GPCRs and activates it. On activation, the α subunit gets separated from the other 2 subunits.

α subunit has GTPase activity. It converts GTP → GDP and liberates energy which is used for downstream reactions.

In inactive state all three subunits are together.

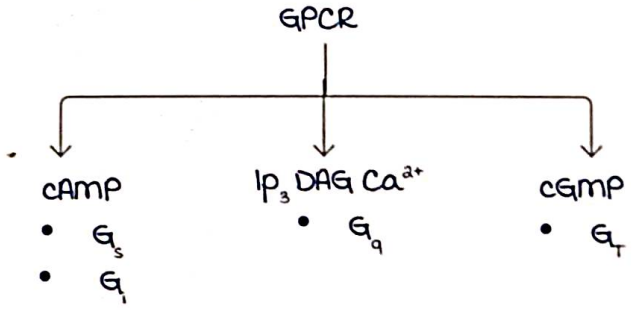
The α subunit is attached to a molecule of GDP.

In active state the α subunit is attached to a GTP molecule which breaks down to liberate energy.

The hormones or ligands bound to the membrane receptor sends certain messengers to the inside of the cell. Those messengers are called second messengers.

The hormone is thus the first messenger.

The second messengers can any of the following three types (3C) :



All the second messengers activate certain protein kinases inside the cell.

These protein kinases phosphorylate certain proteins which causes downstream actions.

GPCRs can use any of the three secondary messengers.
There are different subunits for α :

- G_s (Stimulatory) : Stimulates adenylyl cyclase which increases the cyclic AMP levels.
- G_i (inhibitory) : Inhibits adenylyl cyclase which decreases the cyclic AMP levels.

GPCRs using Ca^{2+} as second messengers :

- G_q : When activated increases calcium levels.

Cyclic GMP :

- G_T (Transducin) : It is seen in rods and cons.
  When G_T is activated, the Transducin activates phosphodiesterase enzyme which causes hydrolysis of cyclic GMP levels.

G_s α when stimulated increase cyclic AMP (cAMP). There is a pathologically high levels of cAMP if there is a gain of function mutation.
People with such a mutation are prone for :

- Precocious puberty.
- Skeletal abnormalities.
- Skin pigmentations: Café au lait spots.

This clinical disorder is called McCune Albright syndrome.

Hormones and their 2nd messengers 00:24:24

cAMP :

- Hormones concerned with metabolism requires cAMP :
  Glucagon in liver causes glycogenolysis uses cAMP as the second messenger.
  cAMP is the first ever second messenger to be discovered.
- Hormones concerned with water reabsorption :
  Vasopressin (antidiuretic hormone) in the collecting duct cells acts on the V_a receptor (GPCR).
  It increases the production of channel protein called aquaporins concerned with water resorption.
- Hormones concerned with electrolyte secretion :
  Secretin is the first hormone discovered.

Active space

It acts on the pancreas to increase electrolyte secretion (HCO_3^-). The pancreatic excretion is exclusively alkaline.

Certain bacterial toxins increase the cAMP levels which increases the electrolyte secretion :

- Cholera toxin : Increases NaCl secretion in the stool leading to diarrhea, dehydration, and death.
  Cholera toxin increases cAMP by stimulating G_s which leads to activation of adenylyl cyclase.
- Pertussis toxin : Increases NaCl secretion in the sputum and causes whooping cough.
  Pertussis toxin acts by inhibiting G_i subunit and causes an indirect increase in the cAMP levels.

Ca^{2+} second messenger system

00:32:43

The Ca^{a+} is involved in two physiological actions :

- Contraction : Oxytocin on uterus in parturition.
- Constriction : Vasopressin causing vasoconstriction by V_1 receptor (Ca^{a+} as second messenger).
  Other constrictors of blood vessels using Ca^{a+} second messenger system are :
  - Endothelin.
  - Angiotensin.
  - α action of norepinephrine.

Cyclic GMP second messenger system is exclusively known to cause relaxation and dilation (opposite action of Ca^{a+}).

- Nitric oxide.
- Natriuretic peptides (ANP, BNP or CNP types).

2. Tyrosine kinase receptors are involved in growth and differentiation. The hormones using these receptors are :
   - Insulin.
   - Growth factors like platelet derived growth factors.
3. Janus kinase (JAK) receptors when activated leads to activation of a downstream pathway called STAT pathway (called JAK STAT pathway).
   - Growth hormone receptors.
   - Prolactin receptor.

- Erythropoietin (EPO) through its JAK action increases RBC production.

4. Serine kinase receptors are exclusively concerned with hormones concerned with hormone reproduction.
   - Activin : Increases follicular stimulating hormone(FSH).
   - Anti mullerian hormone (AMH).

Intracellular receptors 00:40:54

Cytoplasmic receptors :
- Aldosterone : mineralocorticoid receptor (MR).
- Cortisol : Glucocorticoid receptor (GR).
- Testosterone : Androgen receptor (AR).
- Vitamin D receptor.

Nuclear receptors :
- Thyroid hormones.
- Vitamin A.
- Estrogen receptor (ER).
- Progesterone receptor (PR).

Aldosterone crosses the cell membrane and binds to the MR. MR when inactive are combined to certain proteins called heat shock proteins.
MR is activated when aldosterone binds to it and the complex is called hormone receptor complex (HRC).
HRC eventually move into the nucleus to exert its action.
Each steroid hormone has a specific binding site. The HRC formed after binding moves into the nucleus to bind to the hormone responsive elements (HRE).
The HRE activates transcription activators which leads to an increase in transcription (mRNA and proteins).

An increase in hormone levels leads to overactivity. There are safety mechanisms to prevent overactivity.
Downregulation of receptors by :
- Internalization of receptors.
- Desensitization of receptors by modifications making it less responsive.
- Inactivation.

Active space

Receptors for neurotransmitters :

- Ligand gated (Inotropic receptors) : Linked to ion channels and are fast acting. E.g. $GABA_A$, $GABA_C$ and nicotinic cholinergic receptor.
- metabotrophic receptors (GPCRs) : Rely on 2nd messenger systems and are slow responsive. E.g. $GABA_B$ and muscarinic cholinergic receptors.

Q. A 40 year old female is presenting with headache and splenomegaly. Her peripheral blood values were as follows: Hemoglobin 18g/dl, red blood cells 7,000,000/mm^3. The drug Ruxolitinib is prescribed. What is the mechanism of action of this drug?

A. Serine Kinase blocker.
B. MAP Kinase blocker.
C. ACE inhibitor.
D. Janus Kinase inhibitor.

Answer : D. (Polycythemia vera which requires JAK blocker)

Q. A 50 year old male with acute promyelocytic leukemia is started on treatment with all-trans retinoic acid (ATRA). Which of the following characteristics is most important in governing its diffusibility through a cell membrane?

A. Diameter.
B. Electrical charge.
C. Lipid solubility.
D. molecular weight.

Answer : C.

Q. Sildenafil produces its physiological effects by blocking which enzyme that hydrolyzes the second messenger by which nitric oxide produces its physiological effects?

A. cAMP.
B. Calcium.
C. cGMP.
D. Phosphodiesterase.

Answer : D.

Active space

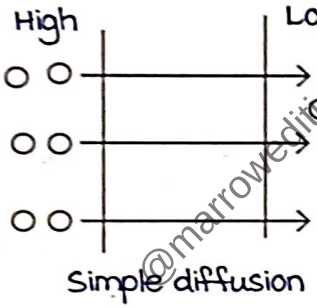
MEMBRANE TRANSPORT

Classification of membrane transport processes :
It is based on energy usage.
ATP is the universal energy currency of the cell.

Passive transport processes : ATP is not required.
Active transport processes : ATP is required.

Passive transport processes 00:12:26

1. Simple diffusion :
Substances move from high concentration to low concentration. No ATP required.
Example : Diffusion of gases in lung alveoli.



Simple diffusion

Diffusion depends on concentration gradient, area of the membrane and thickness of the membrane.

Fick's law :

- Diffusion of a substance is directly proportional to concentration gradient.
- Diffusion is directly proportional to area of the membrane.
- Diffusion is inversely proportional to thickness of the membrane.

$$\text{Diffusion} \propto \frac{\text{lipid solubility}}{\text{size}} \qquad \text{Diffusion} \propto \frac{\text{Conc gradient} \times \text{Area}}{\text{Thickness}}$$

Diffusion is directly proportional to lipid solubility and inversely proportional to size of the particle/molecule.
Emphysema :

Active space

It is characterized by destruction of respiratory membrane → decrease in available surface area → decrease in diffusion of gases.

Pulmonary fibrosis :

Fibrotic membrane → increased thickness of membrane → decreased in diffusion of gases.

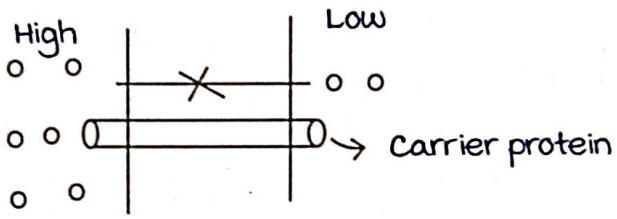
2. Facilitated diffusion :

Substances move from high concentration to low concentration through a carrier protein. ATP is not required.

Examples :

Glucose transport : Glucose transporters (GLUTs).

Water transport : Aquaporins.



Facilitated diffusion

3. Non ionic diffusion :

Substances diffuse easily in non ionized form. Ionized form cannot diffuse. Seen in renal system.

Example : Diffusion of ammonia.

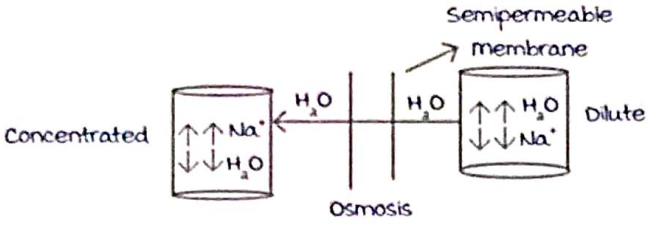
Absorption of salicylates.

4. Osmosis :

Water (solvent) always follows the movement of sodium (solute). Sodium drags water along with it through the membrane.

- Osmosis is diffusion of water (solvent) from an area of high concentration to an area of low concentration through a semipermeable membrane.
- Osmotic pressure is the force required to stop the movement of water through the semipermeable membrane. Osmotic pressure affects water (solvent) movement.
- Sodium is osmotically active (drags water). Concentration is expressed in osmoles. Normal plasma osmolality is around 300 mosm/L.
- Plasma osmolarity is calculated as follows :
  2 (Na^+) + 0.05 (glucose) + 0.36 (blood urea nitrogen).

Active space



Unit of osmolarity : mosm/litre of solvent.
Unit of osmolality : mosm/kg of solvent.
Most commonly used in clinical practice is osmolarity.

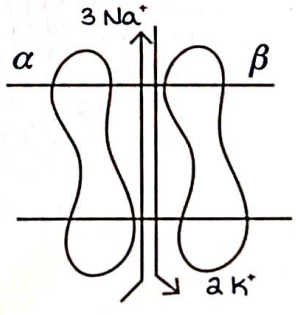
Active transport 00:22:06

Hydrolysis of ATP is required.
2 types : Primary active transport and secondary active transport.

Primary active transport :
Have ATPase enzyme activity.
Example : Na^+– K^+ ATPase, Ca^{2+} ATPase, H^+ ATPase (proton pump).

Na^+ K^+ ATPase :

- Transmembrane protein.
- 2 subunits (heterodimer and heterogenous) : Alpha and beta. Alpha may be α 1, α 2 and α 3. Beta may be β 1, β 2 and β 3.
- Na^+ ions are transported outside and K^+ ions are transported inside.
- For every 3 Na^+ ions that move outside, 2 K^+ ions come inside (Coupling ratio = 3 : 2).
- It is called as electrogenic pump as movement of charges are unequal.
- It is found in all body cells (universal/ubiquitous in expression).
- Alpha subunit has binding sites. One part is extracellular, and the other part is intracellular. Intracellular part has binding sites for Na^+ and ATP. Extracellular part has K^+ binding site.



Na^+ K^+ ATPase

Active space

Functions :

1. Helps in regulation of cell volume :
   Increase in activity of Na^+ K^+ ATPase pump → Increase in movement of Na^+ outside → more water moves outside → cell volume returns to normal.
2. Minor contribution to resting membrane potential (around 4 mv).
3. Indirect energy source for secondary active transport processes.

Regulation of Na^+ K^+ ATPase pump :

Increase in activity is caused by :

- Thyroid hormones.
- Insulin.
- Aldosterone.

Decrease in activity is caused by :

- Digitalis.
- Ouabain (Is a Na^+ K^+ ATPase blocker. Similar to digitalis).
- Dopamine (causes natriuresis in Kidneys).

Secondary active transport

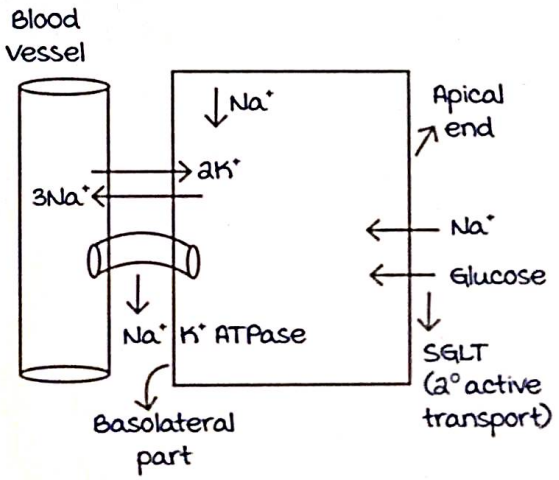
00:33:12

Two or more substances are transported either in the same direction (cotransporters/symporters) or opposite direction (exchangers/antiports).

Example :

Cotransporters/symporters :

- Na^+ Glucose cotransporter.
- Na^+ K^+ $2Cl^-$ cotransporter.
- Na^+ I^- symporter.



Exchangers/antiports :

- Cl^- $HCO3^-$ exchanger (anion exchanger).

Na^+ Glucose cotransporter :

- Also called as SGLT channel protein.
- Na^+ K^+ ATPase pump is expressed on basolateral membrane. It transports 3 Na^+ outside and 2 K^+ ions inside → intracellular Na^+ becomes low.
  ATP hydrolysis occurs during this process. This is called primary active transport.
- As intracellular Na^+ is low, Na^+ moves inside the cell from the apical end and glucose follows Na^+ ion. This transport occurs through SGLT channel protein. It is an example for secondary active transport as it utilizes the gradient established by primary active transport. ATP is not directly used in this process.

SGLT has two isoforms :

- SGLT 1 : Located in intestines (basis of ORS solution for the treatment of diarrhea).
- SGLT 2 : Located in proximal convoluted tubules of kidneys.

Vesicular transport processes 00:41:08

- Substances are transported in the form of vesicles.
- They are energy dependent → active transport.
- Requires calcium.
- Types :
  Exocytosis : Vesicles move from inside to outside.
  Endocytosis : Vesicles move from outside to inside.
- Special proteins are required : SNARE proteins for exocytosis and clathrin, megalin for endocytosis.
- No role for concentration gradient.

Endocytosis :

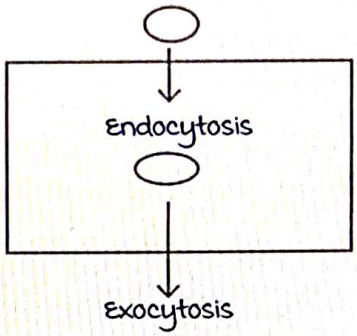
Types of endocytosis :

- Phagocytosis → Microorganism is engulfed inside for destruction.
- Pinocytosis → Fluid filled vesicle is pinched off inside.

Active space

- Receptor mediated endocytosis. Example : LDL receptor mediated endocytosis. LDL receptor has a triskelion shaped clathrin protein. Clathrin along with dynamin takes the LDL cholesterol inside.

Cytopempsis :
Endocytosis on one side and exocytosis on the other side.
Also called as transcytosis (exocytosis + endocytosis).

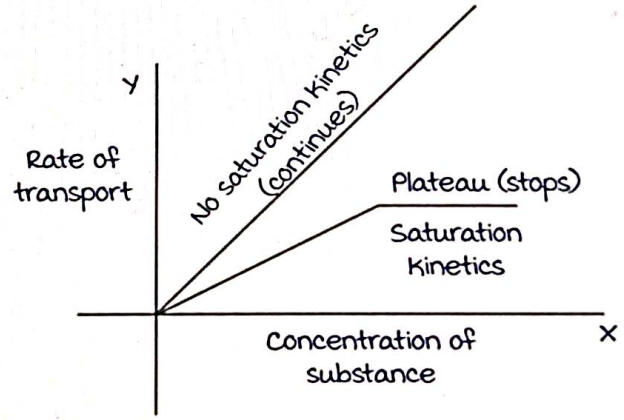


Exocytosis (emeiocytosis) :

- Requires SNARE proteins.
- Synaptobrevin is a SNARE protein that helps in exocytosis of the neurotransmitter acetylcholine concerned with muscle contraction.
- Botulinum toxin degrades synaptobrevin and inhibits acetylcholine release → flaccid paralysis.

Graph

00:50:24



Transport process that is carried out by a carrier protein or a channel protein shows saturation kinetics and stops after some time at a point called plateau point.

Examples : Facilitated diffusion (carrier mediated) and active transport processes (channel protein mediated).

Simple diffusion does not show saturation kinetics.

MCQs :

1. A 29 year old patient was presented with diplopia, vertigo and gait abnormality for the previous 4 days preceded by nausea and stomach ache. Neurological examination revealed mild divergent strabismus of the left eye, bilateral ptosis and flaccid paralysis. This toxin degrades which of the following ?
   A. Clathrin.
   B. Megalin.
   C. Cubulin.
   D. Synaptobrevin.

Answer : D. Synaptobrevin.

2. A 79 year old male patient presenting with features suggestive of congestive cardiac failure and prescribed furosemide. This drug inhibits which transport mechanism ?
   A. Simple diffusion.
   B. Nonionic diffusion.
   C. Primary active transport.
   D. Secondary active transport.

Answer : D. Secondary active transport.
Furosemide blocks $Na^+K^+2Cl^-$ cotransporter found in thick ascending limb of loop of Henle.

3. A 58 year old white male presented with shortness of breath, dry cough, fatigue and weight loss for 2 months and diagnosed with idiopathic pulmonary fibrosis. He will have decrease in diffusion of gases because of ?
   A. Increase in membrane surface area.
   B. Increase in membrane thickness.
   C. Decrease in pCO_2.
   D. Decrease in membrane thickness.

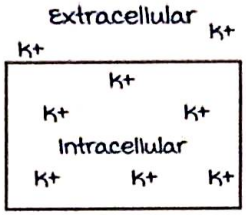
Answer : B. Increase in membrane thickness.
Diffusion is inversely proportional to membrane thickness.

Active space

MEMBRANE POTENTIALS

Resting membrane potential 00:01:05

K^+ is the dominant intracellular ion in any cell.



Passive diffusion of K^+ across cell membrane from inside to outside even at rest.

↓

Accumulation of negative charges inside the cell

↓

Inside of cell becomes more negative at rest

↓

Resting membrane Potential (RMP) or diffusion potential

RMP : −70 mV for neuron.

Cause of RMP : Passive diffusion of only K^+ ion.

Diffusion potential is dependent on :

- Charge of K^+ is positive. When it moves out, inside of the cell becomes negative.
- Permeability : Cell is permeable to K^+ at rest.
- Concentration gradient : K^+ (high concentration on inside) ⟶ K^+ (low concentration outside).

Resting membrane potential values :

Neuron : −70 mV
Skeletal muscle : −90 mV
Cardiac ventricles : −90 mV
} Stable value

Contributions to RMP :

Skeletal muscle RMP −90 mV

↓

- Major : −86 mV by K^+ diffusion
- Minor : − 4mV by Na^+ − K^+ pump
- Diffusion of few Na^+ ions

Active space

RMP is affected only by K^+ ions.

Hyperkalemia :

Increase in K^+ in ECF
↓
Diffusion of K^+ outside is hampered
↓
K^+ tends to stay inside
↓
Inside of cell is positive (depolarized) : more excitable

Hypokalemia :

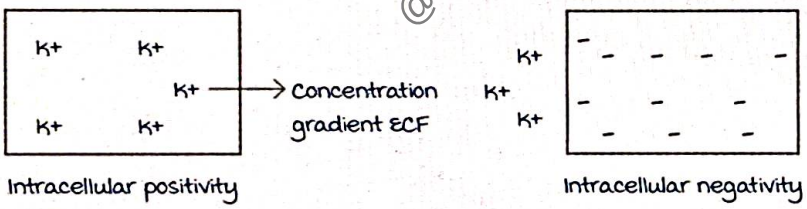
K^+ is low in ECF (concentration gradient favorable to movement of ion)
↓
Diffusion of K^+ outside is enhanced
↓
Inside of cell becomes more negative (hyperpolarized) : Less excitable

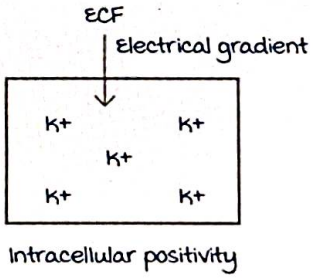
If RMP is unstable i.e. RMP oscillating between -60 mV to -40 mV is known as restless membrane potential. Seen in all pacemakers :

- SA node of heart.
- Interstitial cells of Cajal in GIT.
- Pre botzinger complex neuron in medulla : Pacemaker for respiration.

Equilibrium potential 00:14:25

At isoelectric potential, there is no net ion movement across the cell (no current flow).





Concentration gradient : K^+ moves from inside to outside
↓
Electrical gradient : K^+ outside is attracted inside by the negative charge
↓
At one point, concentration gradient is equal & opposite to electric gradient

Active space

↓

K^+ movement comes to equilibrium

↓

No movement of K^+ across cell membrane

↓

This potential is equilibrium potential

- Ions move from high concentration to low concentration (with concentration gradient).
- Equilibrium potential is always the potential inside the cell.

Na^+	K^+	Cl^-	Ca^{a+}
Na^+ moves from outside to inside. Inside of cell becomes positive.	K^+ moves from inside to outside. Inside of cell becomes negative.	Cl^- moves from ECF to inside of cell. Inside of cell becomes negative.	Ca^{a+} moves from ECF to inside. Inside of cell becomes positive.
E_{Na+} : +60 mV	E_{K+} : −90 mV	E_{Cl-} : −70 mV	E_{Ca2+} : + 130mV

Equilibrium potential of chloride is equal to the RMP of a neuron.

Calculation of equilibrium potential 00:24:48

Nernst equation :

To calculate equilibrium potential of a single ion.

$$E = \pm 61 \log \times \frac{Co}{Ci} \text{ or } E = \pm 61 \log \times \frac{Ci}{Co}$$

Co = Concentration outside.

Ci = Concentration inside.

1. Calculate E of a positive ion, when Co is more, and Ci is less. Here positive ions move from outside to inside. Thus, inside becomes positive. Hence, E is positive.
2. Calculate E of a negative ion, when Co is less, and Ci is more. Here negatively charged ions move from inside to outside. Thus, inside becomes positive. Hence, E is positive.

Goldman-Hodgkin-Katz equation : To calculate equilibrium

potential for multiple ions.
It takes into consideration both concentration and permeability of ions.
Rapid changes in permeability of Na^+, K^+, Cl^- ions needed for action potential generation is understood with the help of this equation.

Driving force 00:32:02

Driving force (DF) = membrane potential − Equilibrium potential.

e.g : For Na^+, DF = (−70 mV) − (+ 60 mV).

DF_{Na} = − 130 mV.

If driving force is negative, a positively charged ion tends to move inside cell i.e. there is a driving force for a cation to enter the cell and anions will be moved out from the cell.

Gibbs-Donnan effect 00:35:33

K^+ and Cl^- are permeant ions (easily diffusible through the permeable membrane).
However, proteins are anions that cannot move across the membrane (non-permeable, non-diffusible).
Presence of non-permeant anions (proteins) on the inside affect the distribution of permeant ions (K^+ and Cl^-).

Gibbs-Donnan effect is exclusively because of protein anions.
RMP : Negativity inside the cell is because of protein anions.
The plasma proteins (albumin) are also responsible for colloid oncotic pressure. It is also a starling force helping in fluid reabsorption.

Q. Extracellular concentration of positive ion is 100ml/L, and its intracellular concentration is 10 mmol/L. Equilibrium potential across the membrane using nernst potential is

A) −60 mV C) 60 mV
B) −10 mV D) 10 mV

Q. Resting membrane potential of nerve is equal to equilibrium

Active space

potential of

A) Na^+ C) K^+

B) Cl^- D) $HCO3^-$

Q. Gibbs Donan effect is due to

A) Na^+ C) K^+

B) Cl^- D) Proteins

Active space

CELLULAR FLUIDS

- Water is the major contributor of body weight.
- In an adult male weighing 70 Kg, total body water is around 42 L – 60% of body weight.
- 18% of body weight is contributed by proteins.
- 15% of body weight is contributed by lipids.
- 7% of body weight is contributed by minerals.

- Total body water = Intracellular fluid + Extracellular fluid.
- Water present inside the cell : Intracellular fluid (ICF).
- Water present outside the cell : Extracellular fluid (ECF).
- 2/3rd of total body water is intracellular.
  Remaining 1/3rd of total body water is extracellular.
- If total body water is 42 L, 28 L is intracellular and 14 L is extracellular.

Extracellular fluid (ECF)

00:04:52

Components of ECF :

- Interstitial fluid.
- Plasma.

Transcellular fluid is a special subtype of ECF. It is around 1-2 L and is found as pleural fluid, pericardial fluid, synovial fluid, intraocular fluid.

- Total body water in male = 60% of body weight.
- Total body water in female = 50% of body weight.
- Total body water in children = 75% of body weight.

Males have more total body water due to lower fat content. Water content is inversely proportional to fat content. Females have more adipose tissue and lower water content compared to males.

Lean body mass : Body mass – (Adipose tissue fat + Non adipose tissue fat + Bone mass).
Water content is around 70 ml / 100g of lean body mass.

Measurement of total body water

00:11:34

- Stewart – Hamilton method :
  Indicator is injected into unknown volume of fluid.
- Amount of indicator = Concentration of indicator × Volume of fluid (A= C × V).
  Therefore, Amount of indicator/Concentration of indicator = Volume of fluid
- This is known as indicator dilution principle.

In human body : Volume of fluid =

$$\frac{\text{(Amount of indicator injected – Amount of indicator excreted)}}{\text{Concentration of indicator}}$$

Indicators for measurement of body fluids :

- Total body water : Deuterium oxide, Tritium oxide.
- ECF : Inulin (most common), Mannitol, Sucrose, Sodium Thiosulphate.
- Plasma : Radio labelled albumin, Evans blue dye (does not cross the plasma membrane).
- Blood volume : Chromium tagged RBCs.

$$\text{Blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

In child, blood volume = 70 ml/kg body weight.

Intracellular fluid (ICF) and interstitial fluid are calculated indirectly. No indicators are available for measurement of intracellular and interstitial fluids.

Total body water = ECF + ICF.

ICF = Total body water – ECF.

ECF= Plasma volume + Interstitial fluid.

Interstitial fluid = ECF – Plasma volume.

ECF and ICF contain water and ions. Ions can be cations (positive ions) and anions (negative ions).

- most dominant ECF cation : Na^+.
- most dominant ECF anion : Cl^-.
- most dominant ICF cation : K^+, Mg^{a+}.
- most dominant ICF anion : Phosphate, proteins.

pH of ECF = 7.4.

pH of ICF = 7.

Water loss :

- Sweating is around 100 ml / day.
- Insensible water loss is usually through evaporation from skin and lungs.
  It amounts to 600-700 ml / day.

Water movement :

- Water is the solvent and Na^+ is the solute.
- Water follows Na^+ movement.
- Na^+ is osmotically active → Drags water along with it.

Osmolarity

00:29:02

Plasma osmolarity = 300 mOsm/L.
Concentration of osmotically active substances are quantified using moles and equivalents.
1 mole = Gram molecular weight of the substance.
Example : 1 mole of NaCl = 23 + 35.5 = 58.5.
Equivalents = Gram molecular weight/valency.
1 equivalent of calcium = 40/2 = 20.

Cell shape changes :

- Cell placed in a solution containing 0.9% NaCl (150 mmol/L) = No change as the fluid is isotonic.
- Cell placed in a solution containing 300 mmol /L of urea (hypotonic solution) = Cell swells and bursts.
- Cell placed in a solution containing 300 mmol /L of mannitol (hypertonic solution) = Cell shrinks.

Plasma osmolarity = 300 mOsm / L.
Major contributor for plasma osmolarity = Na^+ (contributes to 270 mOsm / L).
Proteins contribute to 0.75 mOsm / L as concentration is low.

Fluid accumulation in interstitial space is edema. In healthy individuals, there is no accumulation of fluid in interstitial space due to following safety factors :

1. Low Interstitial space compliance → Less distensibility → No edema.
   Contributes to a safety factor of around 3mmHg.

Active space

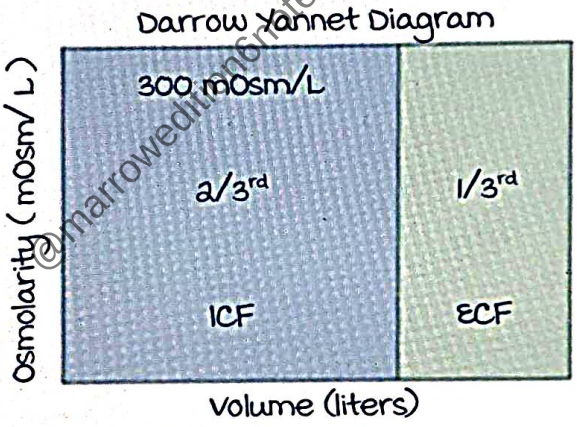
2. Plasma proteins inside cells (albumin) contributes to colloid oncotic pressure → Resorptive force → Helps in movement of water inside cells. If plasma proteins leak outside, lymph moves protein back inside.
   Increase in lymph flow contributes to a safety factor of around 7 mm Hg.
3. Increase in lymph flow causes washout of proteins → Proteins will not accumulate in interstitial space.
   Washout of proteins contributes to a safety factor of around 7 mm Hg.

Total safety factor against the development of edema = 3+7+7 = 17 mm Hg.

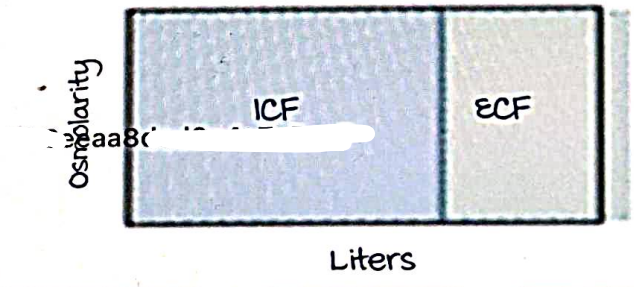
Darrow yannet diagram

00:43:48

Alteration in the volumes and osmolarity of ECF and ICF can be studied using Darrow Yannet diagram.



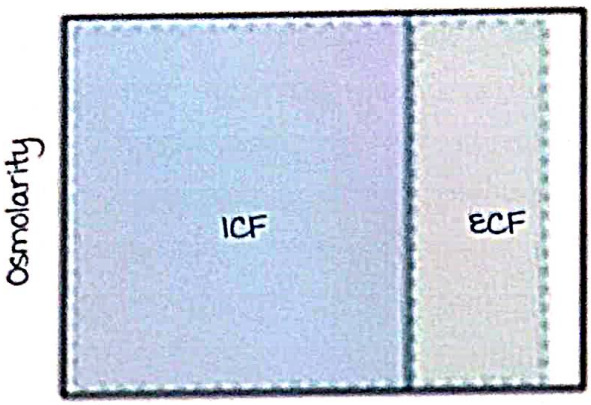
Addition of isotonic solution : Example – 0.9 % saline infusion for the treatment of shock.



ECF volume Increases	ICF volume No change	ECF osmolarity No change

ICF osmolarity No change

Loss of isotonic NaCl; Example : Diarrhoea.



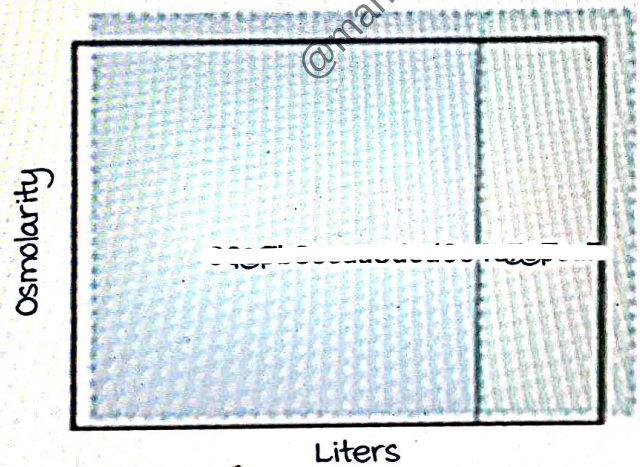
ECF volume decreases

ICF volume No change

ECF osmolarity No change

ICF osmolarity No change

Addition of hypertonic solution / Excess intake of NaCl (Pathogenesis of hypertension) :



ECF volume increases

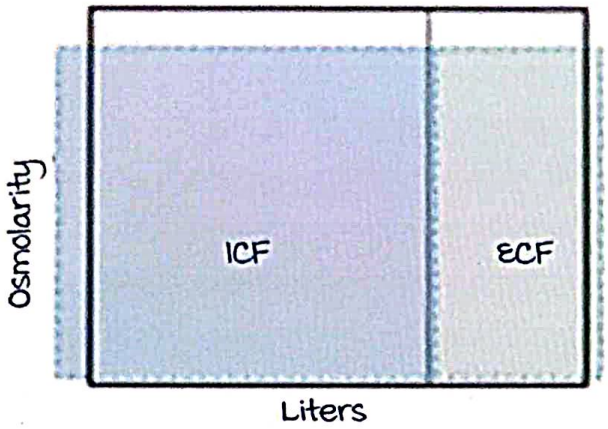
ICF volume decrease

ECF osmolarity increases

ICF osmolarity increases

Active space

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) : Gain of free water.



ECF volume increase

ECF osmolarity decrease

ICF volume increases

ICF osmolarity decreases

MCQs :

1. 10 g mannitol was injected out of which 10% is excreted. After equilibrium, plasma concentration of mannitol is 50 mg/ml. Calculate ECF volume.

   A. 10 L.
   B. 18 L.
   C. 42 L.
   D. 52 L.

   Answer : B. 18 L.

   ECF volume = (Amount injected − Amount excreted)/ Concentration = 10−1/50 = 9/50 = 18 L.

2. Interstitial fluid volume can be determined by:

   C. Radioactive iodine and radiolabelled water.
   D. Radioactive water and radiolabelled albumin.
   E. Radioactive sodium and radiolabelled water.
   F. Radioactive sodium and radiolabelled albumin.

   Answer : D. Radioactive sodium and radiolabelled albumin.

Active space

3. Volume of ICF in body :

D. 0.2 X body weight.

E. 0.4 X body weight.

F. 0.6 X body weight.

G. 0.8 X body weight.

Answer : B. 0.4 X body weight.

Active space

CHARACTERISTICS OF NERVE FIBRES

Neurons/nerve fibres are the functional units of CNS.

Cells in CNS

00:01:30

Ratio of neuron : glial cells is 1 : 10.

Glial (supporting cells) :

1. Macroglial cells : Astrocytes (star shaped), oligodendrocytes, Schwann cells.
2. Microglial cells (phagocytic cells) : Developed from blood – monocyte – macrophage lineage.

Astrocytes :

1. Protoplasmic astrocytes : Seen in grey matter.
2. Fibrous astrocytes : Seen in white matter.

Astrocytes have intermediate filament : GFAP (glial fibrillary acidic protein). GFAP is a tumour marker for astrocytomas.

Functions :

1. Formation of blood brain barrier (BBB) :
   BBB is formed by capillary endothelial cells, which forms tight junctions, further reinforced by foot processes of astrocytes.
2. Synaptic clearing : By uptake of K^+ & neurotransmitters from the synapses to the astrocytes following signals. Hence useful for effective functioning of neurons.

Oligodendrocytes	Schwann cells
Myelination of CNS neurons.	Myelination of PNS neurons.
Multiple myelination.	Single myelination.

Types of neurons

00:11:32

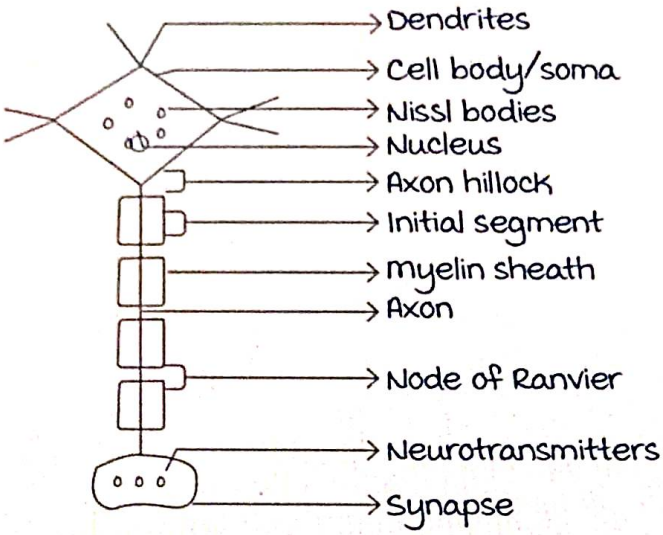
Unipolar : Invertebrates.

Pseudounipolar : Seen in dorsal root ganglion.

Only one process originates from the cell body but bifurcates so that one end reaches upto the skin while the other end reaches the spinal cord.

Bipolar : One end is a dendrite to receive information and the other end is an axon to conduct information. Seen in retina, nose (olfactory epithelium).

Multipolar (most common) : Seen in spinal alpha motor neuron.



Synthesis of proteins : Nissl bodies (RER).

Dendrites :

- Receiving end.

Axon hillock :

- Part of cell body from where axon originates.

Initial segment :

- Initial First proper part of axon.
- Initiation of action potential in motor neurons (axon hillock + initial segment).

Axon terminal / Synaptic terminal :

- Axon ends by forming synapse.

Myelin :

- Conduction in axon can be fast /slow based on presence or absence of myelin.
- If myelin absent, conduction : Slow.
- If myelin present, conduction : Fast.

Nodes of Ranvier :

- It is the area of axon devoid of myelin.
- Maximum number of Na^+ channels are present. (2000 – 12000/sq m).
- Initiation of action potential occurs at the 1st node of Ranvier in sensory neurons.

Axon is for conduction.

Cell body → synapse :

- Anterograde axonal transport.
- With help of Kinesin.
- Fast 400 mm/day or slow 0.5 – 10 mm/day.

Synapse → cell body :

- Reverse axonal transport.
- With help of dynein.
- Fast 200 mm/day.
- Used by viruses for invasion of neurons in infection.

Action potential generation :

- In a motor neuron : From initial segment + axon hillock.
- In a sensory neuron : 1st node of Ranvier.

Myelin

00:27:29

A layer of insulation, increasing a layer of thickness around the axon, hence helps in faster conduction.
It is a combination of

- Lipid (80%) : Sphingomyelin.
- Protein (20%) : myelin basic protein (also called as zero protein). myelin basic protein can be destroyed by autoantibodies : multiple sclerosis.

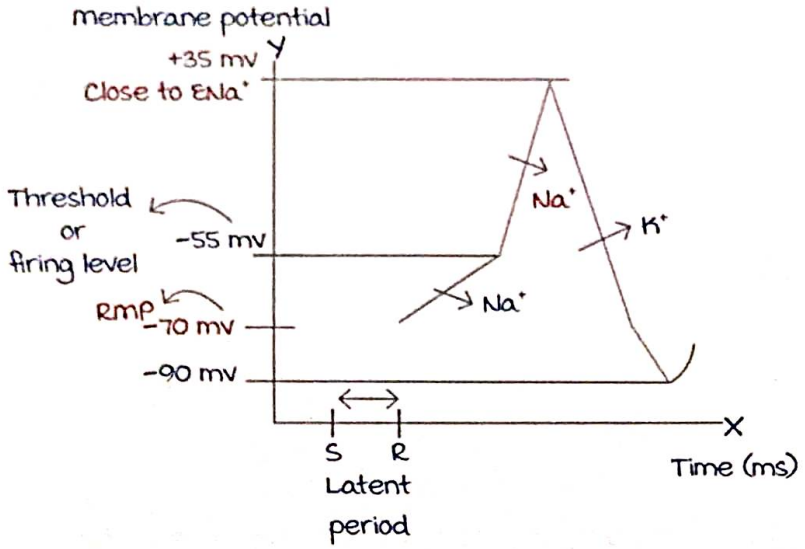
Nerve conduction velocity (NCV) :
Factors affecting conduction are

- Diameter of neuron : Directly related.
- Myelin : Directly related. Increases thickness → increase in axonal resistance → ions move directly to nearby node of Ranvier → increase in conduction.
- Myelin : Increases thickness → decreases membrane capacitance → increase in conduction.
- Temperature : Directly related.

Action potential

00:37:03

Resting membrane potential of neuron : – 70mv



X axis : Time in ms.

Y axis : Membrane potential changes,can be measured with micro electrodes.

S : Stimulus.

R : Response.

Latent period is the gap between the stimulus (S) and response (R).

1. Local potential change : Takes membrane potential from – 70 mv to – 55 mv (threshold or firing level). Occurs due to influx of Na^+ (less & slow).
2. Depolarisation : Because of Na^+ influx (more & fast) through voltage gated Na^+ channels, goes up to a value of + 35 mv (close to equilibrium potential of Na^+ (ENa^+) : 66 mv), and the inside becomes less negative.
3. Repolarisation : Regains its own polarity. Occurs due to efflux of K^+.
4. Hyperpolarisation : Polarity inside the neuron becomes more negative following repolarisation up to – 90 mv, occurs due to
   - K^+ efflux, slow closure of K^+ channels.
   - Cl^- influx.

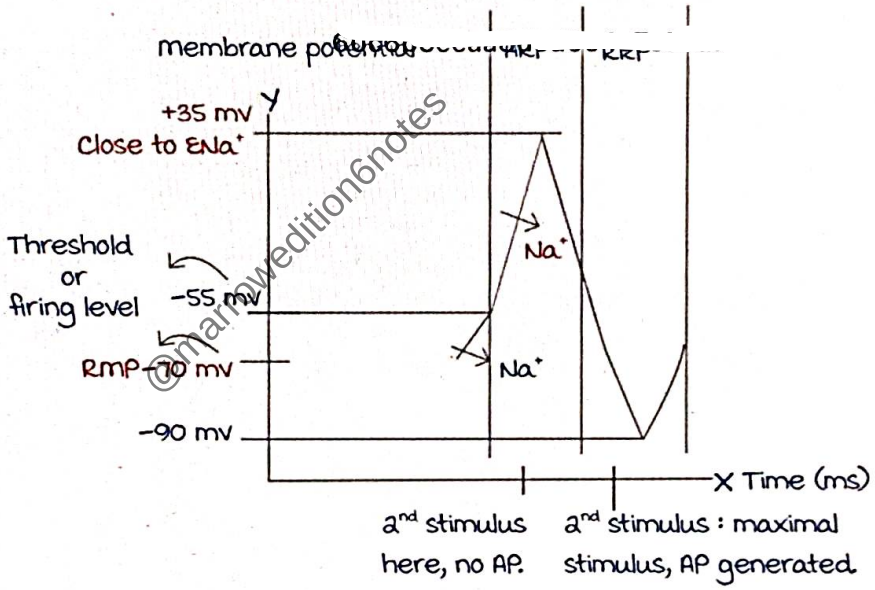
Active space

Hyperpolarisation indicates inhibition of neuronal function, mediated by the inhibitory neuro transmitter GABA (gamma aminobutyric acid). Barbiturates and benzodiazepines are GABA agonists, cause sedation.

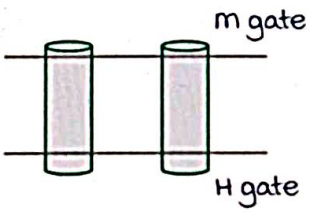
Absolute and relative refractory period 00:50:10

Absolute refractory period (ARP) : A period from firing level to 1/3rd of repolarisation. No action potential is generated with any stimulus during this period. Occurs due to voltage gated Na^+ channel in an inactivated state.

Relative refractory period (RRP) : A 2nd stimulus of maximum strength can produce an action potential. Voltage gated Na^+ channels open on maximum stimulus.



Gate concept 00:55:22



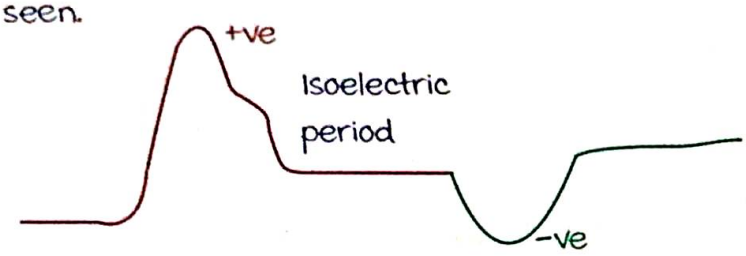
m gate : Activation gate.
H gate : Inactivation gate.

Voltage gated Na^+ channel :

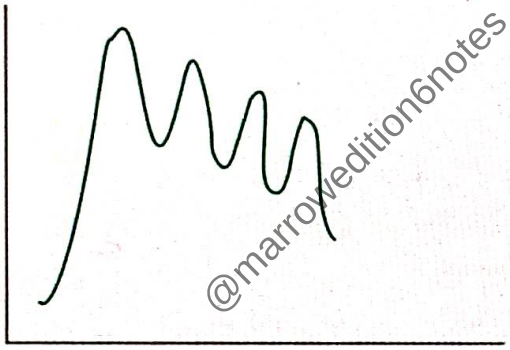
- In closed (resting) state : m gate is closed, H gate is open. Na^+ influx does not occur.

- In open state : m gate is open, H gate is open. Na+ influx occurs.
- In inactivation state : m gate is open, H gate is closed. Na^+ influx does not occur.

Biphasic action potential : When electrodes placed on surface on neurons. Positive phase → Isoelectric phase → Negative phase seen.



Compound action potential : Varying peaks; seen in mixed nerves. They have lot of nerve fibres with varying conduction velocity.



Graded potential vs Action potential 01:02:18

Graded potential	Action potential
Amplitude changes with intensity of stimulus.	Amplitude is always constant; independent of stimulus strength.
No all or none law.	All or none law.
Summation possible.	No summation.
Threshold not needed.	Threshold is required.

MCQ :

Question 1 : A 35 year old female abrupty developed a right hemisensory deficit after several days of work. 2 months ago, the patient was working hard and was under a lot of stress.

Active space

This disorder is due to defect in :

a. Diameter of nerve fibres.

b. Myelination.

c. Gliosis.

d. Neural migration.

Answer : B. Myelination.

Question 2 : Hyperpolarization is caused by which ions ?

a. Sodium.

b. Calcium.

c. Potassium.

d. Magnesium.

Answer : C. Potassium.

Active space

CLASSIFICATION OF NERVE FIBERS

Two types :
Erlanger-Gasser classification.
Lloyd-Hunt classification (sensory classification)

Erlanger-Gasser classification 00:01:15

Based on presence or absence of myelin.
3 types of nerve fibers : A, B and C groups.

- Myelin content, size of nerve fibers and nerve conduction velocity decrease from A to C.
- Myelin content is maximum in A group.
  C group is unmyelinated.
- A group of nerve fibers are thickest. C group of nerve fibers are small, slender and thin.
- A group of nerve fibers have fastest nerve conduction velocity. C group of nerve fibers have slowest nerve conduction velocity.
- A group of nerve fibers are further classified into Aα, Aβ, Aγ and Aδ.
- Aα is the thickest nerve fiber, has maximum myelin content and fastest nerve conduction velocity.
- Nerve conduction velocity of Aα nerve fibers is 120m/sec. Spike duration of action potential is less.
- Nerve conduction velocity of C group of fibers is 2m/sec. Spike duration of action potential is maximum (around 2 ms).

'A' nerve fibers 00:07:49

Aα nerve fiber :
Has both sensory and motor components.
Has fastest nerve conduction velocity (because of maximum myelin) for the sensory function : Proprioception (joint position sense).
Proprioception helps in maintaining balance.
motor function : Alpha motor neuron in spinal cord.

Aβ nerve fiber :
Purely sensory.
Large, myelinated nerve fibers.
Function : Fine touch sensation.

Aγ nerve fiber :
Purely motor.
Gamma motor neuron in spinal cord.
Function : Regulation of muscle tone. Play a role in muscle reflexes.

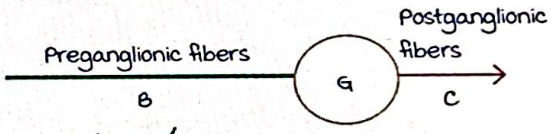
Aδ nerve fiber :
Function : 1st pain → Sharp pain (fast pain) by myelinated Aδ fibers.
2nd pain is through unmyelinated slow C fibers.

A group of fibers are most susceptible to compression/ pressure. Large fibers are more prone (i.e. Aβ)

'B' and 'C' nerve fibers 00:15:10

B nerve fibers :
myelinated.
Seen exclusively in autonomic nervous system.
Preganglionic fibers are B nerve fibers.

C nerve fibers :
Unmyelinated.
Slow conduction velocity around 2m/sec.
maximum spike duration of action potential.
Postganglionic fibers.
Function : 2nd pain → Slow pain.



Preganglionic fibers are B nerve fibers (myelinated).
Postganglionic fibers are C nerve fibers (unmyelinated).

Preganglionic nerve fibers (B nerve fibers) are most susceptible to hypoxia.

C group of nerve fibers are least susceptible to hypoxia and compression.

Lloyd-Hunt classification (sensory classification)

00:19:09

No motor component.

4 types of nerve fibers each corresponding to a type in Erlanger-Gasser classification :

Type 1 corresponds to Aα. Has 2 components Ia (muscle spindles) and Ib (Golgi-tendon organs)

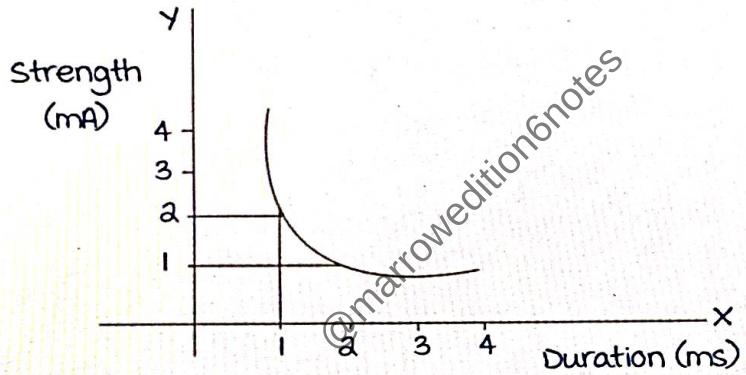
Type 2 corresponds to Aβ.

Type 3 corresponds to Aδ.

Type 4 corresponds to C nerve fibers (unmyelinated).

Strength duration curve :

Threshold stimulus for action potential depends on strength of stimuli and duration of stimuli. Relationship between strength and duration of stimuli is studied using strength-duration graph.



Rheobase = 1 mA

Chronaxie = 1 ms

Strength of current is denoted on Y-axis.

Duration of stimuli is denoted on X- axis.

Rheobase : Minimum strength of current required to produce a response (denoted on Y-axis).

Chronaxie : Time required for twice the strength of rheobase to produce a response (denoted on x-axis).

Chronaxie is inversely related to excitability of the tissue (less chronaxie → more excitable).

Chronaxie of nerve fibers is less compared to chronaxie of muscles (nerve fibers are more excitable than muscles).

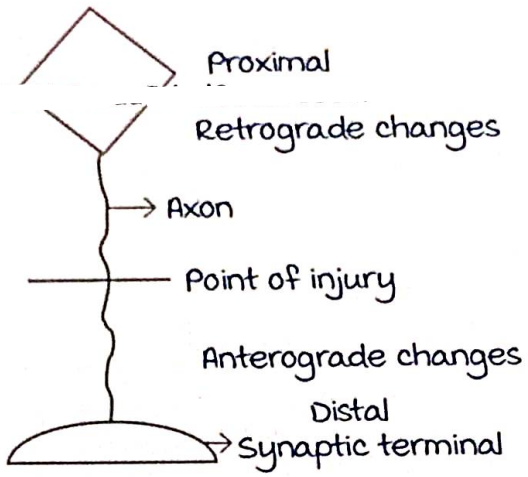
Threshold stimulus is required to generate action potential.

Accommodation : Repeated subthreshold stimuli does not produce action potential.

Adaptation : Repeated suprathreshold (supramaximal) stimuli does not produce action potential.

Injury to nerve fibers

00:31:02



Axon is the most common area to be injured.
In response to injury, there will be changes in proximal and distal parts.
Retrograde changes : Proximal changes.
Anterograde changes : Distal changes.

Degeneration :
Within 24 hours of injury → Earliest changes are distal changes → Wallerian degeneration (named after Waller).
It includes :
Axonal degeneration, followed by
myelin degeneration → Debris are phagocytosed to clean the site of injury.

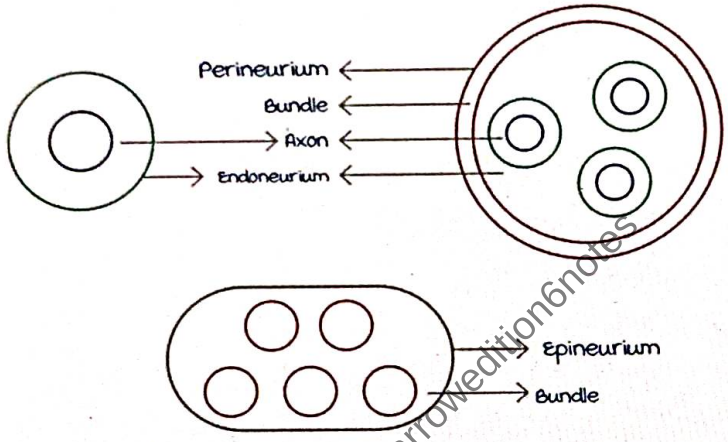
Within 36 hours of injury → Proximal changes are seen in cell body.
Cell body contains nucleus and Nissl bodies (rough endoplasmic reticulum).
1. Nucleus is pushed from center to periphery.
2. Degeneration of Nissl bodies → Chromatolysis (loss of contour).

Regeneration :
After 90 hours of injury → Nerve fibers try to regenerate.
Slow process → Rate is 1 to 3 mm/day.

Tinel's sign : On tapping the injured nerve, tingling sensation is felt along the course of the nerve. Positive sign indicates nerve regeneration.

Classification of nerve injuries 00:40:18

Each individual axon is surrounded by a covering layer called endoneurium.
Groups of axons are found in a bundle which is covered by a covering layer called perineurium.
Groups of bundles are surrounded by a covering layer called epineurium.



Seddon's classification (to determine prognosis) :
3 grades :

- Neuropraxia : Physiological prolongation of nerve conduction velocity.
  Seen in nerve compression. Has good prognosis (spontaneoud recovery is seen).
  Example : Saturday night palsy.
- Axonotmesis : Axonal injury. Intermediate prognosis.
- Neurotmesis : Complete transection of nerve fiber (nerve fiber is split into 2 halves)
  Has the worst prognosis.

Sunderland classification (to determine prognosis)
5 grades :

- 1st degree → Neuropraxia.
- 2nd degree → Axonotmesis (Axonal injury).
- 3rd degree → Axon + Endoneurium disruption.

Active space

- 4th degree → Axon + Endoneurium + Perineurium disruption.
- 5th degree → Complete transection → Axon + Endoneurium + Perineurium + Epineurium disruption.

MCQs :

1. Person wakes up with pain, paresthesia, tingling of the arms. He had slept with arm below the head. Which fibers are involved?
   A. Type A fibers.
   B. Type B fibers.
   C. Type C (Pain).
   D. Type C (Postganglionic).

2. According to Sunderland classification, axonotmesis is :
   A. First degree injury.
   B. Second degree injury.
   C. Third degree injury.
   D. Fourth degree injury.

3. Best prognosis in nerve injury :
   A. Neuropraxia.
   B. Axonotmesis.
   C. Neurotmesis.
   D. Complete transection.

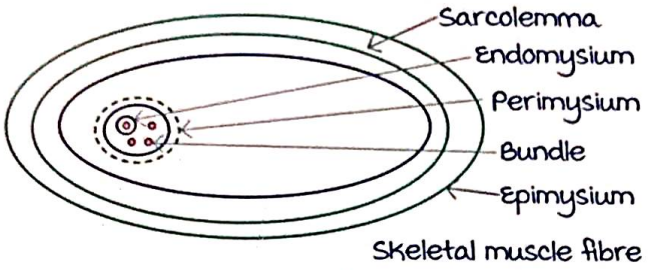
4. Prolonged subthreshold stimulus fails to initiate action potential in nerve fibers. This phenomenon is called as :
   A. Adaptation.
   B. Accommodation.
   C. Refractoriness.
   D. Electrotonus.

Active space

SKELETAL MUSCLE

Skeletal muscle

00:00:48



Skeletal muscle fibre

Parts :

Cell membrane : Sarcolemma.

Connective tissue layers :

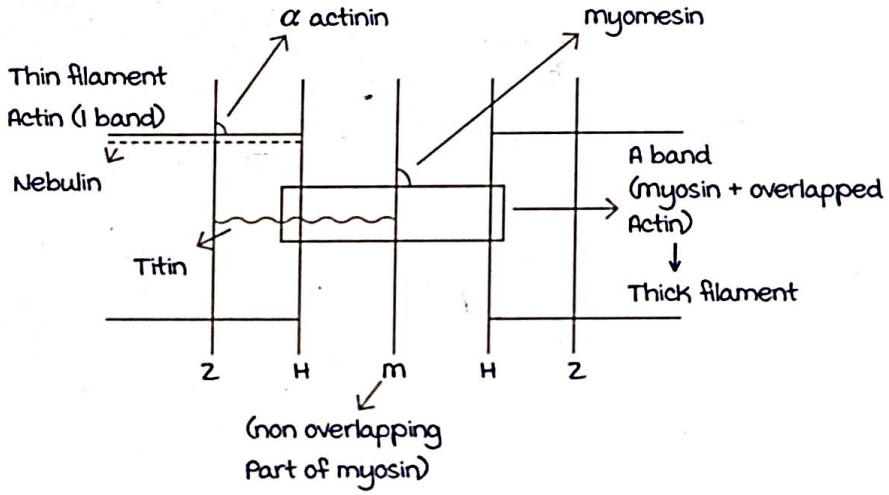
- Endomysium surrounds each muscle fiber.
- Groups of muscle fibers are collected inside a bundle called fascicles.
  Perimysium surrounds each fascicle.
- [illegible] surrounded by epimysium.

Functional units → Sarcomere.

Contains 2 primary proteins : Actin and myosin.

Sarcomere :

- Area between two Z lines is one sarcomere.
- Thin filament : Actin
- I band : Contains actin.
- Thick filament : myosin.



Active space

- A band : myosin + overlapped actin filaments.
- H band : myosin not overlapped by actin.
- M line : Line at the center of the sarcomere.
- Actin is attached to Z line by alpha actinin.
- Myosin is attached to M line by myomesin.
- Nebulin protein runs along the length of actin. It regulates the length of actin filament.
- Titin is a spring like protein that runs from Z line to the M line.

Changes in sarcomere during muscle contraction

00:11:55

- Z lines come closer.
- Length of I band and H band decreases.
- No change in the length of A band.

Actin :

Thin filament.

Myosin :

- Thick filament.
- Has a fixed length of around 1.6 microns.
- Contains 2 heavy chains and 4 light chains.
- Myosin head contains the enzyme ATPase.

Skeletal muscle contains 4 types of proteins :

- Contractile proteins.
- Supportive proteins.
- Regulatory proteins.
- Relaxation proteins.

Contractile proteins :

Microfilaments : Actin and myosin.

Supportive proteins :

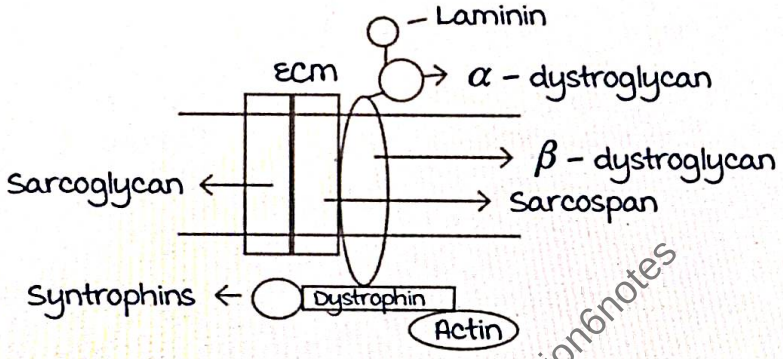
- Desmin.
- Dystrophin glycoprotein complex (D – G complex).
- Titin.

Desmin :

Intermediate filament. Tumor marker for sarcomas.

Dystrophin – glycoprotein complex :
Dystrophin attaches actin to β dystroglycan in the cell membrane which in turn attaches to α dystroglycan.
α dystroglycan is attached to laminin in the extracellular matrix.
Dystrophin requires syntrophins to attach actin to β dystroglycan.
β dystroglycan also attaches to sarcoglycan and sarcospan in the cell membrane.

Dystrophin – glycoprotein complex



Dystrophin – glycoprotein complex involves the following :
Dystrophin, syntrophins, beta dystroglycan, alpha dystroglycan, sarcoglycan and sarcospan.

Dystrophin is also called as anchor protein.
Absence of dystrophin causes Duchenne muscular dystrophy (DMD). Skeletal muscle weakness is the predominant feature.
Weakness of diaphragm causes respiratory muscle paralysis and death in DMD.

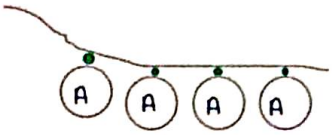
Titin :

- Muscle spring.
- Gives elastic support.
- Largest protein in humans (word 'titus' means giant).
- Extends from Z line to M line.
- Attaches myosin head to Z line.
- Keeps actin and myosin in place (side by side arrangement).

Active space

Regulatory proteins 00:25:37

Tropomyosin :
Actin filaments contain myosin binding sites (active site).
In resting skeletal muscle, tropomyosin covers active site of actin filaments thereby preventing actin - myosin interaction.
1 tropomyosin usually covers 7 active sites.
It is a rope like protein.

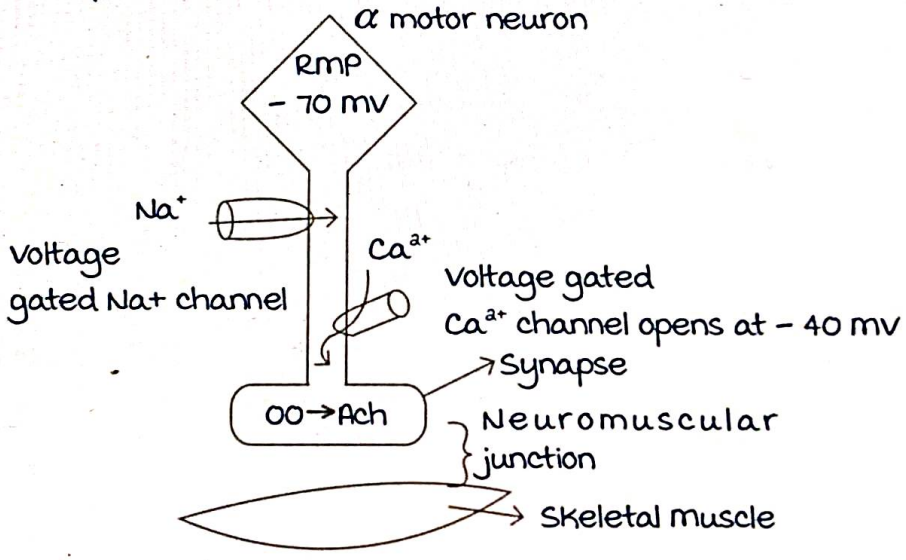


Troponin :
3 subunits.
Troponin T binds tropomyosin.
Troponin I inhibits actin-myosin interaction.
Troponin C binds with calcium.

Relaxation proteins :
Sarcoplasmic reticulum calcium ATPase (SERCA).

Contraction and relaxation of skeletal muscle 00:31:30

Contraction :
Electrical event - action potential (excitation) is the prerequisite.
Mechanical event is muscle contraction.
Action potential (excitation) :



Excitation contraction coupling : Coupling of electrical and mechanical event by calcium.

Motor unit : A single alpha motor neuron innervating many muscle fibers.

Depolarization → Na^+ influx through voltage gated Na+ channel.
Resting membrane potential changes to - 40 mV from -70 mV.
Voltage gated Ca^{a+} channels open at -40 mV → Calcium influx.
Calcium causes release of acetylcholine (exocytosis).
Acetylcholine (Ach) acts on muscle causing contraction.

- Puffer fish contains tetrodotoxin which is a blocker of voltage gated Na^+ channel. It causes muscle paralysis and death.
- Lambert Eaton myasthenia syndrome :
  Autoantibodies cause destruction of voltage gated Ca^{a+} channel → No release of Ach → muscle paralysis.
- Release of Ach requires synaptobrevin which is degraded by botulinum toxin → flaccid paralysis.

Ach acts on nicotinic acetylcholine receptor in the skeletal muscle → influx of Na^+ → end plate potential (EPP), a type of local potential.
EPP summates and crosses threshold → firing of action potential → muscle contraction.

Spontaneous release of Ach vesicles can induce miniature end plate potential (MEPP).

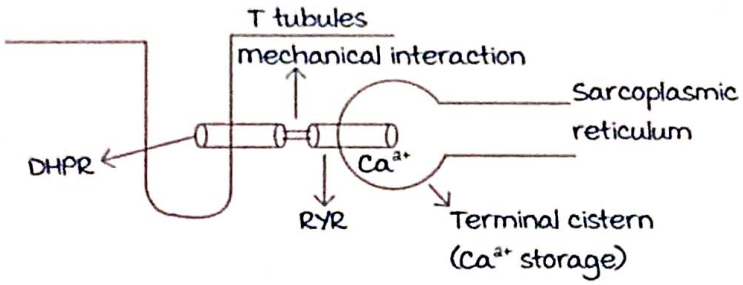
Calcium channels in skeletal muscles 00:45:38

Dihydropyridine receptor Ca^{a+} channel (DHPR) : Found in 'T' tubules. 'T' tubules are invaginations of skeletal muscle cell membrane resembling the alphabet 'T'.
DHPR receptors are located close to sarcoplasmic reticulum.
End part of sarcoplasmic reticulum is called terminal cistern.
Calcium is stored in terminal cisterns.

Ryanodine receptor Ca^{a+} channel (RYR) : Found in sarcoplasmic reticulum.

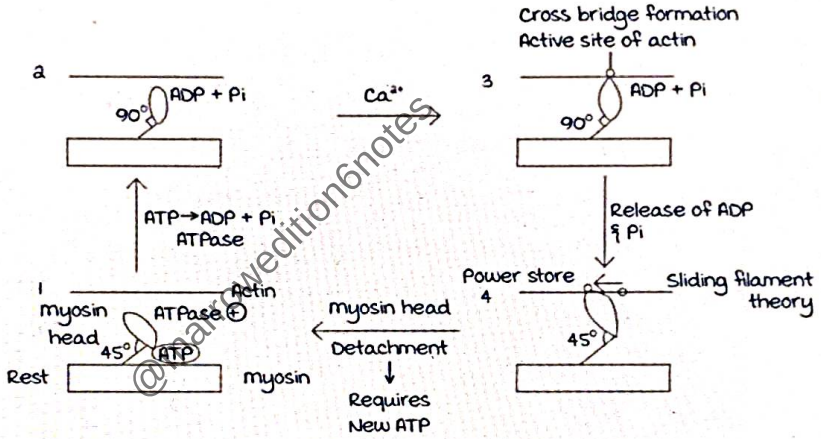
DHPR and RYR calcium channels interact mechanically.
Action potential travels through 'T' tubules and activates DHPR receptors.

Activation of DHPR receptors causes conformational change and opens ryanodine receptors. Calcium is released which helps in contraction.



DHPR : Dihydropyridine receptor
RYR : Ryanodine receptor

Molecular mechanism of muscle contraction 00:49:54



- Actin – myosin interaction is required for muscle contraction.
- myosin head is tilted at 45° during resting state.
- Binding of ATP to myosin head causes activation of ATPase enzyme in myosin head.
- ATP is hydrolysed to ADP and phosphate by ATPase → myosin head moves from 45° to 90°.
- Calcium causes attachment of myosin head to active site of actin filaments → cross bridge formation.
- After cross bridge formation, ADP and phosphate are released from myosin head and myosin head tilts back to 45° (power stroke). In this process, myosin head moves some distance → sliding filament.
- Cross bridge cycling phenomenon : Cycling of formed cross bridges causes power strokes.

- Myosin head detachment requires a new ATP molecule. With new ATP molecule, the above cycle repeats.
- After death, no ATP available → muscles in sustained contraction → rigor mortis.

Relaxation of skeletal muscle 00:59:23

Calcium is stored in terminal cisterns of sarcoplasmic reticulum. Ryanodine receptor helps in release of calcium for muscle contraction. Following muscle contraction, calcium is taken back inside through SERCA pump.
SERCA pump helps in storage of calcium and muscle relaxation.

Ryanodine receptor overactivity → enhanced release of calcium → increased muscle contraction → increased release of heat → Malignant hyperthermia.
Treatment : Blockade of ryanodine receptor by dantrolene sodium.

MCQs :

1. A 8 year old boy presents with muscle weakness, difficulty climbing stairs and falling down more often when playing with his friends. This disorder is because of absence of :
   A. Troponin.
   B. Tropomyosin.
   C. Calmodulin.
   D. Dystrophin.

   Answer : D. Dystrophin.
2. Spontaneous release of acetylcholine at the neuromuscular junction produces :
   A. Miniature end – plate potential.
   B. Action potential.
   C. Post – tetanic potential.
   D. Resting membrane potential.

   Answer : A. Miniature end – plate potential.
3. A 30 year old female presents with little to no pain at the beginning of the day but it progressively gets worse as the day progresses. By the end of the day, she

notices her vision becomes slightly blurred and finds it worsens when driving home. This disorder involves destruction of

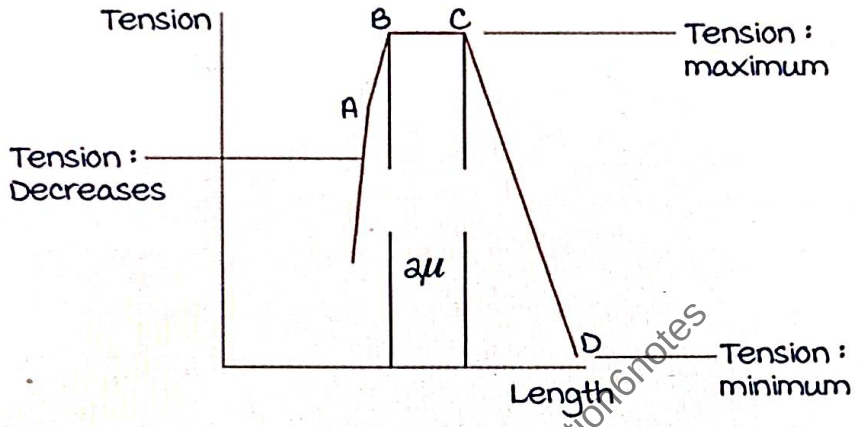
A. Voltage gated calcium channels.
B. Voltage gated sodium channels.
C. Nicotinic Ach receptors.
D. SERCA pump.

Answer : C. Nicotinic Ach receptors.

PROPERTIES OF SKELETAL MUSCLE

Contraction (muscle shortening) : Length changes.
Force of contraction : Tension changes.

Length tension relationship graph 00:01:53



D	C	B	A
Actin and myosin are wide apart : Not overlapping.	Maximum overlapping between actin and myosin : Optimal overlap/ maximum overlap.		Actin and myosin still overlap but not optimal.
Tension : Minimum	Tension : Maximum (corresponds to a sarcomere length of 2μ)		Tension : Decreases

Types of tension :

1. Active tension : Skeletal muscle stimulated → Actin and myosin interacts → muscle contracts (cross bridge formation).
   Active tension α Cross bridge formation.
   Active tension α Diameter of muscle fibre.
   Active tension α Length of muscle fibre.
   Active tension α Frequency of active potential.
   Active tension α Number of motor units recruited.
2. Passive tension : Muscle not stimulated → Elastic stretching (passive : Titin mediated).
3. Total tension : Active tension + Passive tension.

Active space

Important aspects of length :

- When actin and myosin interaction is optimal & tension is maximum (active tension), then the length is called optimal length/resting length (during contraction & at rest)
- Equilibrium length : Seen when muscle is cut from its bony attachments on both ends.

Types of muscle fibers

00:12:33

	Type I	Type IIa	Type IIb
Size	Small	Large	Large
Colour	Red	Red	White
Reason for colour	myoglobin present	myoglobin present	myoglobin absent
Oxygen storage	Possible	Possible	Not possible
metabolism	Aerobic (oxygen)	Aerobic (oxygen)	Anaerobic pathway : Glycolysis (lactate accumulation : leads to pain, fatigue)
	Fatigue resistant	Fatigue resistant	Fatigue prone
mode of contraction and relaxation	Slow	Fast	Fast
motor unit innervation	Slow motor units	Fast, fatigue resistant motor units	Fast fatigable motor units

Type I : Small, slow, red, slow motor unit.
Type IIa : Large, fast, red, fast fatigue resistant motor units.
Type IIb : Large, fast, white, fast fatigable motor units.

Order of recruitment : Small → Large. This is called Size principle.

Example : Sitting ⟶ Standing ⟶ Running

- Sitting → Slow fibres : First Type I
- Standing → Type IIa
- Running → Fast fibres : Last. Type IIb (fatigable)

Motor units

00:23:57

- Consists of a single alpha motor neuron and the muscle fibers it innervates.
- For muscles with fine precise movements.
  Example : Extraocular muscles (1 motor unit innervates only around 3-6 muscle fibers).
- In case of coarse movements. Example : Leg and back muscles (1 motor unit innervates upto 600 muscle fibers).

During the process of muscle contraction & relaxation, heat is generated.

Types of heat :

In a resting state :

- Resting heat : Because muscles undergo basal metabolic process.

During contraction :

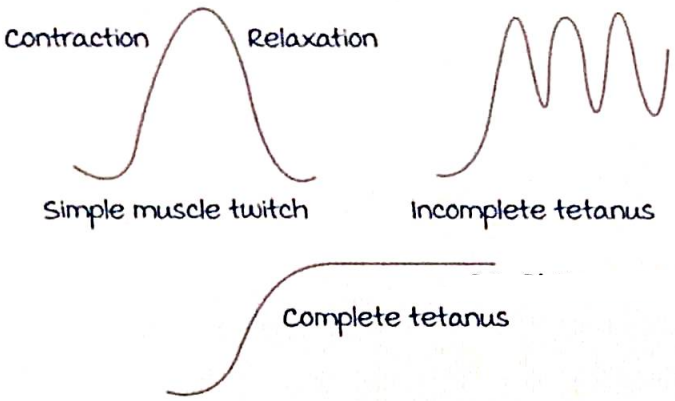
- Activation heat : When actin and myosin are activated.
- Shortening heat : During process of shortening.

During relaxation :

- Relaxation heat : Seen during isotonic contraction (tension is same but length changes). It is the heat that is liberated to bring the length back to its previous length.
- Recovery heat.

Phenomena related to contraction & relaxation :

- Upon stimulation, there is contraction & relaxation : Simple muscle twitch phenomenon.
- In response to multiple stimuli, both Contraction and relaxation are seen but they are not complete. This phenomenon is called incomplete tetanus.
- Further increase in stimuli, muscle will go into a state of sustained contraction. No relaxation in between. This phenomenon is called complete tetanus.
  Pathological : Spastic paralysis (In tetanus by Tetanospasmin toxin).



Tetanizing frequency (TF) : It is a particular frequency of stimulus that is capable of producing a state of sustained contraction (complete tetanus).

$$TF = \frac{1}{\text{contraction period}}$$

Abnormal phenomena

00:35:14

Fibrillation :

- Twitch of a single muscle fiber.
- Due to problem in single alpha motor neuron/its axon.

Fasciculation :

- Twitch of a group of muscles.
- Due to pathological discharge of many motor units.

MCQs :

1. When the tension in a muscle fibre is maximum, its length is called as ?

A. Equilibrium length.
B. Optimum length.
C. Initial length.
D. Final length.

2. Fast fatigable motor unit is recruited :

A. First.
B. Last.
C. During relaxation.
D. During muscle injury.

3. All are true about red muscle fibers except :

A. More mitochondria.
B. More myoglobin.
C. Glycolytic metabolism.
D. More oxidative capacity.

Active space

CARDIAC MUSCLE AND SMOOTH MUSCLES

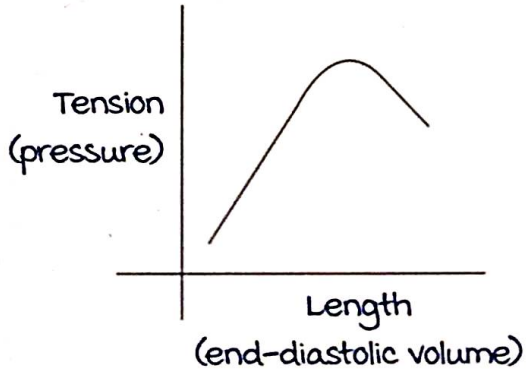
Introduction 00:00:24

Cardiac muscle is similar to skeletal muscle with few differences :

- Contractions are involuntary : Needs pacemaker (SA node).
- Has actin and myosin. It is a striated muscle.
- Myosin heavy chain consists of alpha (mainly in atrium) and beta subunits (mainly in ventricles).
- Has tropomyosin and troponin.
- Elastic nature (elastic recoil phenomenon) due to titin protein.
- Mutation in titin : Dilated cardiomyopathy (no recoiling, only stretches).
- Synchronized contraction happens and is called functional Syncytium because of gap junctions.
- Protein that forms gap junctions : Connexins.
- Histology : Gap junctions are located in intercalated disc region.

Unique features of cardiac muscle 00:07:03

1. Length Tension relationship :
   - Length is determined by blood volume : End diastolic blood volume (EDV).
   - Tension determined by force of contraction : Pressure in left ventricle.

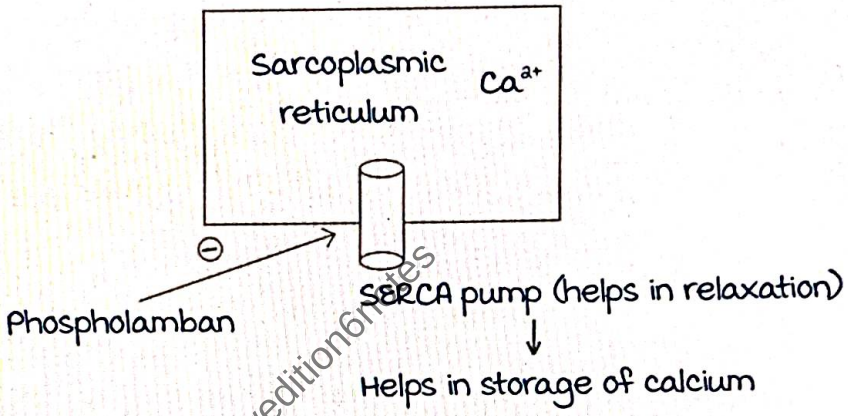


Frank-Starling law :

- Force of contraction (pressure) α Initial length of muscle fibre (EDV).
- Increase in EDV increases the force of contraction within physiological limits.

Calcium induced calcium release (CICR) :

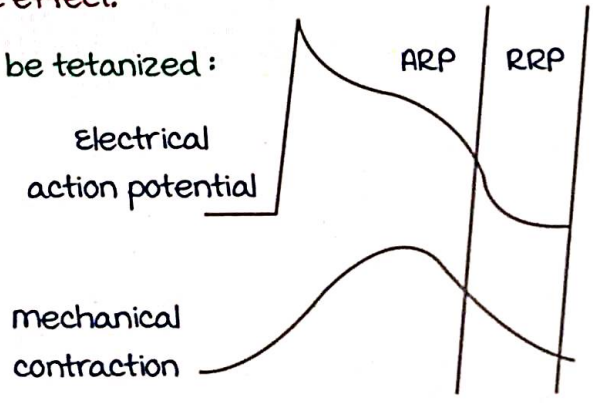
- Some amount of extracellular calcium is always needed to release calcium from intracellular source (sarcoplasmic reticulum).
- For cardiac muscle both extracellular & intracellular Ca^{2+} are needed.



- Phospholamban inhibits SERCA pump thereby interfering with calcium storage.
- Norepinephrine
  ↓
  Phosphorylation of phospholamban
  ↓
  Phospholamban is inhibited
  ↓
  Calcium storage is possible i.e. Relaxation is possible.
  This is called positive lusitropic effect.
- Norepinephrine ensures adequate calcium storage that is required for upcoming contractions, this is called positive inotrophic effect.

Cardiac muscle cannot be tetanized :

ARP : Absolute refractory period.
RRP : Relative refractory period.



Active space

major part of contraction lies in absolute refractory period. Hence, the second stimuli cannot be summated. So, cardiac muscle cannot be tetanized (adequate contraction & relaxation are always needed for proper functioning of heart). This is an evolutionary adaptation.

Smooth muscles 00:21:46

- No striations on the surface.
- Involuntary : Pacemaker : Cajal cells.
- Has actin and myosin, no Z - lines, but has dense bodies.
- No troponin but has calcium binding protein : Calmodulin.
- No titin, not elastic (no elastic recoil).

Types of smooth muscles

Gap junctions present : Single unit/unitary smooth muscles	Gap junctions absent : Multi-unit smooth muscles/ Vascular smooth muscles
• In GIT. • Uterus. • Urinary bladder. • Ureter.	• In blood vessels.

Contraction and relaxation (both are myosin based regulation) :

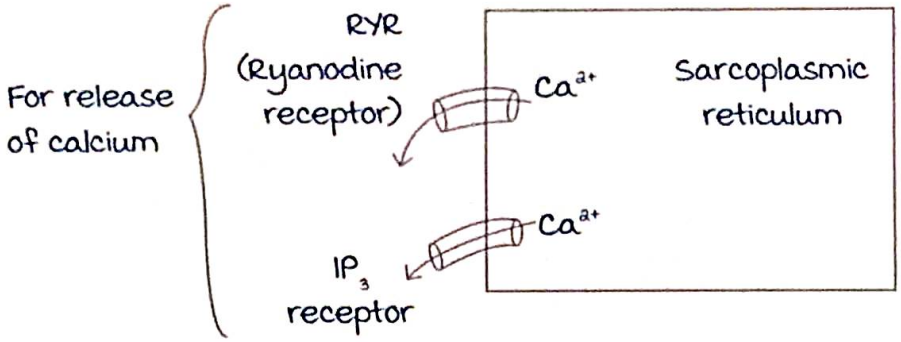
- Contraction : MLCK (myosin Light Chain Kinase) activation → Actin myosin interaction (contraction)
- Relaxation : MLCP (myosin Light Chain Phosphatase) activation → inhibits contraction.
  MLCP inhibited by Rho Kinases → No relaxation.
  Rho Kinase inhibitors (makes relaxation possible), example : Fasudil.

Contraction and relaxation (regulation with help of ANS) :

- Parasympathetic → Excitatory potential → Contraction.
- Sympathetic → Inhibitory potential → Relaxation.

2 receptors for calcium release in smooth muscles :
IP_3 & RYRs

Active space



Unique features of smooth muscle 00:32:38

1. No titin → Not elastic (only stretch, no recoil). This phenomenon is called plasticity. Eg : Uterus during pregnancy, bladder while retaining urine.
2. In GIT, smooth muscles are in state of sustained contraction for hours with little use of ATP. This is called Latch bridge phenomenon.

MCQs :

1. Which of the following mechanism terminates smooth muscle contraction?

A. Activation of myosin light chain kinase.
B. Activation of myosin ATPase.
C. Activation of myosin light chain phosphatase.
D. Activation of Troponin C.

2. Increase in cytosolic calcium from intracellular storage, during smooth muscle contraction is/are due to

A. DAG.
B. Nitric oxide.
C. IP3.
D. Adenosine.

3. Phosphorylation of phospholamban is done by

A. Acetylcholine.
B. Nitric oxide.
C. Dopamine.
D. Norepinephrine.

SYNAPTIC TRANSMISSION AND NEUROTRANSMITTERS

Synaptic transmission 00:00:47

2 types.

Electrical synapses :

Communication through gap junctions.

Fast process.

Chemical synapses :

Involves the release of neurotransmitters.

Slow process.

Synapse :

- Point of communication between two neurons.
- MC type of synapse is axosomatic synapse → Axon of one neuron communicates with the cell body of another neuron.
- Neurotransmitters are released in synapse.
- Neuron above synapse is called as presynaptic neuron. Neuron below synapse is called as postsynaptic neuron.
- Structure of synapse was first identified by Sir Charles Sherrington. He is considered as the 'Father of synaptic transmission'.
- Neurotransmitters act on postsynaptic neuron → produce post synaptic potentials → can be
  Excitatory (excitatory post synaptic potential) or
  Inhibitory (inhibitory post synaptic potential).
- Excitatory and inhibitory post synaptic potential can be fast or slow.
- Excitatory post synaptic potential (EPSP) can be brought about by glutamate.
- Inhibitory post synaptic potential (IPSP) can be brought about by glycine or GABA.

Fast EPSP :

Cell interior becomes less negative due to influx of positive ion : Either Na^+ or Ca^{2+}.

Fast IPSP :

Cell interior becomes more negative either due to influx of negative ion Cl^- or efflux of positive ion K^+.

Slow EPSP and Slow IPSP :

Latency up to 500 ms.

Seen in autonomic ganglia, cardiac muscle, smooth muscle.

Only brought about by K^+ ions.

Slow EPSP :

Cell interior becomes less negative due to decrease in K^+ efflux.

Slow IPSP :

Cell interior becomes more negative due to increase in K^+ efflux.

Excitatory postsynaptic potential :

Type of local potential (not action potential).

Example : Neuromuscular junction → End plate potential.

Can undergo summation and cross the threshold producing action potential.

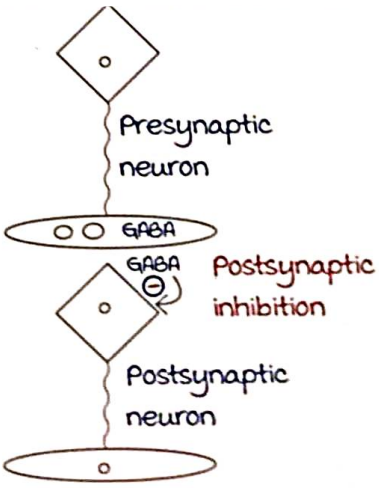
Regulation of postsynaptic potential 00:14:55

- Facilitation
- Inhibition.

Facilitation : Ca^{2+} channels remain open for a long time → Enhanced Ca^{2+} influx.

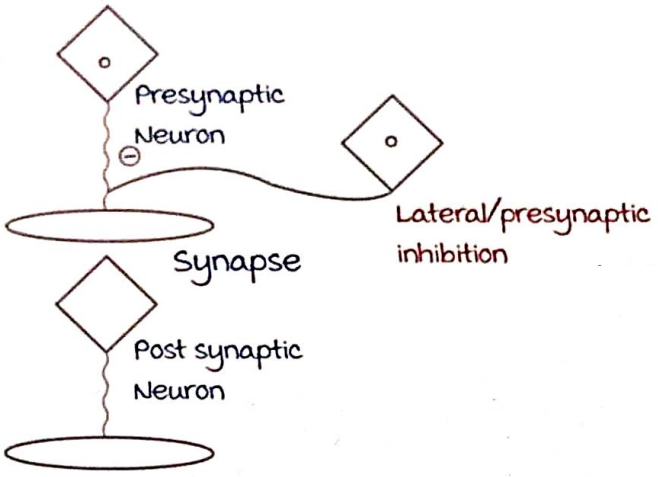
Inhibition :

1. Postsynaptic inhibition → Inhibitory neurotransmitter released inhibits postsynaptic neuron.

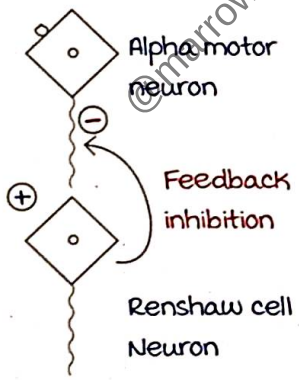


Active space

2. Lateral inhibition → Presynaptic neuron is inhibited by another neuron from the lateral side. It is also called as presynaptic inhibition. Example : Retina.



3. Feedback inhibition → Alpha motor neuron activates another neuron called as Renshaw cell neuron which in turn inhibits the alpha motor neuron.
   - Renshaw cells utilize glycine for feedback inhibition.
   - They are useful to control firing of alpha motor neuron.



Neurotransmitters 00:21:22

Otto Loewi discovered the first neurotransmitter → A chemical that decreases heart rate called vagusstoff. It was later identified as Acetylcholine.

Criteria for neurotransmitters :

- Neurotransmitter should be synthesized and stored in the presynaptic neuron.
- Release of neurotransmitter into the synapse should occur in response to a signal.

Active space

- Postsynaptic neuron should have a receptor for the neurotransmitter for the latter to act.

Neurotransmitter receptors :

1. Ligand gated (ionotropic) receptor :
   Opens ion channels. Responses are fast.
   Example : GABA A, GABA C, nicotinic Ach receptor.
2. Metabotropic receptor :
   G protein coupled receptor mediated.
   Involves the use of second messenger.
   Responses are slow.
   Example : GABA B, muscarinic Ach receptor.

Neurotransmitter classification :

Class 1 : Acetylcholine.

Class 2 : Biogenic amines. Examples : Norepinephrine, Dopamine, Serotonin.

Class 3 : Amino acids. Eg., Excitatory : Glutamate.
Inhibitory : GABA.
Both excitatory & inhibitory : Glycine.

Class 4 : Gases. Examples : Nitric oxide, Carbon monoxide.

Acetylcholine 00:29:40

Neurotransmitter in :

- Neuromuscular junction → Plays a role in muscle contraction.
- Nucleus basalis of meynert → memory.
- Sleep → REM sleep.
- Sweat glands (sympathetic cholinergic system).

Ach release :

- Ach release from synapse is through exocytosis.
- For exocytosis, Synaptobrevin, which is a type of SNARE protein is required.
- Botulinum toxin degrades synaptobrevin → No Ach release → Flaccid paralysis. Botox treatment is useful for blepharospasm, achalasia cardia.

Ach receptors :

- Either nicotinic or muscarinic.

- Nicotinic receptor is an inotropic receptor.
- Muscarinic receptor is a metabotropic receptor.

Biogenic amines 00:35:04

Norepinephrine :

- Synthesized from dopamine with the help of dopamine beta hydroxylase.
- Norepinephrine is exclusively distributed in locus coeruleus. Through locus coeruleus, it has widespread connections to major parts of the brain.
- Neurotransmitter of arousal → Helps to keep in awake state.

Dopamine :

3 pathways :

- Nigrostriatal pathway in basal ganglia → motor movement control.
- Deficiency leads to development of parkinsonism.
- Mesocortical pathway → 2 areas :
  Ventral tegmental area (VTA) → Reward pathway.
  Nucleus Accumbens → Addiction behavior.
- Tuberoinfundibular pathway → Dopamine inhibits the release of prolactin from anterior pituitary.

Dopamine receptors :

D1, D2, D3, D4 & D5 receptors. All are G protein coupled.

Serotonin :

- Major inhibitory neurotransmitter in brain.
- Location : Raphe nuclei, GI tract, blood platelets.
- Another name is 5-Hydroxy Tryptamine (5HT).
- There are 7 receptors : $5HT_1$ to $5HT_7$. All are G protein coupled except $5HT_3$ which is ligand gated (ionotropic).
- Actions are based on receptors :
  $5HT_{2a}$: Platelets → Platelet aggregation.
  $5HT_{2c}$: GIT → Decreases food intake (satiety).
  $5HT_3$: Area postrema → Vomiting.
  $5HT_4$: GIT → Peristalsis.
  $5HT_6$ and $5HT_7$ → Limbic system.

Active space

Serotonin promotes wakefulness → Neurotransmitter of arousal.

Histamine :

- Exclusively distributed in hypothalamus.
- Promotes wakefulness.
- Histamine blocker such as Chlorpheniramine maleate causes sedation.
- Through H_a receptor in parietal cells, histamine increases gastric acid secretion.

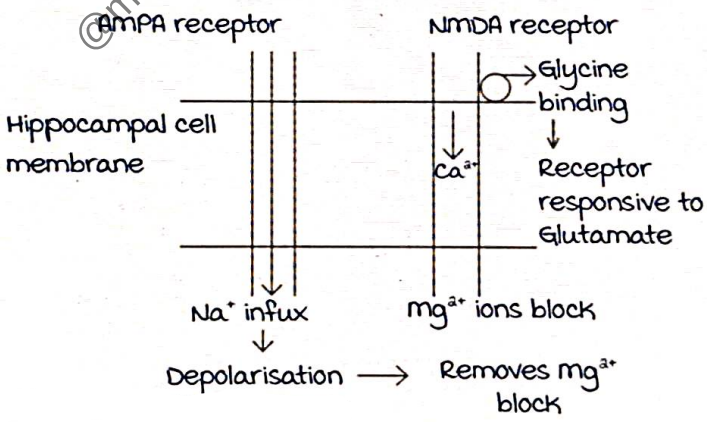
Amino acid neurotransmitters 00:46:40

Glutamate :

- Major excitatory neurotransmitter.
- Hippocampus → memory.
- Neurotransmitter of subthalamic nucleus in basal ganglia.
- Mediates first pain (transmitted by A delta nerve fibers).

Receptors of glutamate :

- AMPA receptors → Na^+ channel.
- NMDA receptors → Ca^{a+} channel.



NMDA receptor has a binding site for glycine. Binding of glycine activates the receptor.
At resting state, NMDA receptor is blocked by mg^{a+} ions. Na^+ influx through AMPA receptor leads to depolarization and removes the block due to mg^{a+} ions → Influx of calcium ions through NMDA receptor.

Overactivity of NMDA receptor → Enhanced Ca^{a+} influx → Cell death → Excitotoxicity. Seen in amyotrophic lateral

sclerosis. Riluzole is a NMDA receptor blocker used in the treatment of amyotrophic lateral sclerosis.

GABA :

- GABA is a predominantly inhibitory neurotransmitter.
- Distributed throughout the brain.
- GABA produces inhibition through hyperpolarization (cell interior is more negative). Hyperpolarization is due to Cl^- ion influx.
- GABA agonists : Benzodiazepines, Barbiturates are used as sedatives.
- GABA effects : Basal ganglia → Striatum → Inhibition of involuntary movements.
  Loss of GABA along with loss of cholinergic neurons containing Ach in the striatum leads to an involuntary movement disorder known as Huntington's chorea.

GABA receptors :

- GABA A, GABA B, and GABA C.
- GABA A & GABA C are linked to ion channels.
- GABA B is a G protein coupled receptor.

Glycine :

- Both excitatory and inhibitory neurotransmitter.
- Inhibitory effect is predominantly seen in Renshaw cell neurons in spinal cord. Alpha motor neuron activates Renshaw cell neuron which in turn inhibits alpha motor neuron through glycine.
- Excitatory effect is seen in hippocampus (activation of NMDA receptor).
- Strychnine is an antagonist of glycine.
  Strychnine poisoning causes overactivity of α motor neurons → spastic paralysis.

Tetanospasmin also causes spastic paralysis. Tetanospasmin inhibits inhibitory ~~interneuron (uses GABA)~~ → No GABA release from inhibitory interneuron → spastic paralysis.

Active space

Gases

01:03:46

Nitric oxide, Carbon monoxide act as neurotransmitters.

Nitric oxide :

- Produced from arginine.
- Requires cyclic GMP second messenger.
- Nitric oxide is synthesized from arginine by neuronal nitic oxide synthase in hippocampus. It increases glutamate release from presynaptic neuron → Plays a role in learning and memory.

Carbon monoxide :

- Produced from heme by enzymatic degradation using heme oxygenase 2.
- Plays a role in olfaction, pain processing, learning and memory.

MCQs :

1. Release of synaptic vesicles from the presynaptic terminals is inhibited by ?
   A. Preventing depolarization of nerve terminal.
   B. Inhibition of conduction of nerve impulse.
   C. Prevention of Ca^{a+} influx.
   D. Prevention of Na^{+} influx.

   Answer : C. Prevention of Ca^{a+} influx.

2. A 63 year old male presents wit a year history of repetitiveness, memory loss, and executive function loss. Rivastigmine is prescribed for his condition. This drug increases the levels of ?
   A. Dopamine.
   B. Norepinephrine.
   C. Serotonin.
   D. Acetylcholine.

   Answer : D. Acetylcholine.

3. The hyperkinetic features of the Huntington's disease are due to the loss of ?
   A. Nigrostriatal dopaminergic system.
   B. Intrastriatal cholinergic system.
   C. GABAergic & cholinergic system.
   D. Intrastriatal glutaminergic system.

   Answer : C. GABAergic & cholinergic system (in striatum).

SENSORY RECEPTORS

Neurophysiology can broadly be classified into :

- Sensory physiology.
- motor physiology.
- Higher mental functions.

Sensory pathways are afferent, ascending pathways.
Gives input to the central nervous system.
motor pathways are efferent, descending pathways.
Carries impulses from central nervous system.

Sensory physiology

00:02:38

Two important group of senses :

1. General senses/somatic senses : Receptors in skin.
    - Touch.
    - Pain.
    - Temperature.
2. Special senses are 5 in number.
   Receptors inside the skull.
    - Vision.
    - Hearing.
    - Olfaction.
    - Taste.
    - Balance : maintain erect posture (by vestibular apparatus).

Sensory control is bottom up control system/ascending pathways :
Lower most control point lies in skin.
Skin receptors (Sensation like touch/pain)
↓ Primary afferents/1st order neurons
Spinal cord
↓ Secondary afferents/2nd order neurons
Thalamus
Thalamus (sensory relay station)
↓ Tertiary afferents/3rd order neurons
Sensory cortex

Information from spinal cord reaches the thalamus via 2 ascending afferent pathways called Spinothalamic tracts.

- Dorsal column pathway
- Anterolateral pathway

Tracts are group of nerve fibres.

Receptors 00:10:34

Classification :

- Mechanoceptors (Touch receptors) : Respond to mechanical stimuli.
  Example : Skin stretch.
- Nociceptors : Respond to pain.
- Thermoceptors : Respond to temperature changes.
- Proprioceptors : Joint position sense.
- Exteroceptors : Respond to external stimuli (touch). Can also be called as mechanoceptors.
- Interoceptors : Respond to internal stimuli.
  Example : Osmoreceptors.
- Teleceptors : Respond to distant stimuli.
  Example : Light Vision photoreceptors.

Receptor properties :
[Mnemonic : MLID]
Modality, Location, Intensity and Duration.

- Modality : Type of stimuli a receptor detects. Example : pain and touch are modalities detected by nociceptors and mechanoceptors respectively.
- Location for general senses : Skin.
  For special senses : Skull.
  Responsive area in which the receptor responds to a stimulus is called as receptive field.
  Receptor density is the number of receptors.
  Example : High receptor density in lips and finger tips.
  Low receptor density in trunk and hip region.

Two point discrimination : Two closely placed points that are identified/felt as two separate points.
Distance is lowest if receptor density is high (lips, fingertips).
Distance is greatest if receptor density is low (trunk, hip).

- Intensity :
  Conveyed through action potential that obeys all or none law (amplitude is always constant, frequency can change).
  More intense stimuli is conveyed through increase in frequency of action potential.
  Less intense stimuli is conveyed through decrease in frequency of action potential.
- Duration : Time interval between starting and stopping of a response.

General senses receptors

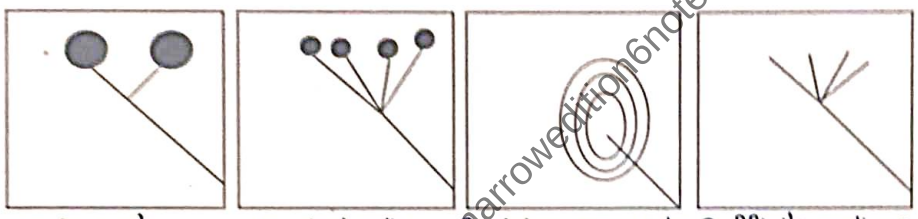
00:24:54

Touch, pain and temperature receptors.

Touch receptors (4 types) :

Superficial : Meissner's corpuscle and merkel cells.

Deep : Pacinian corpuscle and Ruffini's endings.



1. Meissner's corpuscle :
- Abundant in lips and fingertips.
- Responds to gentle tap, low frequency vibrations (around 5-40 Hz).

2. Merkel cells :
- Respond to touch, sustained pressure (estimating pulse).
- Sensitive to edges and corners (Braille reading in blind people).

3. Pacinian corpuscle :
- Largest.
- Encapsulated receptor.
- Responds to deep touch (deep pressure), high frequency vibration (60-500 Hz).

4. Ruffini's endings :
- Exclusively abundant in joint spaces. Also called as joint capsule receptors.

Active space

- Respond to skin stretch, vibrations.

Aβ afferents (large, myelinated nerve fibers) are 1st order neurons that carry sensation from touch receptors.

Pain receptors

00:35:25

Pain receptors (nociceptors) are free nerve endings. They belong to Aδ and C type of nerve fibers (1st order neurons).

Aδ nerve fibers	C nerve fibers
Convey 1st pain/Fast pain/Epicritic pain/acute pain/sharp pain	Convey 2nd pain : Slow pain/ Protopathic pain/chronic/burning pain (in elderly individuals)
Myelinated	Unmyelinated
New in evolution (neo spinothalamic)	Oldest in evolution (paleo spinothalamic)
Fast due to neurotransmitter : glutamate	Slow due to substance P

Hyperalgesia : Increase in intensity of pain.
Analgesia : No pain.

Hyperalgesia:
Important component of inflammation (Dolar).
Mechanism : Chemicals accumulate around free nerve endings as a part of inflammation (prostaglandins, serotonin, substance P, histamine, bradykinin).

They act on free nerve endings and lower threshold → Increase in firing → Increase in pain perception.
It is called as sensitization.
Chemicals capable of causing pain are termed as algogen.
Most powerful/most potent algogen is bradykinin.

Allodynia :
Simple touch (non-nociceptive stimulus) is felt as pain. It is different from hyperalgesia as stimulus is non-nociceptive.

Analgesia 00:47:46

Activated free nerve endings convey the information using depolarization. For depolarization, voltage gated Na^+ channels are required.

If voltage gated Na^+ channels are blocked, local anaesthesia is produced (mechanism of action of Lignocaine).

If voltage gated Na^+ channels undergo mutation, no pain is felt. It is a called Congenital insensitivity to pain syndrome (CIPS).

Endogenous opioid analgesic system (morphine like) consist of endorphins, dynorphins, enkephalins. It is found in PAG (periaqueductal gray matter).

Acupuncture activates periaqueductal gray matter → Release of endogenous opioids → Analgesia.

Stress induced analgesia :
Pain is abolished in stressful conditions (eg: soldiers in war).
It is due to endogenous cannabinoids : Anandamide.
Anandamide containing neurons are found in periaqueductal gray matter.

Perception of pain :

Aδ and C nerve fibers
↓ activates
Projection neurons in spinal cord
↓
Relays pain to cortex → Pain sensation is felt.

GATE control theory proposed by Melzack and Wall explains how massaging relieves pain.

Massaging is a form of gentle touch.
↓ activates
Aβ nerve fibers
↓ activates
Inhibitory interneurons
↓
Inhibition of projection neurons → No pain.

Note :

Projection neurons are found in substantia gelatinosa of spinal cord.

Specific activation of Aβ nerve fibers to inhibit pain : TENS (Transcutaneous Electrical Nerve Stimulation). It is based on GATE control theory.

Visceral pain :

Unpleasant pain.

Poorly localized.

Usually associated with autonomic symptoms like nausea, vomiting, sweating.

Conveyed by C group of nerve fibers.

Note : Liver capsule and parietal pleura are sensitive to pain. Alveoli in lung are not pain sensitive.

Thermoceptors 01:05:55

Types : Cold sensing and warm sensing receptors.

Cold sensing	Warm sensing
10 times more in number.	-
Conveyed by Aδ and C nerve fibers that contain Transient receptor potential channel : TRP m (m stands for menthol).	Conveyed by C nerve fibers that contain Transient receptor potential channel : TRP V (V stands for Vanilloid).
Temperature sensitivity range is 10-24°C.	Temperature sensitivity range is 30-45°C.

Normal body temperature (37°C) is exclusively detected by TRP V_3.

Warm pain and cold pain :

warm temperature (> 45°C) and cold temperature (< 5°C) are felt as pain.

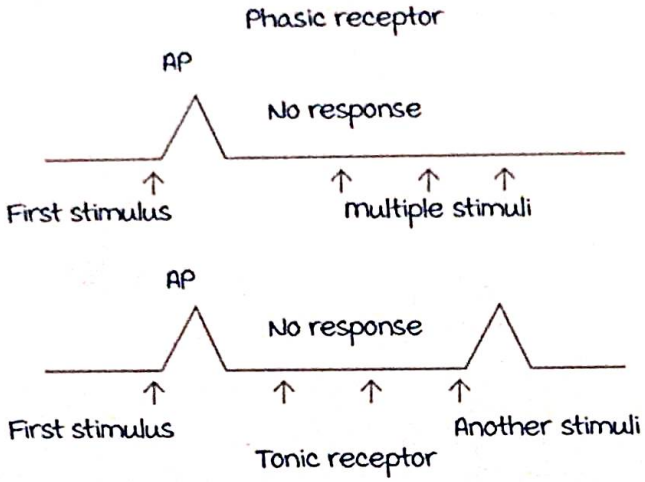
Adaptation 01:11:21

Rapidly adapting receptors (phasic receptors) :

No action potential is produced if a receptor is stimulated multiple times except during the first stimulus.

Example : meissner's corpuscles and Pacinian corpuscles.

Slowly adapting receptors (tonic receptors) :
First stimulus produces an action potential followed by no response. Another action potential is produced because of a stimulus some time later.
Example : merkel cells, Ruffini's endings, free nerve endings.



MCQs :

1. Massage and the application of liniments to painful area in the body relieves pain due to :
   A. Stimulation of endogenous analgesic system.
   B. Release of endorphins by the first order neurons in the brain stem.
   C. Release of glutamate and substance P in the spinal cord.
   D. Inhibition by large myelinated afferent fibers.
   Answer : D (Gate control theory using touch receptors).

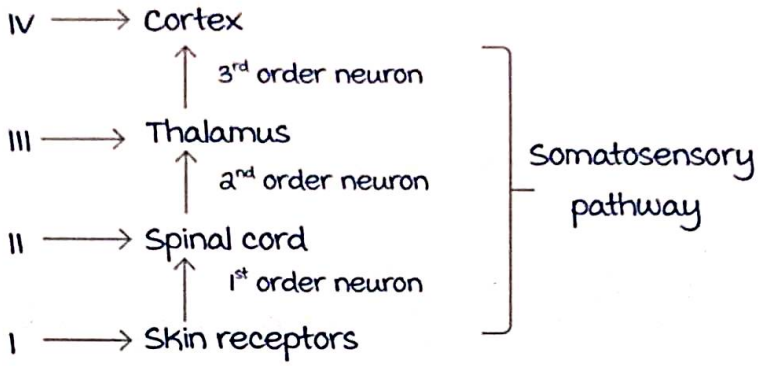
2. Pain relief in acupuncture is mediated by:
   A. Endogenous opioids.
   B. Kinins.
   C. Substance P.
   D. Prostaglandins.
   Answer : A.

3. Phasic receptors is
   A. Merkel's disc.
   B. Ruffini's end organ.
   C. Pacinian corpuscle.
   D. Pain receptors.
   Answer : C.

Active space

SOMATOSENSORY PATHWAYS

Sensory control :

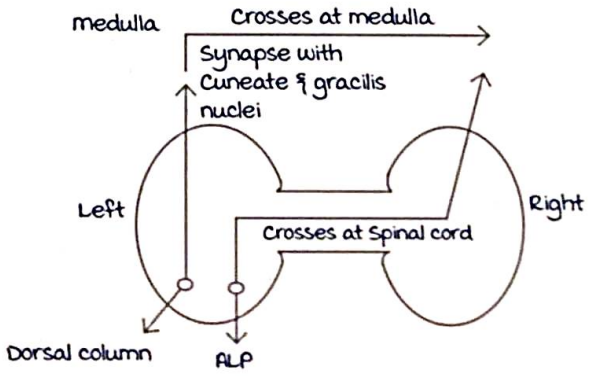


Spinal sensory pathways

00:01:26

From spinal cord, a important spinothalamic tracts arise :

Dorsal column pathway (medial lemniscal system)	Anterolateral pathway
Majority myelinated fibers	Majority unmyelinated fibers
Fast conduction	Slow conduction
• Joint position sense : Conscious proprioception (also through spinocerebellar pathway, Olivocerebellar pathway & cuneocerebellar pathway). • Fine touch. • Vibration sense. • Stereognosis : Ability to identify shape with eyes closed.	• Pain. • Temperature. • Crude touch. • Pressure. Lateral pathway : Pain transmission. Anterior pathway : Crude touch, pressure.
Crosses over at medulla	Crosses over at spinal cord
Ipsilateral symptoms	Contralateral symptoms



Active space

Brown Sequard syndrome : Hemisection of spinal cord.
Clinical features :

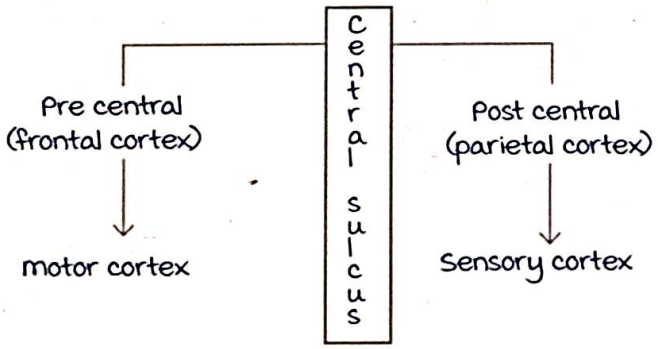
- Ipsilateral loss of dorsal column sensations (proprioception, fine touch, vibration).
- Contralateral loss of anterolateral pathway sensations (loss of opposite side pain and temperature).
- Ipsilateral motor paralysis.

Spino-Thalamic pathway 00:13:50

- Third level of control system : Thalamus.
- Thalamus is considered to be the sensory relay station.
- Ventro Postero Lateral nuclei (VPL) : Thalamic nuclei associated with touch, pain and temperature (general senses)
- If VPL gets infarcted in stroke, the patient presents with excruciating pain : Dejerine Roussy syndrome.
- 3rd order neurons originate from VPL nuclei.

Sensory cortex 00:17:20

Sensory cortex is located in parietal cortex.
Brodmann areas 3, 1 & 2 forms the sensory cortex.
Responsible for localization of sensation.
All body parts are represented here by which the brain recognizes the specific body part.
The representation is known as sensory homunculus.

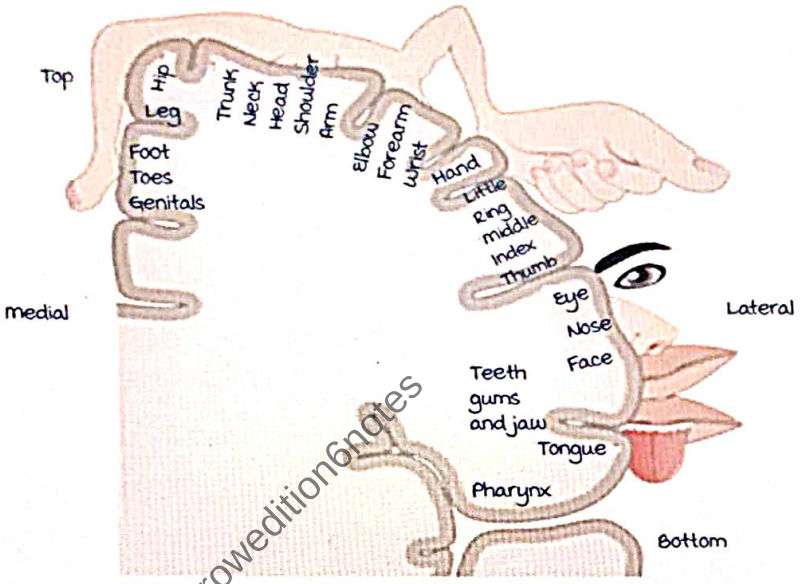


Sensory homunculus :

- Seen in the parietal cortex.
- Plotted by Penfield : Hence known as Penfield homunculus.
- Medial & top part represented by legs.

Active space

- Lateral & bottom part represented by face
- Maximum representation by lips and thumb.
- Minimum representation by hips and trunk.
- Representation of body parts is based on maximally used & not based on the size of body part.
- No visceral organ representation. Any associated pain is referred to somatic structure that has the same embryonic origin. This is called as referred pain.



Laws in sensory physiology 00:27:15

Law of specific nerve energies/muller's doctrine :
Receptors are specifically activated by a certain type of stimulus only.
E.g. meissner's corpuscles are activated by touch sensation only.
Photoreceptors are specific for light alone.

Bell-Magendie law :
In spinal cord : Dorsal roots are always sensory.
Ventral roots are always motor.

Law of projection :
Wherever the sensory pathway is stimulated, cortex always projects it to lowermost receptor location.
Explains pain in amputated patients : Phantom limb.
e.g. On amputation of the thumb, the patient may still feel its existence, as the cortical representation of thumb is still

present and it projects the sensation to the lowermost receptor (phantom thumb).

Cortical plasticity : Any region in the sensory cortex which becomes unused following loss of the body part, gets encroached upon by nearby regions. Plays a more important role in explaining phantom limb.

Weber–Fechner law :
Magnitude of sensation felt is always directly proportional to the log intensity of initial stimulus.

MCQs :

1. An anterolateral cordotomy relieving pain in the right leg is effective because it interrupts the :
A. Left Dorsal column.
B. Left ventral spinothalamic tract.
C. Left lateral spinothalamic tract.
D. Right lateral spinothalamic tract.
Pain is conducted through contralateral lateral spinothalamic pathway.

Q. Loss of feel of size and shape of an object is seen in lesion of :
A. Pons. B. Midbrain.
C. Thalamus. D. cerebral cortex.
Astereognosis is seen in lesions of cerebral cortex.

Q. Which of the following has small representation in somatosensory area of cerebral cortex?
A. Lips. B. Thumb/fingers.
C. Tongue. D. Trunk.

VISION

I Receptor : Retina.
II Thalamus : Lateral geniculate body (LGB).
III Visual cortex.

Retina 00:01:58

Retina :
Has 7 types of cells.
1 & 2. Rods and cones : These two cells are neurons and use glutamate as their neurotransmitter.

Rods	Cones
Vision in dim light and night vision	Vision in bright light or day vision and color vision
> 100 million rods are present	Only about 5 million cones are present
Peripheral retina has more of rods	Central Retina has more of cones. Foveola has abundance of cones, it is a rod free zone.

3. Bipolar cells :
Rods and cones relay to bipolar cells.
This cell has two poles.

4. Ganglion cells :
Bipolar cells relay to these cells.
The axons of these cells converge to form the optic nerve.
It is the only output cell of retina.
Only cell capabale of producing action potential.

5. Horizontal cells :
Connects the rods and cones in the horizonatal plane.

6. Amacrine cells :
Connects the bipolar cells and ganglion cells.
These cells use acetylcholine as neurotransmitter.

7. Retinal glial cells (RGC)/muller's cells :

It has no role in vision.

It is a simple supporting cell.

Rods 00:10:28

The rods contain a visual pigment called visual purple or rhodopsin.

Rhodopsin is comprised of the protein opsin with an isomer of vitamin A.

Form of vitmain A :

In the dark state : 11-cis retinal.

In light state : All trans retinal.

Phototransduction :

It is the process of converting a light stimulus into an action potential.

Light converts 11-cis retinal ⟶ All trans retinal.

Dark state :

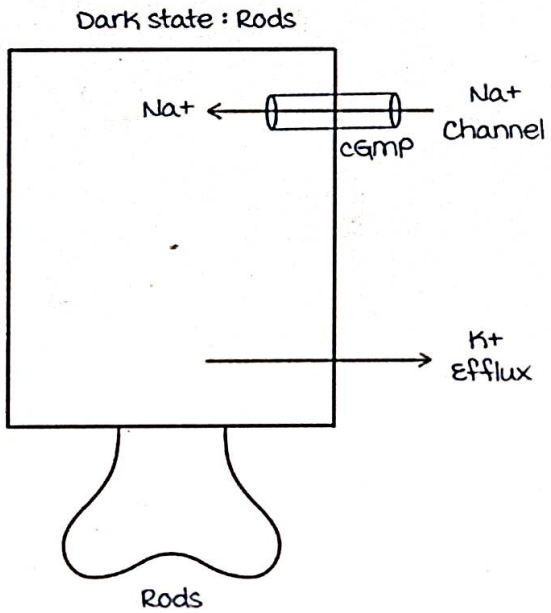
The resting membrane potential of the rods is -60 mV.

There is K^+ efflux.

Na^+ channels open with the help of increased cGMP to bring about Na^+ influx, this is called as dark current.

This leads to depolarisation.

11-cis retinal is present.



Light state :

11-cis retinal is converted to all trans retinal.

All trans retinal ⟶ G-protein coupled recepter called transducin

↓

Activates Phosphodiesterase (PDE)

↓

Causes hydrolysis of cGMP

↓

cGMP

↓

Na^+ channels close

K^+ efflux

↓

Hyperpolarisation

Dark state	Light state
• ↑cGMP. • Na^+ channels open. • Depolarisation. • 11-cis retinal.	• ↓cGMP. • Na^+ channels closed. • Hyperpolarisation. • All trans retinal.

Depolarisation in dark state and hyperpolarisation in light state is true for all cells on the retina except : Amacrine cells.

Amacrine cells always undergo depolarisation and are called as purely depolarising cells of retina.

Funny currents channels 00:21:20

They are the Na^+ channels present in retina, that open in dark state and close in light state.

These Na^+ currents are also called as funny current (I_f).

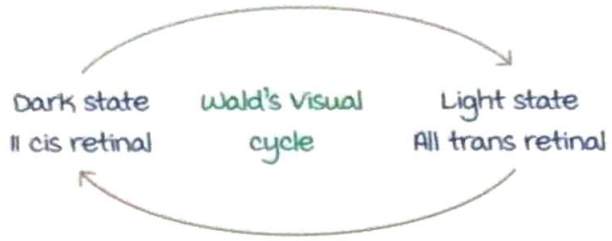
These currents are seen in

1. Retina : For vision.
2. SA node in heart : For pacemaking.

These channels are opened by cGMP.

These channels are also called HCN channels (hyperpolarisation cyclic nucleotide gated channels).

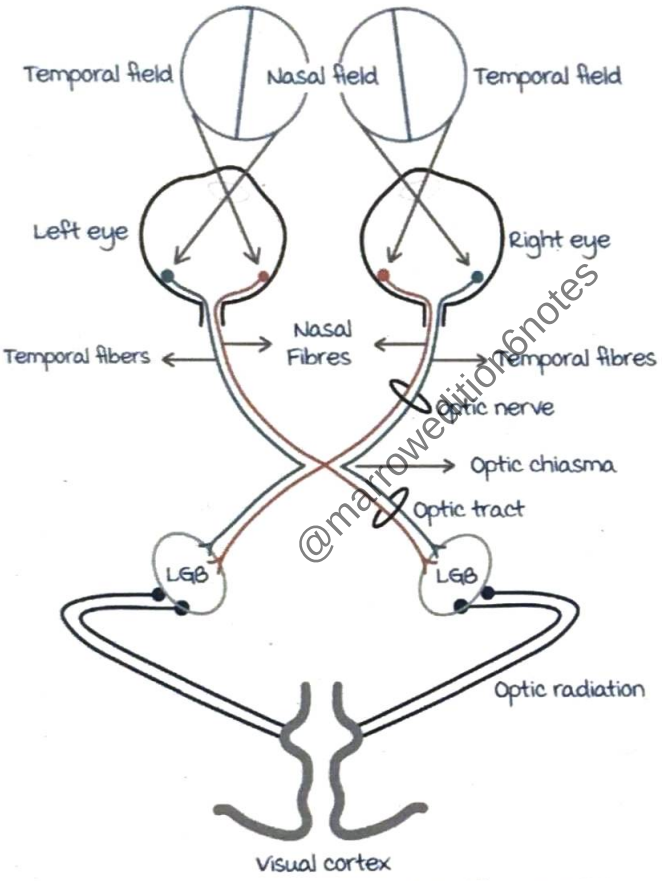
Vitamin A isomers :



Visual pathway

00:27:58

The only output cell in the retina is ganglion cells, the axons of which make the optic nerve.



The nasal fibers see temporal field of vision and temporal fibers see the nasal field of vision.
The temporal and nasal fibers together for the optic nerve.
The nasal fibers decusate at the level of the optic chiasma.
The ipsilateral temporal fiber with the contralateral nasal fiber forms the optic tract.
This relays in the lateral geniculate body of the thalamus.
The fibers from here reach the visual cortex through the optic radiation.

Active space

Lateral geniculate body

00:34:46

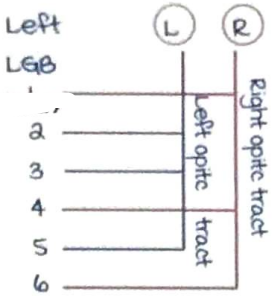
The thalamic nucleus is lateral geniculate body.

Layers :

Cells from layers 1 and 2 :

Magnocellular pathway.

This pathway is for eyeball movements and flickers.



Cells from layers 3, 4, 5 and 6 :

Parvocellular pathway.

This pathway is for color vision and identifying fine details in visual field.

Layers 2, 3 and 5 receive fibers from ipislateral optic tract.

Layers 1, 4 and 6 receive fibers from contralateral optic tract.

LGB relays to visual cortex.

Visual cortex

00:41:22

Located in the occipital region.

Brodmann areas 17, 18 and 19 which corresponds to calcrine sulcus.

This area has abundance of heavily myelinated fibers, which look like stripes or straited appearance, which was first observed by Gennari.

Hence, visual cortex is also called as straited cortex and the straie are called as the Striae of Gennari.

Straited cortex has 3 cells :

1. Simple cells.
2. Complex cells.

   Both of these cells are higher order processing cells, the help identify individual features in the visual field.

   They are also called as feature detectors.
3. Blobs : They help is color vision.

Color vision :

Pathway :

1. Cones in the retina :

   3 types of cones for three primary colors.

- Red : Long wavelength → L cones.
- Blue : Short wavelength → S cones.
- Green : Medium wavelength → M cones.

2. Parvocellular pathway in LGB.
3. Blobs in visual cortex.

L cones are congenitally absent : Red defect → Protanopia.
S cones are congenitally absent : Blue defect → Tritanopia.
M cones are congenitally absent : Green defect → Deutranopia.

Color blindness :
Most common defect : Red green defect.
X-linked inheritance.
Males are usually affected and females are carriers.

Extra striate cortex 00:53:14

Parietal cortex and temporal cortex also take part on visiual functions.
Magnocellular pathway projects to parietal cortex thereby plays a role in eye ball movements.
Parvocellular pathway projects to temporal cortex and plays a role in color vision.

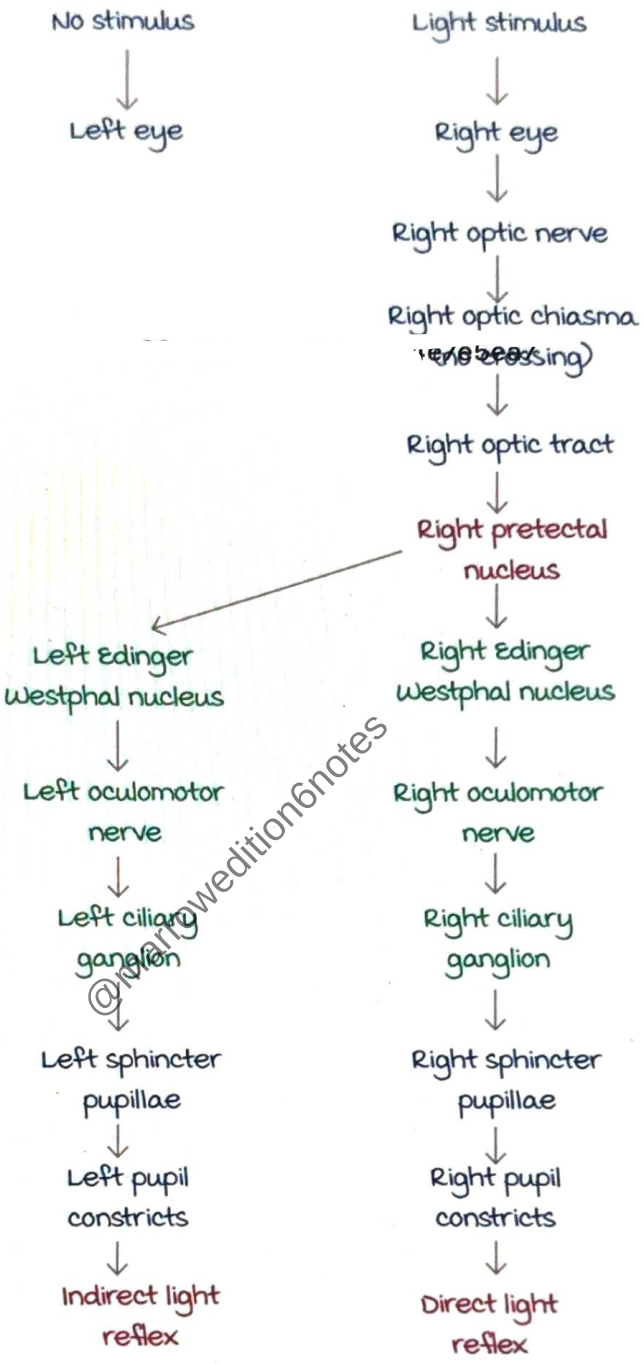
Inferior temporal cortex is for : Facial recognition.
Lesion in this area, presents as an inability to recognise people by looking at their face : Prosopagnosia.

Order of neurons in visual pathway :
1st order neurons : Photoreceptors (rods and cones)
Use neurotransmitter glutamate.
2nd order neuron : Bipolar cells.
3rd order neuron : Ganglion cells (optic nerve).
4th order neuron : LGB.
5th order neuron : Visual cortex.

Active space

Light reflex

01:00:36



Afferent : Optic nerve.

Centre : Pretectal nucleus.

Efferent : Oculomotor nerve

Q. Which are first order neuron in optic pathway ?

A. Bipolar cells.

B. Ganglionic Cells.

C. Cells of lateral geniculate body.

D. Rods and cones.

Answer : D

Q. The parvocellular pathway, from the lateral geniculate nucleus to the visual cortex, carries signals for the detection of

A. Colour contrast.

B. Luminance contrast.

C. Temporal frequency.

D. Saccadic eye movements.

Answer : A

Q Protonopes have defect in identifying which color?

A. Red.

B. Blue.

C. Green.

D. Black.

Answer : A

Active space

HEARING, OLFACTION AND TASTE

Hearing

Vestibulocochlear nerve :

Vestibular part : Associated with vestibular apparatus, for balance.

Cochlear part : Associated with hearing.

Cochlea:

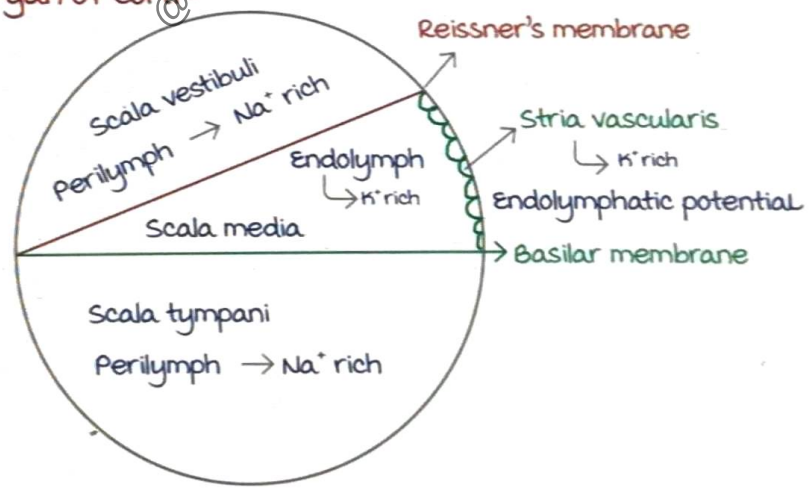
It has 3 parts (scala vestibuli, scala media, scala tympani) divided by 2 membranes (Reissner's & basilar membrane).

Endolymphatic potential : +80 mV, due to K^+ ions in endolymph. It is rich in K^+ as Stria vascularis lining the scala media secretes K^+.

Scala media contains receptors for hearing : Hair cells.

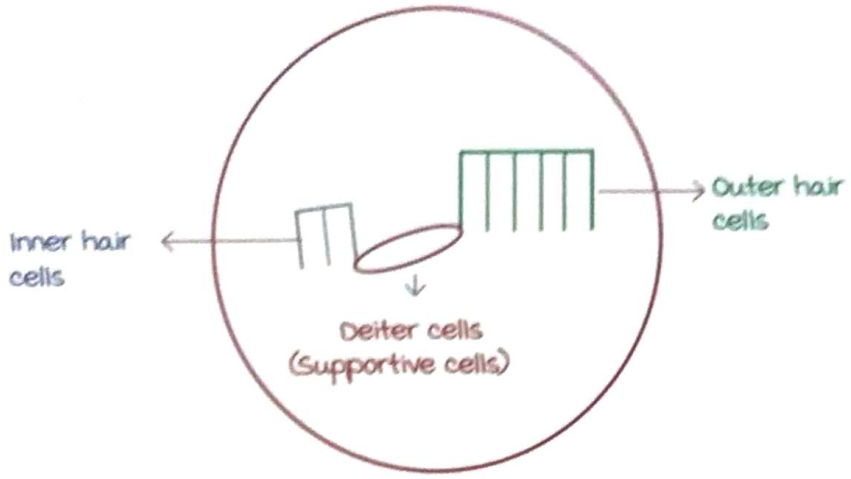
Hair cells are localized in a specialized region known as Organ of corti.

Organ of corti:



Outer hair cells (OHC)	Inner hair cells (IHC)
More numerous.	Less numerous.
Less innervated.	Maximally innervated.
Exposed outside : more prone for damage from ototoxic drugs like Aminoglycosides.	Present inside.

Innervation is from spiral ganglia, from cochlear division of VIII nerve.



Hair cells contain cilia. The tallest cilium is known as Kinocilium, and the other shorter ones are known as stereocilia.

If all the hair cells bend towards the Kinocilium, it leads to depolarization or activation of signal conduction.
Depolarization is due to K^+ influx from endolymph to hair cells.
If all the hair cells bend away from Kinocilium, it leads to hyperpolarization or inhibition of signal conduction.

The K^+ current responsible for depolarization from the outer hair cells can be measured by otoacoustic emissions (OAE).
OAE is first measured by Kemp, hence called Kemp waves.
OAE is a sensitive test for hearing.

Auditory pathway 00:15:57

Mnemonic : ECOLIMA
E : Eighth nerve.
C : Cochlear division.
O : Superior Olivary nucleus → Processing of direction of sound starts from here.
L : Lateral lemniscus.
I : Inferior colliculus → For direction of sound.
M : Medial geniculate body in thalamus.
A : Auditory cortex.

Auditory cortex is located in Brodmann area 41 : Superior temporal gyrus (Heschl's gyrus) in temporal cortex.

This is the area for higher order processing of hearing.

Stapedial reflex :

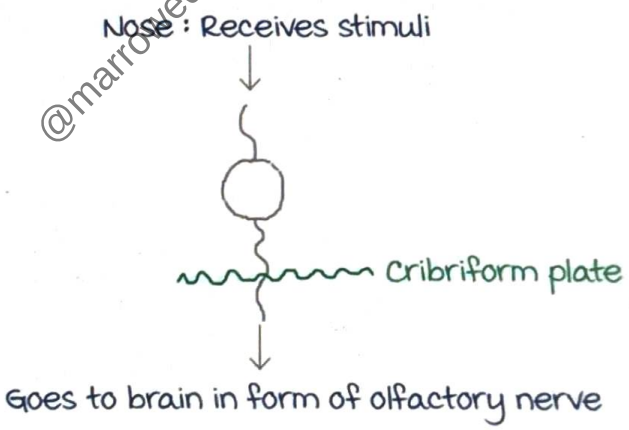
- Exposure to loud noise ~ 160 dB can cause rupture of tympanic membrane.
- But in all healthy individuals, this rupture of TM can be prevented due to contraction of stapedius muscle. This preventive reflex is known as stapedial reflex.
- Around 30–40 dB is attenuated due to stapedial reflex, hence also known as attenuation reflex.
- Afferent : VIII nerve.
- Centre : Superior Olivary Nucleus.
- Efferent : VII nerve → Contraction of stapedius.
- In facial nerve palsy, stapedial reflex is affected causing hyperacusis.

Olfaction

00:24:50

Olfactory receptors are located in olfactory epithelium in the roof of nasal cavity.

Olfactory receptor is type of bipolar neuron.



Olfactory nerve pierces cribriform plate while going to the brain.

Any fracture of cribriform plate can damage CN I.

In the brain, the information of smell first goes to olfactory bulb. It has 4 types of cells :

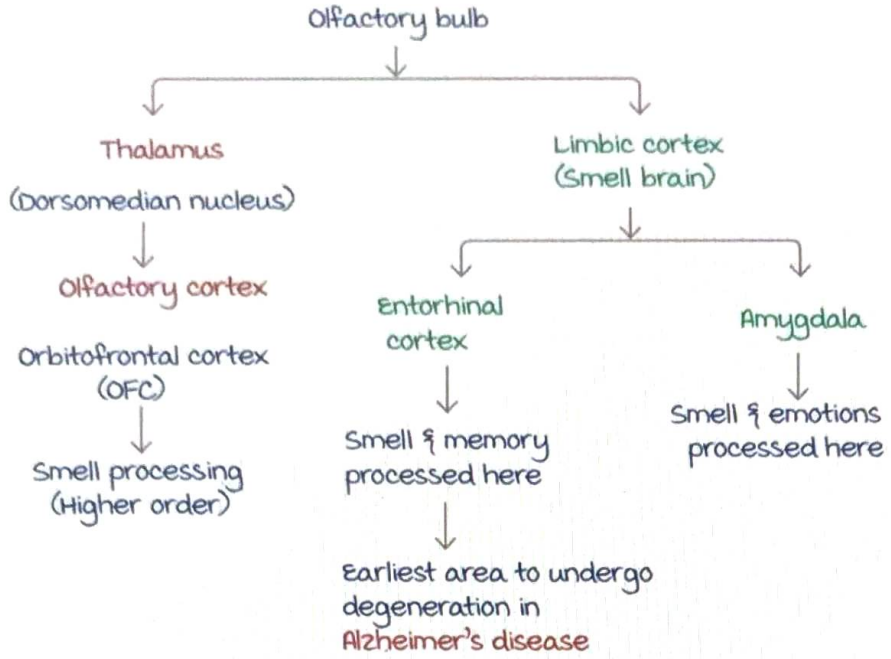
- Mitral cell
- Tufted cell

} Excitatory. Neurotransmitter : Glutamate

- Granule cell
- Periglomerular cell

} Inhibitory. Neurotransmitter : GABA

Olfactory pathway :



Olfaction has the smallest range of intensity discrimination. Only smell identification is sufficient for response. Gradation of smell intensity into mild, moderate, severe is not done.

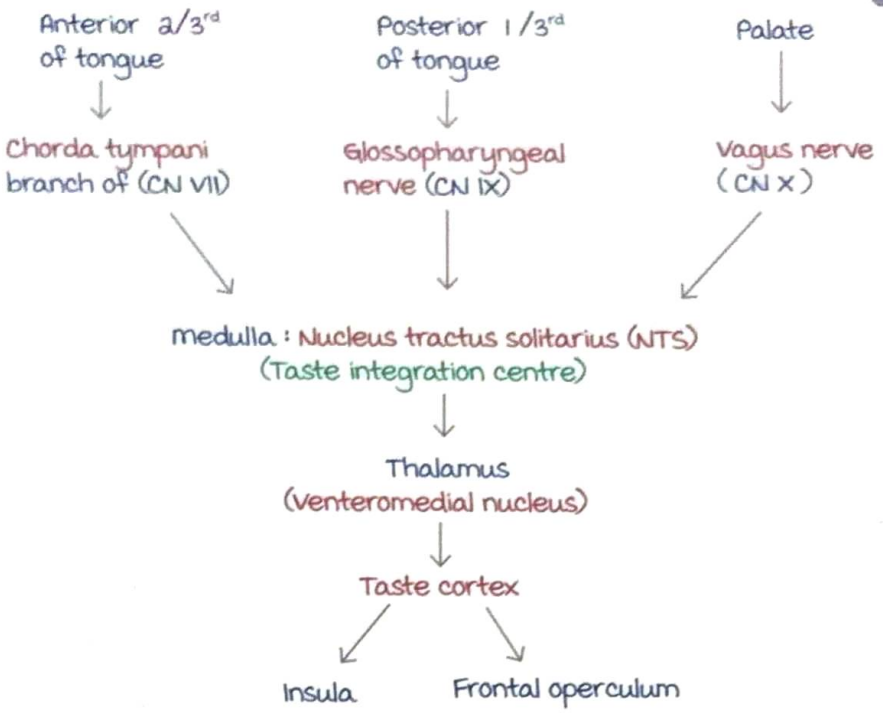
Taste (Gustation) 00:35:57

Gustatory receptors are found in tongue known as taste buds, which can detect 5 basic tastes :

- Sweet.
- Salt.
- Bitter.
- Sour.
- Umami : Addictive sensation due to addition of monosodium glutamate (MSG).

Taste pathway :

- From anterior 2/3rd of tongue : Chorda tympani branch of CN VII.
- Posterior 1/3rd of tongue : Glossopharyngeal nerve CN IX.
- Palatal region : CN X (Vagus nerve).



Q. Hair cells in inner ear are unique in the sense that their depolarization is due to

A. Calcium ions. B. Sodium ions.

C. Potassium ions. D. Chloride ions.

Ans. Potassium ions.

Q. Recently a newer pathway was found out in which olfactory signals pass through which thalamic nucleus ?

A. Anterior nuclei. B. Venteropostero lateral nuclei.

C. Venteropostero medial nuclei. D. Dorsomedial nuclei.

Ans. Dorsomedial nuclei.

Q. Type of G protein present in taste receptors is called

A. Transducin. B. Megalin.

C. Gustducin. D. Cubulin.

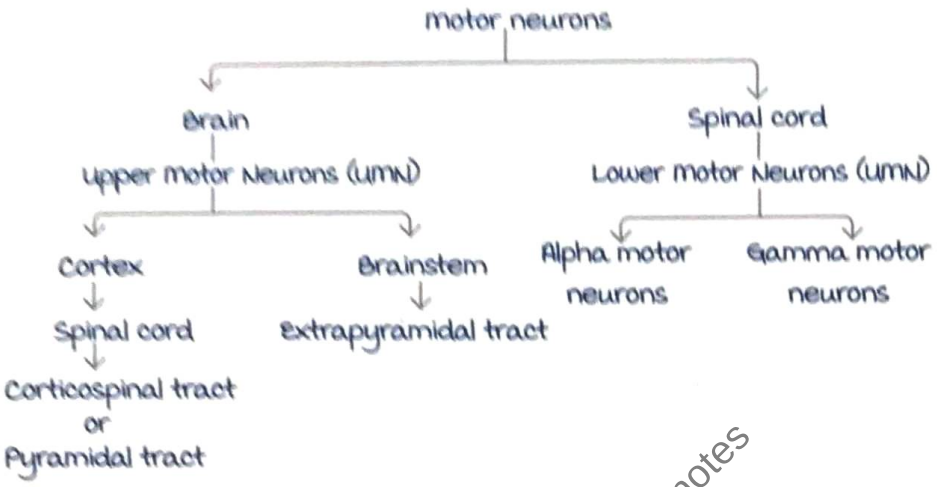
Ans. Gustducin for taste, Transducin for vision.

Active space

DESCENDING MOTOR PATHWAYS

Motor physiology 00:00:20

These are efferent (output) pathways.
Descending pathway → Top - down control.



motor neurons in the brain are Upper motor Neuron (UMN).
motor neurons in the spinal cord are Lower motor Neurons (LMN).

Cortical motor areas 00:04:44

motor cortex is present in frontal lobe.
Corresponds to Brodmann Area (BA) 4 and 6.
Motor cortex is always precentral.
Primary motor cortex corresponds to BA-4 : Controls the final execution of movement.
Cortical association areas : Controls the initiation or ideation. They feed information to the primary motor cortex to execute the movement.
Premotor cortex corresponds to BA-6 : Performs postural setups before movement.
Supplementary motor cortex corresponds to BA-6 : Bimanual co-ordination.

Corticospinal tract 00:08:38

Originates from cortex to spinal cord.
Also known as pyramidal tract.

It is a lateral motor pathway as the fibers go along the lateral column.

Origin : Layer 5 of motor cortex (Betz cells).

Contribution :

30% from primary motor cortex.

30% from premotor and supplementary motor cortex.

40% from sensory cortex (parietal cortex), maximum fibers.

80% of CS tract : Crosses to opposite side and forms :

Lateral corticospinal tract.

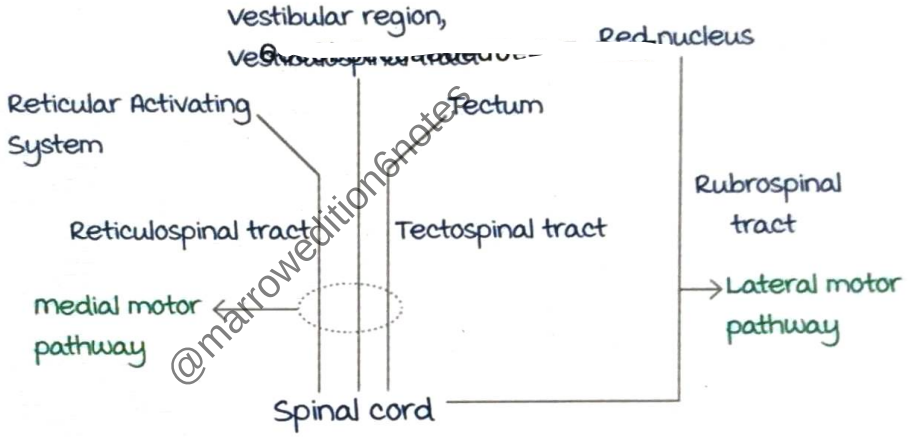
20% of fibres : Remain uncrossed, known as :

Ventral corticospinal tract.

Brainstem : Motor areas

00:12:45

Extrapyramidal tract : Has 4 tract pathways.



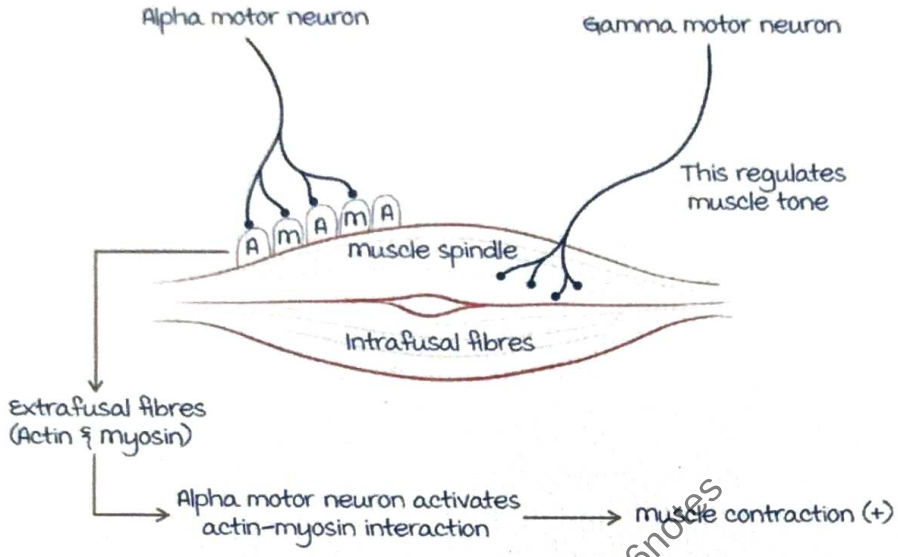
- Reticulospinal tract primarily excites extensor muscles through gamma motor neurons.
  Pontine reticulospinal tract : Usually excitatory.
  Medullary reticulospinal tract : Usually inhibitory.
- Rubrospinal tract : Primarily controls flexor muscles of upper limb.

Lateral motor pathway	Medial motor pathway
Corticospinal tract. Rubrospinal tract.	Reticulospinal tract. Vestibulospinal tract. Tectospinal tract.
Newer in evolution.	Older in evolution.
Fine, skilled, voluntary motor movements (like writing).	Maintaining erect posture.

Distal muscle control.	Proximal muscle control like paraspinal muscles (Antigravity muscles).

Spinal cord : Motor neurons 00:22:52

Lower motor neurons 2 in number :



Alpha motor neuron :

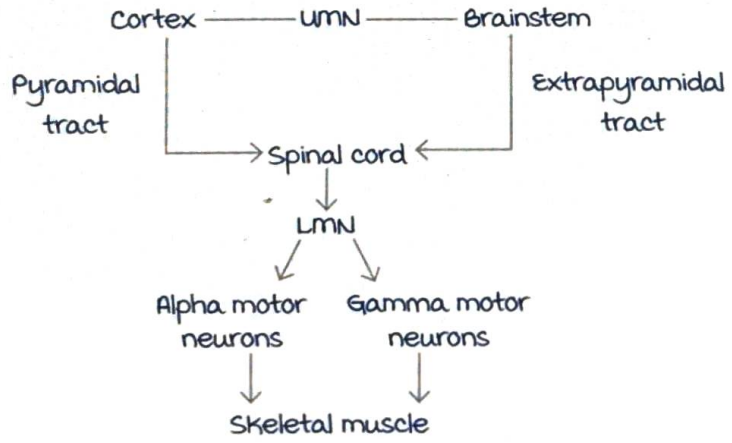
Activates extrafusal fibres → muscle contraction.

Gamma motor neuron :

Activates intrafusal fibres → Regulates muscle tone.

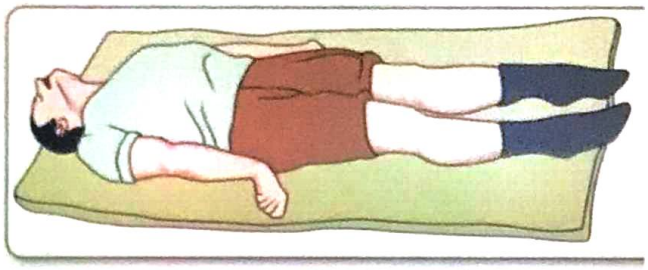
Motor hierarchy and lesions of motor pathway 00:27:02

Motor hierarchy :



Decerebrate rigidity : Created by complete transection at brainstem level between superior colliculus and inferior colliculus.

Active space



Decerebrate rigidity

Influence of corticospinal tract and rubrospinal tract are lost.
Reticulospinal tract becomes overactive which activates :
Extensor muscles (extensor rigidity).
Gamma motor neurons (gamma rigidity).

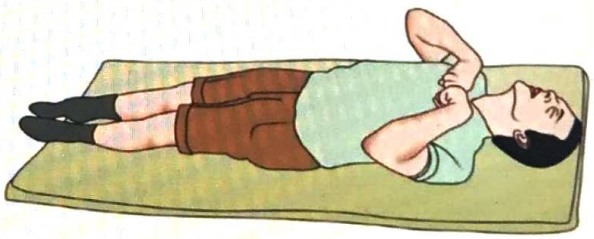
Decerebrate rigidity, features :

- Extension of neck.
- Extension of all 4 limbs.
- Forearm is pronated.

If additionally anterior surface of cerebellum is removed → Exaggeration of extensor rigidity (due to alpha motor neuron overactivity), this is known as alpha rigidity or decerebellate rigidity.

Decerebrate rigidity : Gamma rigidity.
Decerebellate rigidity : Alpha rigidity.
Decerebrate rigidity is seen in uncal herniation.

Decorticate rigidity :
Removal of cerebral cortex.
Influence of corticospinal tract is lost.
Rubrospinal tract is intact : Increased flexion of upper limbs.
Overactive reticulospinal tract : Extension of lower limbs.
Clinically, seen in patients with thrombosis of internal capsule.



Decorticate rigidity

UMN lesions	LMN lesions
muscle atrophy is less.	Prominent muscle atrophy.
muscle fasciculations not seen.	Prominent muscle fasciculations.
Reflexes : Hyperactive or exaggerated.	Hypoactive reflexes.
Spastic muscle tone.	Reduced muscle tone.

Babinski's sign :

When sole of the foot is gently stroked by a sharp object from lateral border to medial side :

Plantar flexion of all toes → Normal : Negative Babinski's sign.

Dorsiflexion (extension) of great toe + fanning out of other toes → Positive Babinski's sign : UMN lesion.

Q. Which pathway excites proximal limb flexor group of muscles?

A. Vestibulo spinal tract.
B. Tecto spinal tract.
C. Rubro spinal tract.
D. Reticulo spinal tract.

Ans : C.

Q. Hyperactivity in extensor muscles in decerebrate rigidity is due to

A. Vestibulo spinal tract.
B. Tecto spinal tract.
C. Rubro spinal tract.
D. Reticulo spinal tract.

ANS : D.

Q. Decerebellate rigidity is due to exaggerated

A. Alpha motor discharge
B. Gamma motor discharge
C. Upper motor neuron discharge
D. Pontine neuron discharge

ANS : A.

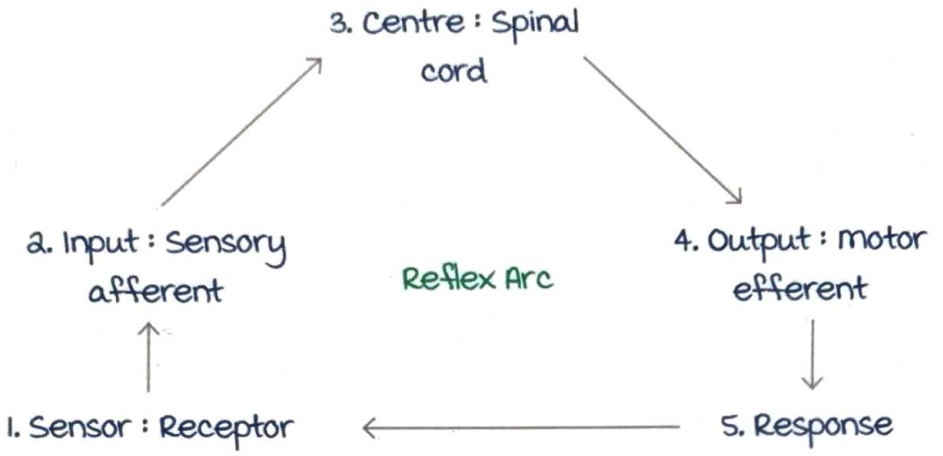
SPINAL REFLEXES

Reflexes

00:00:20

Sensory motor integration.

5 components :



1. Stretch reflex : Simplest reflex.

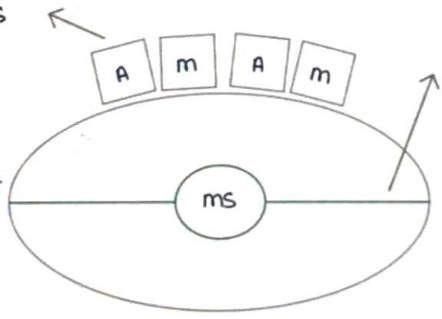
~~Passive~~ stretch → contraction.

Knee Jerk : MC stretch reflex.

Procedure : Using knee hammer, gently tap over the tendon of quadriceps. In response to that passive stretch, quadriceps undergoes contraction.

Receptor : Muscle spindles/ Kuhne spindles present inside the muscle.

Extra fusal fibers (EFF) : Actin (A) & myosin (m). motor fibers that bring about contraction.



Intra fusal fibres (IFF) : muscle spindles (ms). 1 ms → 3 – 12 IFFs. Purely sensory. Receptors for stretch reflex. Positioned parallel to EFFs.

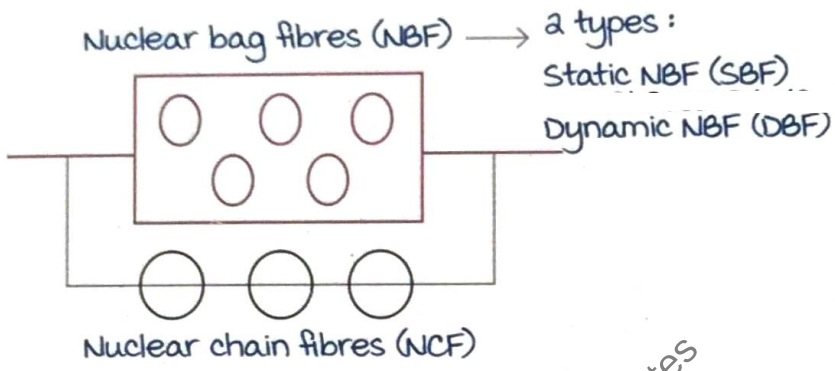
Active space

Muscle spindle innervation 00:10:02

Has both sensory & motor supply.

Sensory supply	motor supply
Group Ia : Primary afferent. Group II : Secondary afferent.	Gamma motor neurons (GMN).

Muscle spindles : 2 types of fibers.



Group Ia/ annulo spiral endings : Innervates SBF, DBF, & NCF.
Group II/ flower spray endings : Innervates SBF & NCF. Not DBF.

Muscle spindles : Motor supply 00:18:01

Center Portion : Receptor part.
Peripheral end : Innervated by Gamma motor neurons.

Gamma motor neurons	
Dynamic gamma efferents/ plate endings. ↓ Dynamic NBF.	Static gamma efferents/ trail endings. ↓ Static NBF, NCF.

Motor supply of EFF & IFF :

Extra fusal fibres	Intra fusal fibres
Actin & myosin. ↓ motor supply : Alpha motor neurons.	muscle spindles. ↓ motor supply : Gamma motor neurons.

Stretch reflex pathway :

Components of reflex pathway :

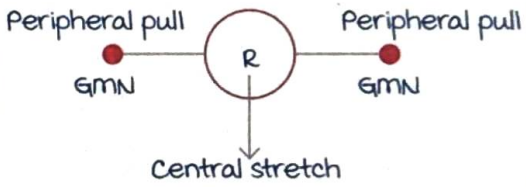
Component	Stretch reflex
Receptor	Muscle spindles.
Input : Sensory afferent	Group Ia & group II fibers.
Center	Spinal cord.
Output : Motor efferent	Alpha motor neurons → EFF → actin & myosin.
Response	Muscle contraction.

Simplest reflex. Why?

Has only one synapse between sensory input & alpha motor neuron.

Classical example of monosynaptic reflex.

Mechanism of muscle contraction 00:26:38

Direct	Indirect
Activation of alpha motor neurons. ↓ Activation of EFF. ↓ Actin & myosin interaction. ↓ Muscle undergoes contraction.	Activation of gamma motor neurons.  The peripheral pulling causes the central receptor to stretch → stretch reflex activated → indirect muscle contraction/ stretch reflex induced contraction.

Alpha gamma co - activation :

For all useful muscle contraction, alpha & gamma motor neurons are activated together.

When contraction occurs by activation of alpha motor neurons, the stimulated EFFs cause muscle shortening.

This shortening can cause the centrally present muscle spindle to relax/become flabby.

So, the gamma motor neurons are also activated to prevent this relaxation.

Activation of gamma motor neurons in the periphery cause peripheral pulling of muscle leading to central stretching even during muscle contraction.

Classical example : Jendrassik manoeuvre. Clenching teeth or holding hands & pulling them apart causes a brisk knee jerk reflex (as this manoeuvre activates GMNs as well).

Alpha + gamma motor neurons activation → increased spindle afferent firing → brisk knee jerk.

Myotatic reflex : Any muscle that is stretched under physiological limits will undergo contraction.

Inverse stretch reflex (ISR)/ lengthening reflex 00:36:16

Any muscle that is over stretched always undergoes relaxation.

Protective reflex to prevent muscle injury.

Components of ISR :

Components	ISR
Stimulus	Over stretch of the muscle.
Receptor	Golgi tendon organ (GTO). Each GTO encloses 3 – 20 muscle fibers.
Input : Sensory afferent	Group Ib fibers.
Centre	Spinal cord.
Output : Motor efferent	Ib → activates inhibitory neuron → Inhibition of alpha motor neurons.
Response	Relaxation of muscle.

Synapses of ISR : Disynaptic reflex.

1st : Ib & inhibitory neuron.

2nd : Inhibitory neuron & alpha motor neuron.

Active space

Components of SR & ISR

00:43:16

Components	Stretch Reflex	Inverse stretch reflex
Stimulus	Stretch.	Overstretch.
Receptor	Muscle spindles.	Golgi tendon organ.
Sensory input	Group Ia, II fibers.	Group Ib.
Centre	Spinal cord.	Spinal cord.
motor output	Activation of alpha motor neurons.	Inhibition of alpha motor neurons.
Response	Contraction.	Relaxation.
Other names	Myotatic reflex.	Lengthening reflex.
No. of synapses	1 (monosynaptic).	2 (disynaptic).

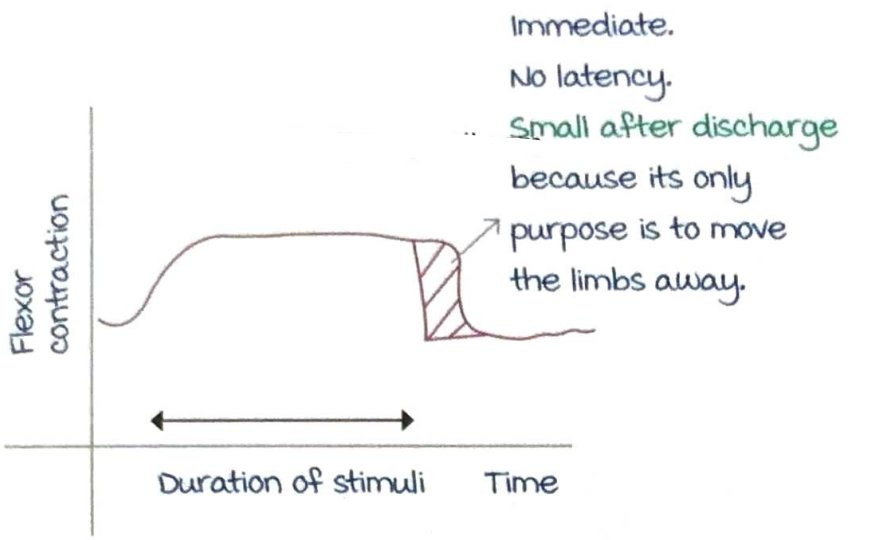
Muscle spindles monitor length changes.
Golgi tendon organs monitor tension changes.

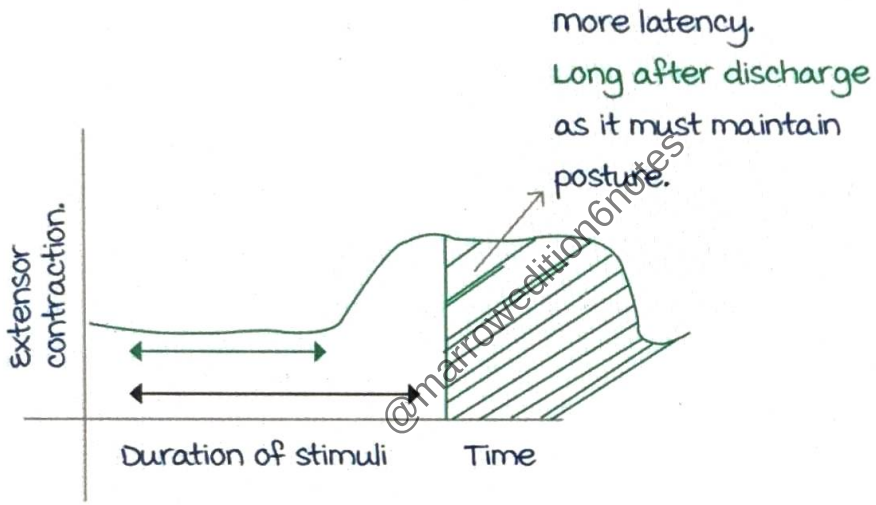
Clinical importance :
Clasp Knife spasticity : Initial increase in resistance is due to stretch reflex followed by decreased resistance due to ISR later.
Cycles of SR – ISR – SR – ISR – SR : Clonus (sudden & sustained stretch).

3. Polysynaptic reflex : Flexor withdrawal reflex.
e.g., Pin prick in right foot.

Right Limb	Left Limb
Flexed to move limb away from painful stimuli. Flexors activated. Extensors inhibited.	Extended to support body & maintain posture. Flexors inhibited. Extensors activated.

Early flexion & late extension on a graph :





Positive supporting reaction/ Magnet reaction 00:59:06

4. Pressure on foot pad → Limb undergoes extension to maintain posture and support.
   Reflex at the spinal cord level.
   This is called positive supporting reaction/magnet reaction.

5. Righting reflex :
   Commonly seen in dogs & cats.
   When animals are laid down at their sides, they undergo a series of movements to raise themselves to standing position.

Active space

6. Hopping & placing reflex :

Hopping reflex	Placing reflex
If an animal, standing on one leg, is moved horizontally, it will quickly hop to maintain balance.	Touch the dorsum of foot to any table surface, there will be flexion of knees & hips quickly. This is needed for firm placement of foot on table.
Both reflexes are integrated at the level of cerebral cortex. Lost in decorticate conditions.	

7. Mass reflex :

Done in paraplegics.

Mild painful stimulus → mass reflex : Profuse sweating, systolic blood pressure raises to > 200 mmHg & evacuation of bowel of paraplegics for evacuation of bowel & bladder.

This is because many spinal segments are activated at the same time.

MCQs :

Q. When compared to a monosynaptic reflex arc, a polysynaptic reflex arc includes which of the following?

A. Receptor.

B. Afferent.

C. Efferent.

D. Interneuron.

Answer : D. Interneuron.

Q. An 18 year old boy after lifting a heavy weight suddenly drops it. Which receptors are activated?

A. Muscle spindles.

B. Golgi tendon organ.

C. Pacinian corpuscles.

D. Merkel cells.

Answers : B. Golgi tendon organ.

Active space

Q. In decorticate animal which reflex is lost?

A. Stretch reflex.

B. Inverse stretch reflex.

C. Withdrawal reflex.

D. Hopping and placing reactions.

Answer : D. Hopping and placing reactions.

CEREBELLUM AND BASAL GANGLIA

Cerebellum : Introduction

00:00:39

Cerebellum → Start-stop signalling.
Timing and coordination of motor movements.

5 Cells	4 Nuclei	3 parts/ functions
1. ☆ → Stellate cell → Inhibitory 2. → Basket cell → Inhibitory 3. → Granule cell → Excitatory 4. → Purkinje cell → Inhibitory 5. Golgi cell → Inhibitory Inhibitory → GABA. Excitatory → Glutamate. Arranged in 3 layers : • External molecular layer : Stellate + Basket. • Purkinje cell layer : Purkinje cells (largest). • Inner granular layer : Granule + Golgi cells.	All cerebellar nuclei are excitatory. Types of nuclei seen : Dentate. Emboliform. Fastigial. Globose.	1. Vestibulocerebellum : Flocculus + Nodulus. Flocculonodular lobe. 2. Spinocerebellum : Vermis + medial part of cerebellar hemisphere. 3. Neocerebellum : Lateral part of cerebellar hemisphere. New in evolution.

2 sensory sources which serve as input for the cerebellum (motor output) :
Inferior olivary nuclei : Climbing fibers (Olivocerebellar).

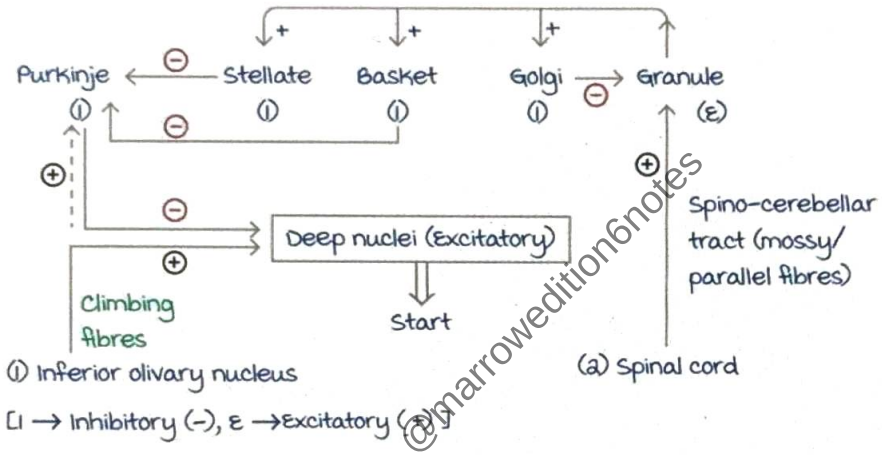
Spinal cord : mossy fibres (Spinocerebellar tract).

Dorsal SCT :	Ventral/Anterior SCT :
Enters cerebellum through inferior cerebellar peduncle	Enters cerebellum through superior cerebellar peduncle

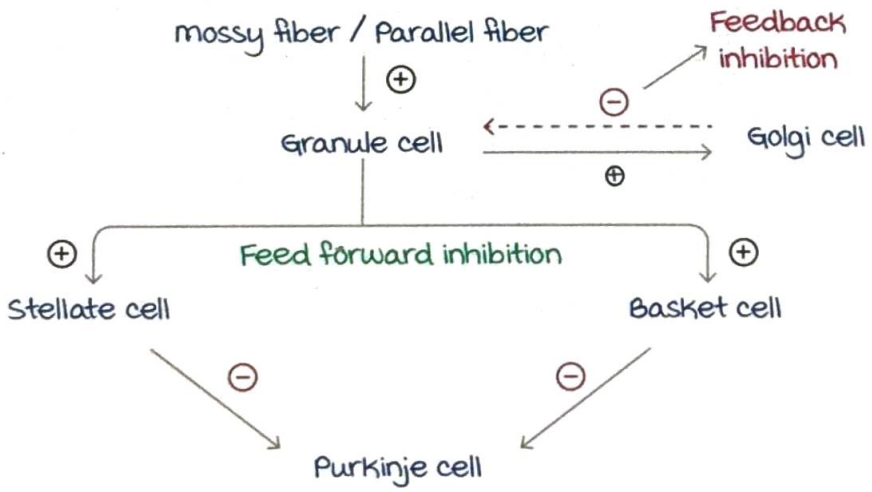
Cerebellum : mechanism of action 00:15:05

Start - stop signalling :

Firing from cerebellum is required to start a movement and to stop a movement.



Feed Forward inhibition and Feedback inhibition :



Active space

Start-stop signalling is the basis for 3 vital functions of cerebellum :

	Spinocerebellum	Vestibulo cerebellum	Neocerebellum
Function	Coordination of motor movements.	Maintaining equilibrium/ balance.	Planning of motor movements.
Nuclei	Fastigial, globose and emboliform	No nuclei in cerebellum. Vestibular nucleus in vestibular apparatus	Dentate (lateral most nucleus of cerebellum).

Cerebellar lesions :

- Gait abnormality : Balance is lost → Ataxic/drunken gait (Vestibulocerebellum affected).
- Past pointing (stop beyond target).
- Rebound phenomenon (moving back & forth of limb after resistance is removed).
- Nystagmus, Pendular knee jerk.
- Dysdiadochokinesia : Alternate supination and pronation is not possible.
- Intention tremor : During activity, not during rest. (Resting tremor : Basal ganglia lesion.)

Basal ganglia 00:32:44

At rest → Predominantly inhibitory.

Functions :

1. Suppression of both voluntary and involuntary movements.
2. Planning of motor movements.
3. Caudate nucleus plays a role in cognition (memory) : most recent function.

Components :

1. Caudate nucleus.
2. Putamen.

Caudate + Putamen = Striatum → Input nuclei of basal

ganglia. Striatum uses GABA as neurotransmitter.

3. Globus pallidus : Globus pallidus interna + Globus pallidus externa → GABA (inhibitory neurotransmitter).

4. Substantia nigra : Pars compacta and Pars reticulata.
   Neurotransmitter is dopamine.

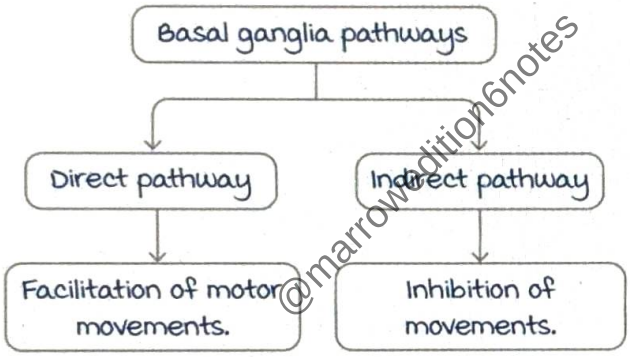
5. Subthalamic nucleus : Only excitatory nucleus.
   (Glutamate is neurotransmitter)

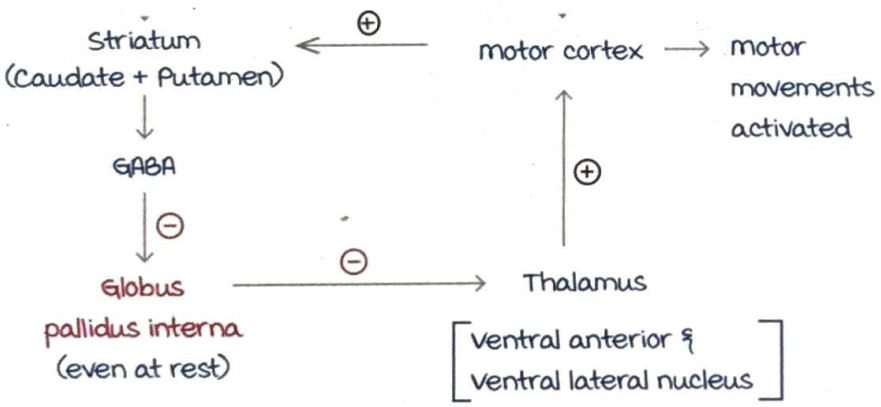
Input nucleus : Striatum.

Output nucleus : Globus pallidus Interna (GPI) & Substantia nigra → Pars reticulata.

Functions of basal ganglia 00:39:52

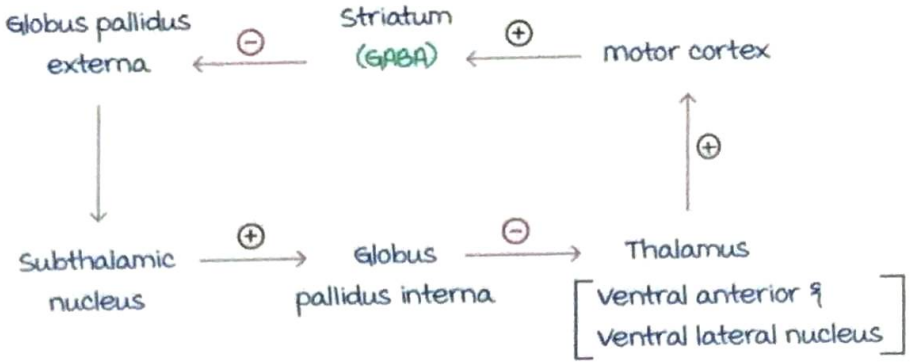
Basal ganglia pathways :





Direct pathway

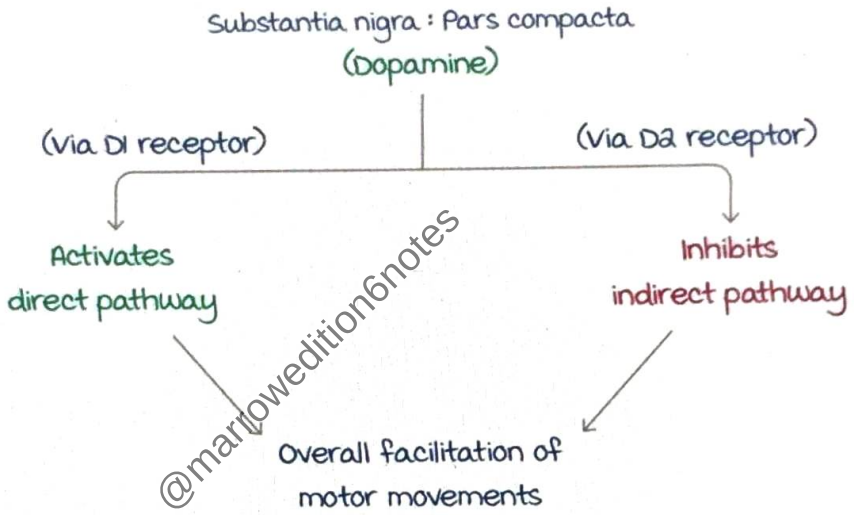
Inhibition of GPI → Facilitation of movements.



Indirect pathway

Activation of GPI → Inhibition of movements.

Normally, Globus pallidus externa inhibits sub-thalamic nucleus.



Basal ganglia lesions

00:52:31

Lesions cause involuntary movements.

Chorea → Caudate nucleus lesion (Eg: Huntington's chorea - dancing like movements)

Also cause cognition problems (involvement of striatum).

Athetosis : Globus pallidus lesion.

Hemiballismus : Subthalamic nucleus lesion (violent contraction of one large joint).

Parkinsonism : Loss of dopamine from substantia nigra pars compacta.

Dopamine cannot cross blood brain barrier, hence L-Dopa is

used as treatment.

Effect of long term treatment with L-Dopa gradually wears off because of continuous loss of dopaminergic neurons from substantia nigra pars compacta.

Hence, surgical treatment for parkinsonism like Stereotactic ablation of thalamic nuclei (ventral anterior and ventral lateral nuclei) is tried to alleviate symptoms.

Loss of dopamine causes,
Paucity of movements → Bradykinesia.
Pill rolling tremors even at rest.

MCQs :

Q. A 60-year-old man is taken to the physician because of a tremor in his hands, trouble sleeping, constipation, and dizziness. Physical examination shows a resting tremor, rigidity, and bradykinesia. The man is alert, engaging, and optimistic. He speaks in a low, soft voice. Which of the following is most likely to be decreased in this man ?

A. Serotonin neurons in the raphe nuclei.
B. GABA neurons in the caudate nucleus and putamen.
C. Dopamine neurons in the substantia nigra.
D. Acetylcholine neurons in the magnocellular forebrain nucleus.

Q. A 55-year-old woman's cognitive functions have progressively deteriorated for several years, to the point of needing nursing home-level care. She is depressed, easily irritated, and prone to aggressive outbursts, a dramatic change from her premorbid personality. She also presents with irregular, purposeless, and asymmetrical movements of her face, limbs, and trunk, which worsen when she is upset and disappear in sleep. Which of the following is most likely to be decreased in this woman ?

A. Acetylcholine neurons in the magnocellular forebrain nucleus.

B. Dopamine neurons in the substantia nigra.

C. Gamma-Aminobutyric acid (GABA) neurons in the caudate nucleus and putamen.

D. Serotonin neurons in the raphe nuclei.

Q. All the following are seen in cerebellar lesions except

A. Nystagmus.

B. Ataxia.

C. Past pointing.

D. Resting tremor.

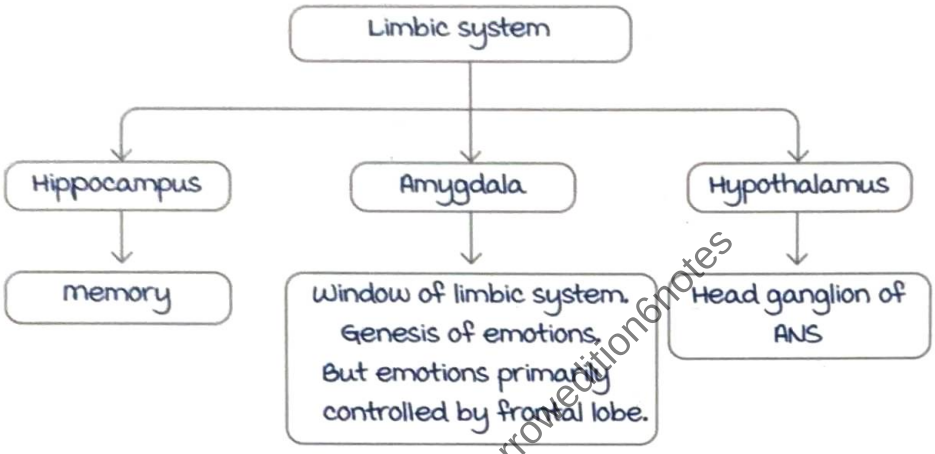
Active space

LIMBIC SYSTEM

Limbic brain or limbic cortex 00:00:16

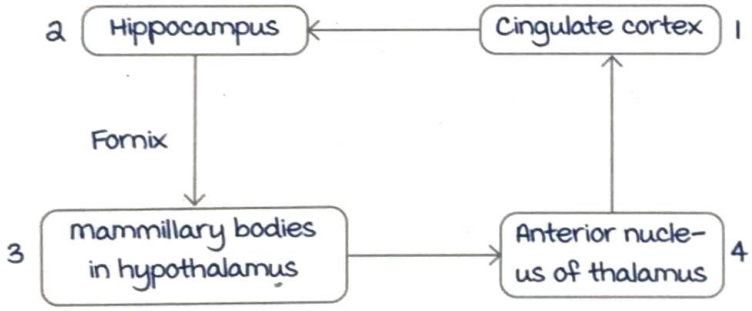
- Rim of cortical tissue.
- Very old in evolution.
- AKa Rhinencephalon/smell brain (concerned with olfaction).

Limbic brain and its components :



Limbic brain is exclusively concerned with memory and emotions.

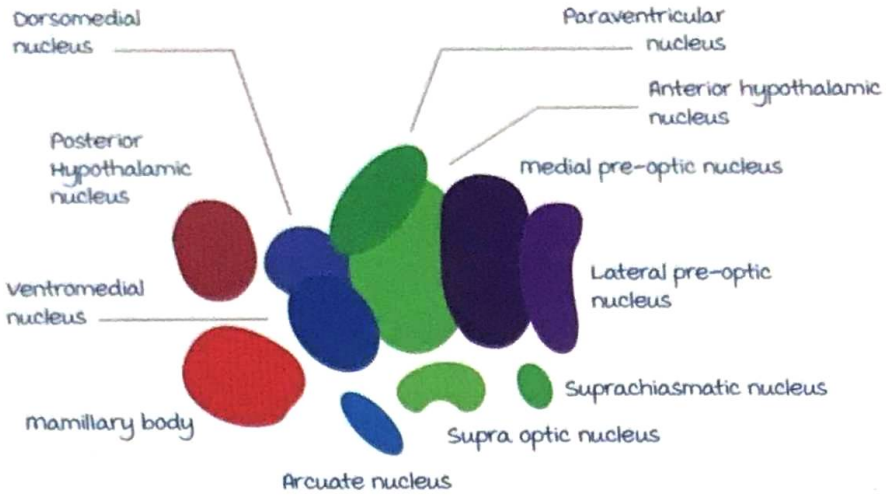
Usually taken care with help of Papez circuit.



Hypothalamus 00:05:29

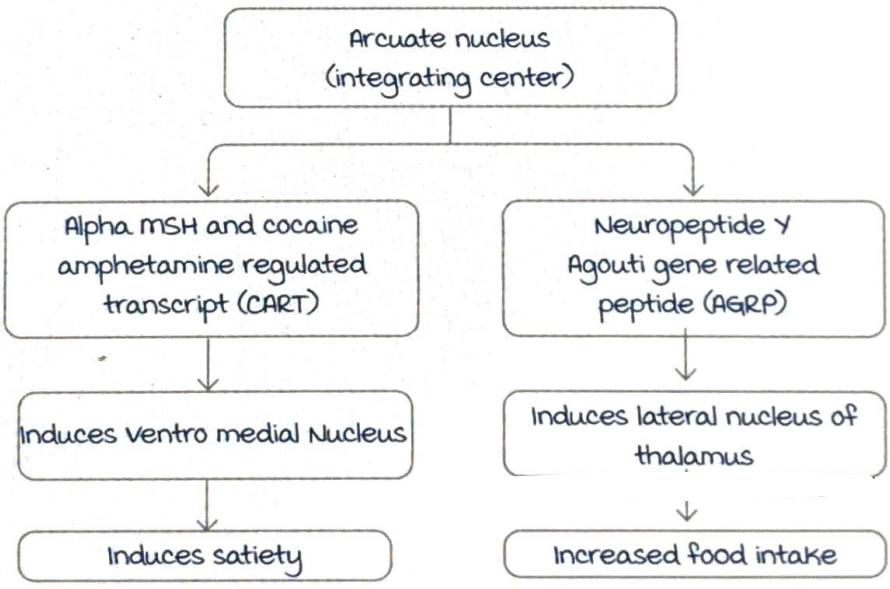
Hypothalamus and its function :

1. ACTH : Highest around 5 am and lowest around 3 pm.
   This cyclical change is called as circadian rhythm.
   Regulated by suprachiasmatic nucleus : master clock.



2. Regulation of food intake :

- Lateral nucleus → Increases food intake with the help of neurotransmitter orexin (Lateral nucleus lesion → Decreased food intake).
- Ventromedial nucleus (Satiety behavior) → Decrease in food intake (Ventromedial nucleus lesion → Increased food intake).
- Food intake is tightly regulated by arcuate nucleus (integrating center regulating food intake).

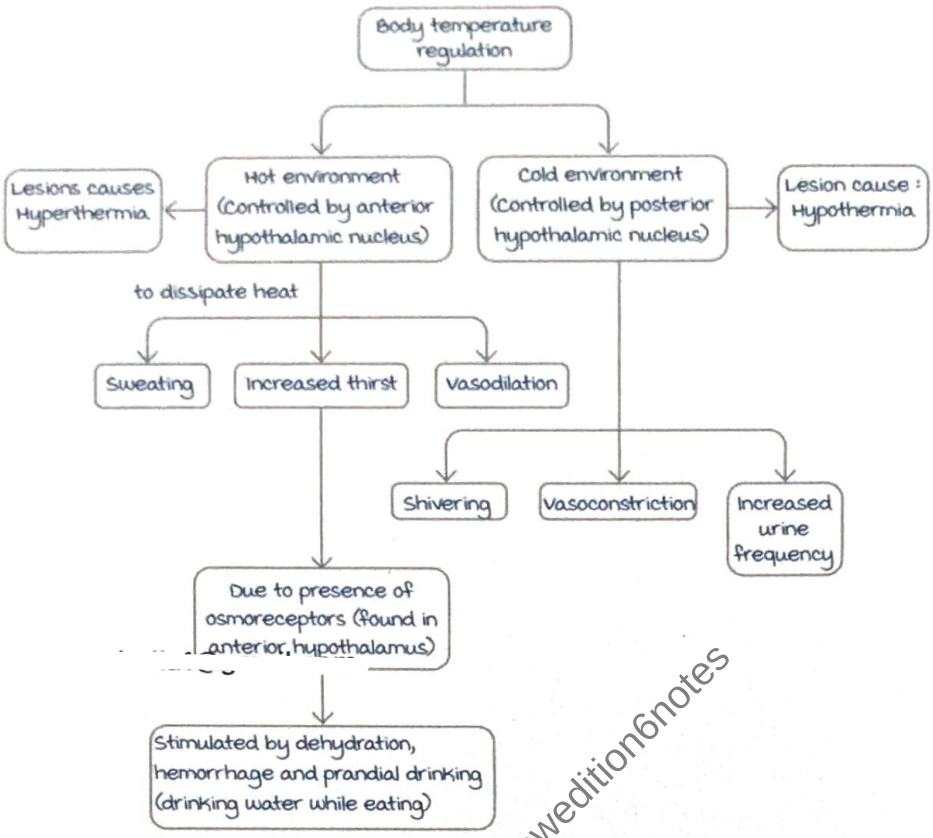


Medial forebrain bundle passing through lateral nucleus and ventro-medial nucleus → Reward center.

Active space

Regulation of body temperature 00:14:43

3. Regulation of body temperature :



4. Sleep regulation and wakefulness :
   - Lateral hypothalamic nucleus + Orexin (neurotransmitter of arousal) → Keeps us awake.
   - Posterior hypothalamic nucleus + Histamine → Keeps us awake.

Sleep center : Ventro lateral preoptic nucleus (VL PON) in hypothalamus.

Memory 00:22:25

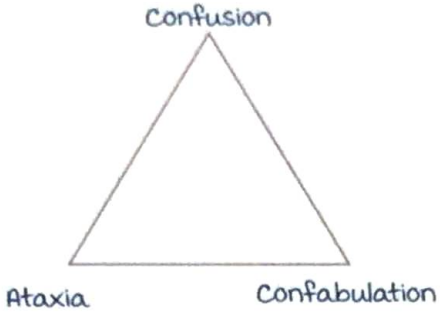
Hypothalamus can also play a role in memory with the help of Mamillary bodies.

In chronic alcoholics → Degeneration of mamillary bodies → Confusion, ataxia and special type of memory loss.

Active space

This special type of memory loss is Confabulation.

The triad is called as Wernicke's Korsakoff psychosis.



Regulation of endocrine hormones :

Hypothalamus ⟶ Send releasing factors and inhibitory factors to anterior pituitary.

- Stimulatory : GnRH from hypothalamus ⟶ LH and FSH from anterior pituitary.
- Inhibitory : Dopamine from hypothalamus inhibits prolactin release from anterior pituitary.

7. Synthesis of vasopressin and oxytocin.

Vasopressin : Mainly Supra optic nucleus.

Oxytocin : Paraventricular nucleus (parturition = Fetal delivery).

Synthesized in hypothalamus and stored in posterior pituitary.

8. Dorsomedian nucleus of hypothalamus :

Mild or weak stimulus (mild touch) on an animal ⟶ Biting, hissing and arching its back.

This phenomenon is called as Sham rage.

Removal of hypothalamus ⟶ Abolishes sham rage.

Cerebral cortex inhibits hypothalamus ⟶ No sham rage in healthy individuals.

Removal of cerebral cortex : Decortication ⟶ Sham rage present.

MCQs :

Q. Loss of orexinergic neurons from lateral hypothalamus causes

A. Schizophrenia.
B. Mania.
C. Depression.
D. Narcolepsy (periodic sleep disorder).

Q. Degeneration of which area caused by thiamine deficiency, associated with chronic alcoholism causes Wernicke's Korsakoff's psychosis?

A. Lateral Hypothalamus.
B. Suprachiasmatic nucleus.
C. Venteromedial nucleus.
D. Mamillary Bodies.

Q. Which of the following nucleus is not involved in papez circuit ?

A. Hippocampus.
B. Cingulate gyrus.
C. Caudate nucleus.
D. Thalamic nuclei.

Active space

LEARNING AND MEMORY

Function of dominant hemisphere.

Cerebral hemispheres

00:01:14

1. Left hemisphere :
   - Previously called dominant hemisphere → dominant in 96% right handed and 70% left handed people.
     Now, left hemisphere is called categorical hemisphere.
   - Processes :
     a. Language.
     b. Speech.
     c. Learning.
     d. memory.
   - Logic based thinking.
   - Lesion → Aphasia, dyscalculia.

2. Right hemisphere :
   - Previously called non dominant hemisphere.
   - Now, called representational hemisphere.
   - 3D orientation : Visuo spatial relationship.
   - Intuition based thinking.
   - Responsible for :
     a. Creativity.
     b. Music ability.
   - Lesion :
     i. Astereognosis (inability to recognize objects by touch in the absence of vision).
     ii. Agnosia.
     iii. Hemi spatial neglect (thinks only one side of the body exists).

Learning

00:07:34

Learning : Process of acquiring information.
Memory : Storage of information.
Memory engram : Collection of memories.

Types of memory :

1. Explicit memory/ Declarative memory :
   - Semantic memory (facts, places).
   - Episodic memory (events).
   - Brain areas highly responsible for explicit memory : Hippocampus, medial temporal lobe.
2. Implicit memory/ Non declarative :
   Example : Changing gears while driving, subconsciously.
   - Procedural memory/skills memory : Basal ganglia (striatum).
   - Priming (sensitization) : Neocortex.
   - Conditioning : Amygdala, cerebellum.

Memory types - based on time 00:14:23

1. Short term memory :
   - Lasts for seconds - minutes.
   - Attention dependent.
     i. Immediate memory :
     Digit subtraction test : (100 - 7) upto 5 steps.
     ii. Working memory :
     Example : Remembering OTP, phone numbers.
2. Long term memory :
   - Lasts for weeks to months.

Memory :

Synaptic plasticity : Repeated activity of a synapse.

1. Increased synaptic response :
   - Post tetanic potentiation.
   - Long term potentiation (LTP) : Hippocampus.
   - Sensitization.
2. Decreased synaptic response :
   - Long term depression (LTD) : Cerebellum.
   - Habituation.

Functions of hippocampus 00:20:32

- Consolidation or long term potentiation (converts short term memory to long term memory).
- Occurs in CA - 1 neurons (memory neurons).

Pathways :

Sensory afferent input pathway/ perforant pathway :

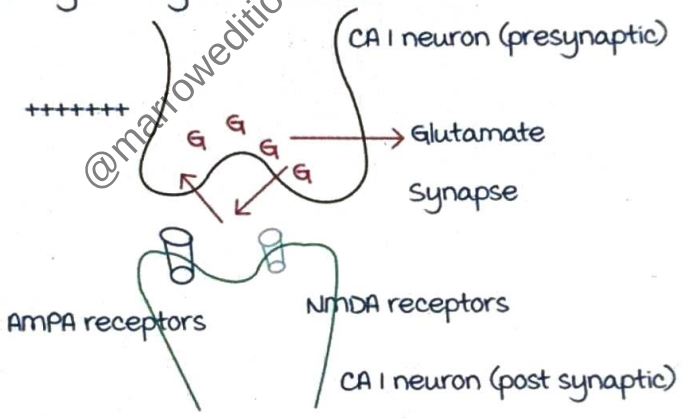
2 types :

i. Direct pathway
   - Entorhinal cortex, a component of limbic system, activates CA 1 neurons (found in hippocampus).

ii. Indirect pathway
   - Entorhinal cortex also activates dentate part of hippocampus → Activates CA 3 neurons → Activate CA 1 neurons.
   - CA 3 to CA 1 = Schaffer's collateral.

Mechanism of long term potentiation (LTP) 00:25:12

- Conversion of short term memory (STM) to long term memory (in hippocampus) by CA 1 neurons.
- CA 1 neuron ⇔ CA 1 neuron (synapse).
- Repeated activation of this synapse → Synaptic strengthening (Hebb's rule) → LTP.



NMDA receptor at resting state is blocked by Mg^{2+}. So, through AMPA receptors → Na^{+} comes in → depolarization → removes Mg^{2+} block → Ca^{2+} (2^{nd} messenger) enters through NMDA receptors → activates lots of protein → synaptic strengthening → LTP (STM → LTM).

Long term depression (LTD) 00:32:10

- Occurs in cerebellum.
- Synaptic weakening
- Childhood → while learning walking → faulty synapses activated → frequent falling.

Active space

LTD → faulty synapses will no longer be activated → correct synapses activated → proper walking.

Other areas of brain concerned with memory :

1. Mamillary bodies : Recollective memory.
   - Degeneration : Triad of ataxia + confusion + confabulation = Wernicke Korsakoff psychosis (in chronic alcoholism).
2. Anterior nucleus of thalamus lesion : Loss of recent memories.
3. Nucleus basalis of meynert in hippocampus contains acetylcholine. Lesion : Alzheimer's disease (loss of Ach).
4. Entorhinal cortex : Relation between memory and olfaction (smell).
5. Amygdala : Memory and emotions.
6. Corpus callosum : Hemispheric transfer of memory.
7. Hippocampus : CA I neuron belongs to Sommer sector. Lesion : Explicit memory affected (cannot form new long term memories). Leads to anterograde amnesia. Implicit memory like procedural & skills memory will be intact.

Speech 00:41:51

a. Broca's area :
   - Found in inferior frontal cortex.
   - Called motor speech area.
   - Concerned with :
     i. Speech output.
     ii. Verbal expression.
     iii. Word formation.
     iv. Vocalization.
   - Lesion : Broca's aphasia.
     i. Reduced speech output.
     ii. Impaired repetition → non fluent aphasia.

b. Wernicke's area :
   - Found in superior temporal gyrus.
   - Sensory speech area.
     i. Understanding.
     ii. Comprehension.

Active space

- Lesion : Wernicke's aphasia.
  Patient speaks but without any meaning → fluent aphasia but impaired comprehension.

c. Broca's area ⟷ Wernicke's area
Arcuate fasciculus

- Lesion in arcuate fasciculus : Information from Wernicke's not passed to Broca's → Conduction aphasia.

d. Angular gyrus :
- Brodmann area 39.
- Vision and speech interconnected here.
- Lesion : Anomic aphasia (cannot name what they see)

Clinical case scenarios :

Q. A 37 year old man suffered a traumatic brain injury. He could no longer facilitate the recognition of words by prior exposure to them. What type of memory deficit is this and which brain part is affected ?

A. Declarative memory and hippocampus.
B. Procedural memory and striatum.
C. Conditioning memory and cerebellum.
D. Priming and neocortex.

Q. A 20 year old male cannot anything that happened after he recovered from a head injury, but he has no difficulties with remote meories. Which part of the brain is lesioned?

A. Cerebellum.
B. Mammillary bodies.
C. Basal ganglia.
D. Hippocampus.

Q. Motor aphasia refers to defect in :

A. Peripheral speech apparatus.
B. Verbal expression.
C. Auditory comprehension.
D. Verbal comprehension.

CSF, CBF AND BBB

Fluids in brain

00:00:17

For lubrication and protection : Cerebrospinal fluid (CSF).
For nutrition, oxygen supply and CO_2 removal : Cerebral Blood flow.

Cerebrospinal fluid (CSF) :
Normal CSF : 150ml.
Rate of CSF production : 550ml/day.
Recycled around 3.7 times/day.
Normal pressure : 70–180 mm H_2O.
Production : 50–70% at Choroid plexus (major site of production).
Choroid plexus → Foramen of magendie and Luschka → Sub arachnoid space → Arachnoid villi (major site of absorption).
Cribriform plate (minor site of absorption) → Cervical lymphatics.
At average CSF pressure 112 mm H_2O, filtration = absorption.
Entire CSF production is regulated at the level of absorption.

Plasma vs CSF

00:06:32

Compared with plasma, CSF has high concentration of (CSF > Plasma Concentration) :

- Chloride.
- Magnesium.

Concentration equal in CSF and plasma (CSF = plasma concentration) :

- Osmolality.
- Bicarbonate ions.

Compared with plasma, CSF has low concentration of (CSF < Plasma concentration) :

- Potassium.
- Calcium.
- Glucose (CSF glucose is 2/3rd of plasma glucose).
- Proteins (CSF protein is 15–45 mg/dl).

β_a transferrin : CSF marker (present only in CSF).
In cases of CSF rhinorrhea, CSF otorrhea β_a transferrin levels are estimated to confirm if the fluid is CSF.

Lumbar puncture : Removal of CSF.
Headache followed by LP is due to loss of Cushion effect/ lubrication and traction leading to pain.

Cerebral blood flow (CBF) 00:11:32

Major source : Circle of Willis.
CBF : 750 ml/min or 55 ml/100g of tissue/min.
Highest blood flow : 1500ml/min → Liver.
Only 1/2 of liver blood flow is received by brain.
Blood flow : Grey matter > white matter.
O_2 Supply to brain/O_2 consumption : 46 ml/min.
(20% of total body O_2 consumption).
Brain → Extremely sensitive to hypoxia.
Most susceptible to hypoxia :

- Hippocampus.
- Thalamus.
- Inferior colliculus.
- Basal ganglia.

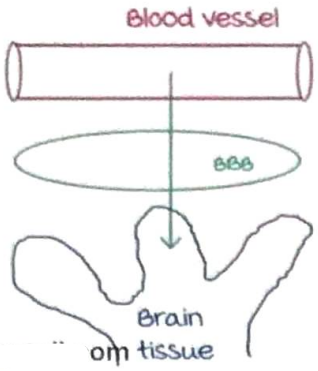
Regulation of CBF 00:15:28

Pressure range : 65–140 mmHg.
Even if pressure changes within the range, CBF remains constant : Concept of autoregulation.

Partial pressure of CO_2 : Increase in pCO_2 → Increase in CBF.
Body temperature :
Every 1°C fall in temperature → CBF decreases by 7%.
Therapeutic hypothermia : Used in neurosurgery to minimize blood loss.

Blood Brain Barrier/ BBB 00:19:24

BBB is formed by :
Tight junctions between endothelial cells of blood vessels.
Further reinforced by foot processes of astrocytes (star shaped cells).



Substances which can cross BBB :

- Lipid soluble hormones (steroids).
- Gases like CO_2, O_2, N_2.
- Glucose (90% energy source) :
  GLUT-1 present in BBB.
- Water : Aquaporin-4.

(Auto antibodies against aquaporin-4 lead to demyelinating disease called neuromyelitis optica : Devic's disease).

Substances that cannot cross BBB :

- Protein hormones (steroid hormones can - lipid soluble).
- H^+ ions.
- Dopamine.
  (L-Dopa can cross BBB. Used in treatment of parkinsons disease).

In case, any drug enters brain tissues via blood vessel, it is immediately taken back to blood by P-glycoprotein.
P-glycoprotein blockers : Helps to selectively concentrate drugs in brain.
Useful in treatment of CNS neoplasms.

Circumventricular organs 00:28:48

Areas outside BBB/absent BBB (mnemonic : SOAP)
Subfornical organ.
Organum vasculosum of lamina terminalis.
Area postrema.
Posterior pituitary.
Importance :Protein hormones can use this to enter brain.
Angiotensin II : Acts on area postrema to increase BP.

Can act on sub forniceal organ, OVLT to increase thirst sensation.

Skull (Cranium) :

Volume of CSF, blood & brain tissue always remain constant.

If any one of the above parameters rises → Compresses the other 2 parameters.

Called as Munroe Kellie doctrine.

Example : Increase in CSF pressure → Compresses blood flow and brain tissue.

MCQs :

Q. Which of the following is not permeable through the blood brain barrier?

A. Water.
B. Lipophilic drugs.
C. Gas.
D. Proteins.

Q. CSF Plasma glucose ratio is

A. 0.2–0.4.
B. 0.6–0.8.
C. 1.2–1.6.
D. 1.6–2.2.

Q. A 45-year-old male is undergoing surgery for medulloblastoma in the posterior fossa of brain. Best measure to reduce cerebral oxygen consumption is

A. Administration of barbiturates.
B. Hyperventilation.
C. Administration of Opioids.
D. Institution of hypothermia.

EEG AND SLEEP

Electroencephalography (EEG) 00:00:21

Recording of brain waves.
First recorded by a psychiatrist Hans Berger.
Not individual action potentials.
It is the overall electrical activity in the form of a summated potential.

Frequency (Hz) :
Number of waves in a given second.
Directly related with activity state of brain.
Eg., Sleep ⟶ less activity ⟶ less frequency.

Amplitude (μV) :
Height of the wave.
Frequency α $\frac{1}{\text{amplitude}}$.

EEG waves :
Classified according to their frequency.

Wave	Frequency
Gamma wave	> 60 Hz. Highest frequency.
Beta wave	13 – 30 Hz
Alpha wave	8 – 12 Hz
Theta wave	4 – 7 Hz
Delta wave	1 – 3 Hz. Lowest frequency.

Alpha wave 00:07:00

- Seen when eyes are closed but not sleeping.
- Wave of relaxed state, mind wandering.
- Predominantly generated from occipital cortex.
- Also, from parietal cortex. 8 – 12 Hz frequency.
- Wave of inattention.

Beta wave :

- Wave of wakefulness, attention.
- 13 – 30 Hz frequency.
- Predominantly generated from frontal cortex.

Prefrontal cortex (PFC) area of frontal cortex regulates attention.

Theta wave :

- Associated with memory functions : memory wave.
- Generated from hippocampus.
- Function of hippocampus : Conversion of short term memory to long term memory.
- 4 – 7 Hz frequency. Can also be seen during sleep.

Delta wave :

- Associated with NREM (non rapid eye movement) sleep.
- Lowest frequency : 1 – 3 Hz. So, called slow waves.

Gamma wave :

- Highest frequency of >60 Hz.
- Seen when brain is most active focussed attention.

Sleep

00:15:38

2 stages of sleep :

NREM sleep : Non rapid eye movement sleep.

REM sleep : Rapid eye movement sleep.

NREM sleep stage :

Stage I : 4 – 7 Hz. Theta waves are seen.

Stage II : 8 – 12 Hz. K complex and sleep spindles. Not alpha waves. Biphasic wave (K complex) followed by a sinusoidal wave pattern (sleep spindle).

Stage III and IV : 1 – 3 Hz. Delta waves are seen.

Slow wave sleep, synonym of NREM sleep.

According to new nomenclature :

Stage I : N 1.

Stage II : N 2.

Stage III and IV : N 3.

Active space

REM sleep

00:21:19

Rapid eye movement.

13 – 30 Hz frequency : Beta wave (wave of wakefulness).

Also called paradoxical sleep as EEG shows wave of wakefulness.

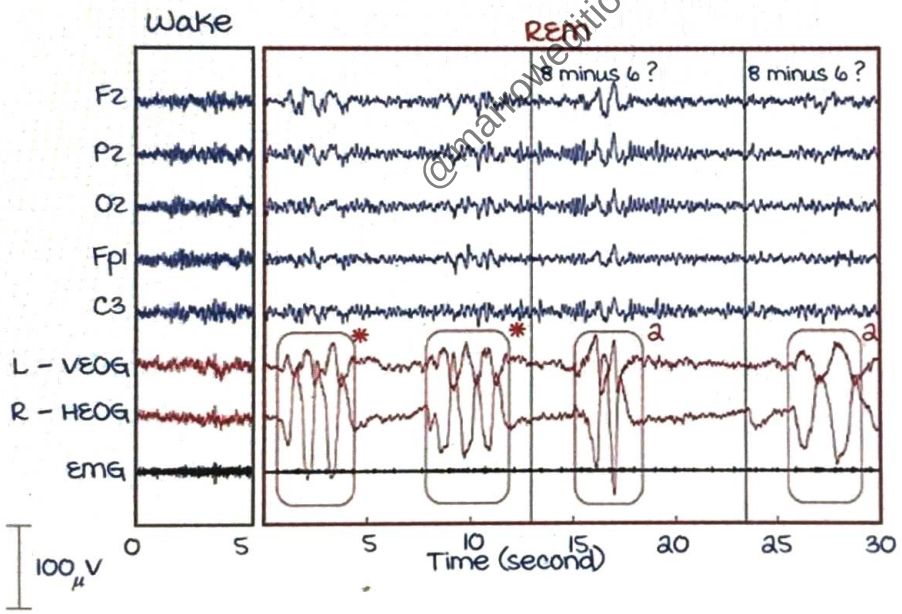
Impulse originates in pons, travels through lateral geniculate body & ends in occipital cortex (PGO).

Magnocellular pathway in lateral geniculate body is activated & is responsible for eye ball movements.

PGO spikes are seen.

Physiological changes during sleep :

NREM sleep	REM sleep
Respiratory rate : Low. BP : Low. Body temperature : Low.	Muscle atonia. All muscles except diaphragm and extraocular muscles.
Respiration : Slow and deep.	Genital organ enlargement.



Eye ball movement is recorded by Electro-Oculography (EOG).

In the above graph, the eyeball movements recorded show activity.

Electromyography is to record muscle activity.

Straight line in REM due to muscle atonia.

Active space

Hormonal changes during sleep 00:29:46

Growth hormone level rises during NREM sleep (stages III and IV).
Prolactin levels rise during REM sleep.
Around the time of puberty, there is nocturnal surge in LH.
As it turns dark, melatonin levels rise to induce sleep.

Dreaming : Can happen in both REM and NREM sleep.

Dream in REM sleep	Dream in NREM sleep
Occurs in early morning. Long duration. Emotional component. Not related to day to day activities.	Short duration. Conceptual dream. Related to day to day activities.

Regulation of Sleep 00:33:51

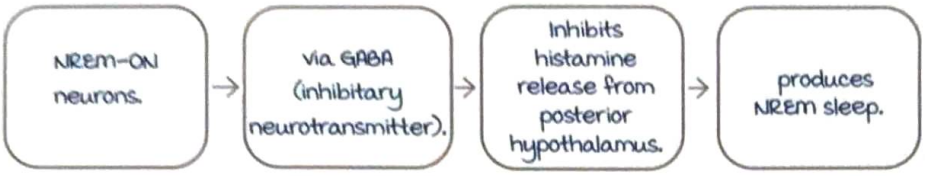
Controlled by areas in brain and neurotransmitters.
Wakefulness promoting areas :

- Reticular activating system (RAS).
  Neurotransmitter of arousal : Norepinephrine.
  Polysynaptic pathway, activates widespread brain areas.
  Any high frequency stimulus to RAS, results in waking up from sleep, called as EEG alerting response.
- Lateral hypothalamus.
  Orexin : Neurotransmitter of arousal.
  Also increases food intake.
  Also called hypocretin.
  Loss of orexin causes narcolepsy.
  ] Difficult to sleep while hungry.
- Posterior hypothalamus.
  Neurotransmitter of arousal : Histamine.
  Hence, earlier generation of anti histamines had sedative effects.
- Raphe nuclei.
  Neurotransmitter of arousal : Serotonin.

These neurotransmitters decrease during sleep.

Sleep promoting areas 00:40:38

- Hypothalamus.
  Sleep center : Ventrolateral preoptic nucleus (VLPON).
- Pineal gland.
  Melatonin induces sleep.
- Cholinergic neurons in pons and midbrain.
  Neurotransmitter : Acetyl choline.
  Induces REM sleep.



REM-ON neurons release acetyl choline from cholinergic neurons, produce REM sleep.

Parasomnias 00:45:20

Events happening during sleep :

NREM sleep	REM sleep
• Sleep walking : Somnambulism (stage III & IV). • Sleep talking. • Sleep bruxism : Teeth grinding (stage II). Seen in some emotionally deprived children. • Nocturnal enuresis : Bed wetting. • Night terrors/pavor nocturnus.	• Nightmares. • Narcolepsy.

Q. A 25 year old male presents with episodes of sudden onset sleep accompanied by sudden loss of muscle tone and followed by quick entry into rapid eye movement (REM) sleep. These findings are characteristic of which one of the following ?

A. Sleep changes associated with depression.
B. Obstructive sleep apnoea/hypopnea.
C. Insomnia disorder.
D. Narcolepsy.

Narcolepsy is due to loss of orexin from lateral hypothalamus.

Q. EEG rhythm recorded from the surface of scalp during REM sleep is?

A. Alpha wave.

B. Beta wave.

C. Theta wave.

D. Delta wave.

Q. Which of the following events happen during stage II NREM sleep ?

A. Somnambulism.

B. Sleep terrors.

C. Nocturnal Enuresis.

D. Bruxism.

STRUCTURE- FUNCTION RELATIONSHIP IN LUNG

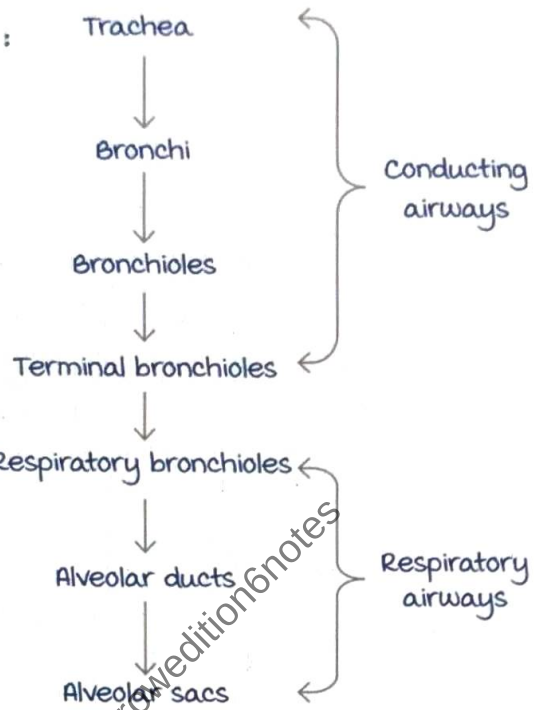
Lung airway generations

00:01:37

Largest airway passage : Trachea.

Smallest airway passage : Alveoli.

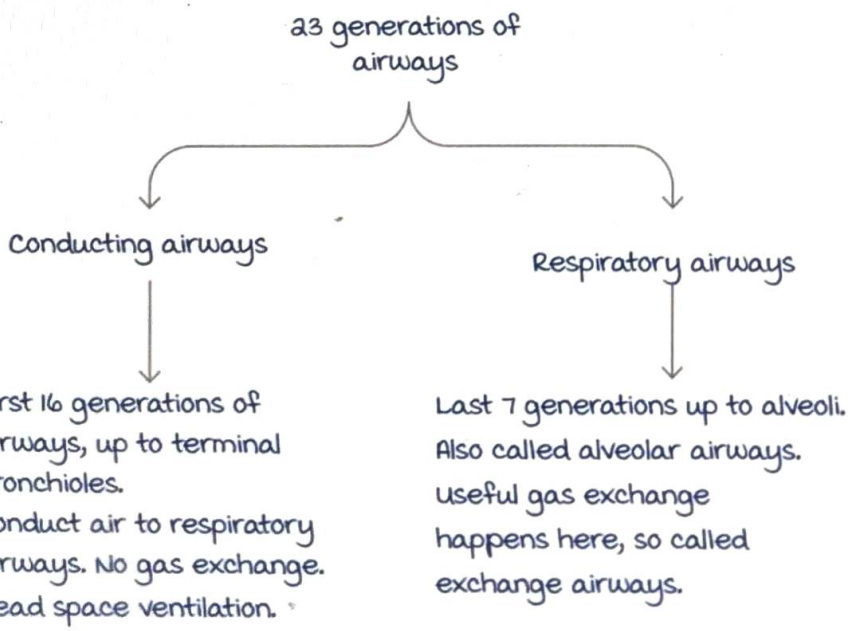
Trachea progressively branches and divides, eventually giving rise to alveoli.



Branching/generations :

- Trachea divide 23 times to become alveoli.
- Discovered by the anatomist, Weibel.
- 23 generations of airways.

Weibel's model of airways :



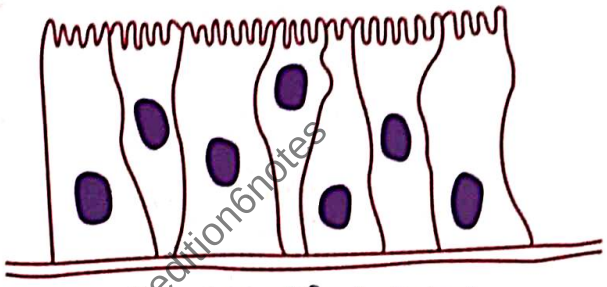
Active space

Conducting airways

00:05:07

First 16 generation of airways, up to terminal bronchioles.

- Lining epithelium : Pseudostratified ciliated columnar epithelial cells (have finger like projections = cilia).
- Cilia is always capable of movement.
- movement of cilia is directed towards the nasopharynx.
- This helps in expelling the sputum.
- Cilia have synchronized movement : metachromism.
- Ciliary movement is due to the protein, dynein.
  Also helps in sperm movement and fallopian tube motility.



Pseudostratified ciliated columnar epithelium

Functions of ciliary movement :

- Protective, as it helps in clearing the sputum.
- During development, it helps in rotation of internal organs.
  Heart rotates to left, from right side due to ciliary movement.

Immotile cilia syndrome :
Absent dynein protein.
e.g. : Kartagener syndrome.

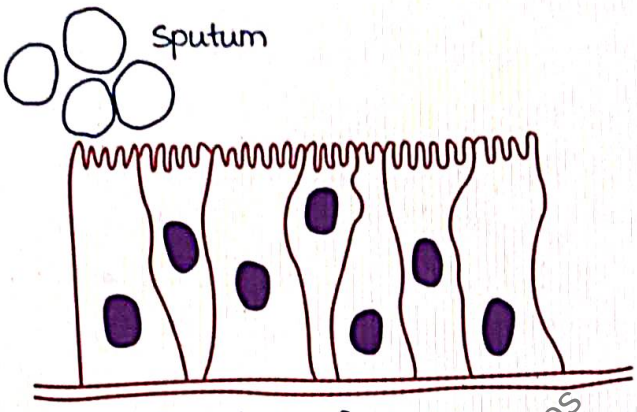
Accumulation of sputum causing long standing sinusitis.
Can cause bronchiectasis.
Situs invertus (internal organs don't rotate) } Classical triad
Prone for infertility.
Immotile sperm : Asthenospermia.

Cystic fibrosis :

CFTR gene mutation (cystic fibrosis transmembrane regulator).

Defective chloride ion channel opening.

- Leads to the formation of very thick sputum.
- The thick sputum cannot be cleared by the cilia despite normal ciliary movement and dyenin protein.



Pseudostratified ciliated columnar epithelium

Treatment :

Ivacaftor : Chloride channel opener.

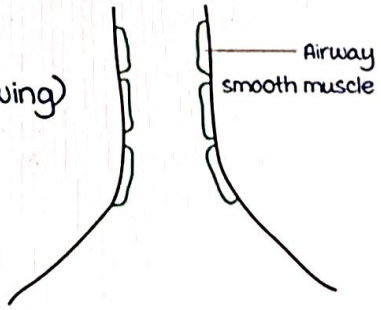
Conducting airway smooth muscles 00:17:46

Lines the conducting airways.

Normal bronchoconstriction in response to :

- Dust particles.
- Cold environment.

Bronchoconstriction (lumen narrowing) decreases airflow but increases airway resistance.



Exaggerated bronchoconstriction is seen in bronchial asthma (enhanced airway resistance).

- Treatment is by bronchodilation.
- Bronchodilation : Increases airflow and decreases airway resistance.

Active space

Bronchoconstriction	Bronchodilation
Parasympathetic stimulation : Acetyl choline, methacholine. • Anticholinergics used in bronchial asthma treatment like Ipratropium bromide. Histamine. Most potent bronchoconstrictor : Leukotrienes. Leukotriene antagonists like montelukast, zafirlukast can be used.	Sympathetic stimulation : βa receptor action. • βa receptor agonist like salbutamol used for bronchial asthma. Nitric oxide. Vasoactive intestinal peptide (VIP) : Belongs to non-adrenergic non- cholinergic (NANC) system.

Airway resistance is seen in conducting aiways.

Maximum airway resistance seen in : Medium sized bronchi.

Special cells in conducting airways :

Stem cells (to regenerate in response to injury) :

Lung, in general, has 3 stem cells.

- Two exclusively found in conducting airways.
  Basal cells (stem cells anywhere in the body).
  Clara cells : Also called club cells.
- One in alveolar airways.

Air in conducting airways (first 16 generations) is useless (no gaseous exchange), so called dead spaces.

Alveolar airways :

Air present here undergoes gaseous exchange : Exchange airways.

Last 7 generations of airways.

Cells of alveolar airways : Pneumocytes.

- Type I :
  Large and flat.
  Occupies large surface/cross sectional area.
  Less numerous.
- Type II :
  More in number.
  Small in size.
  Produces surfactant : Surfactant producing cells.
- Stem cells of the alveolar airways.

Surfactant

00:35:40

Lipid-protein complex.

Lipid	Protein
major : Lecithin (L). • DPPC : Dipalmitoyl phosphatidyl choline. minor : Sphingomyelin (S).	Surfactant proteins (SP). • SP- A. • SP- B. • SP- C. • SP- D.

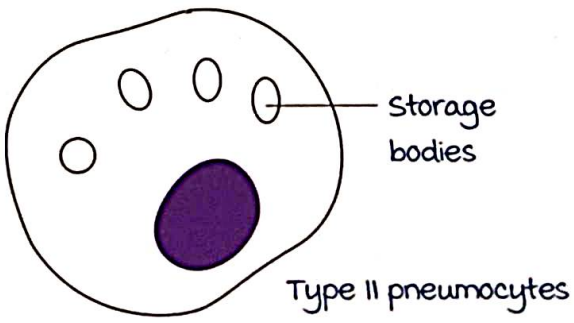
Surfactant lipids :

- L/S ratio ≥2, normally.
  To assess fetal lung maturity.
- Surfactant appears around 28-32 weeks of gestation.
- Shake test/Bubble test :
  Also called Clement test.
  Amniotic fluid is taken in a test tube, and shaken.
  Lipids form bubbles on shaking.
  Formation of bubbles taken as a positive sign for the presence of surfactants.
  To assess fetal lung maturity.

Lamellar bodies :
Storage bodies with surfactants seen in type II pneumocytes.

Easily observed under the microscope ⟶ can be counted.

- Tested to assess fetal lung maturity.



Active space

Functions of surfactant

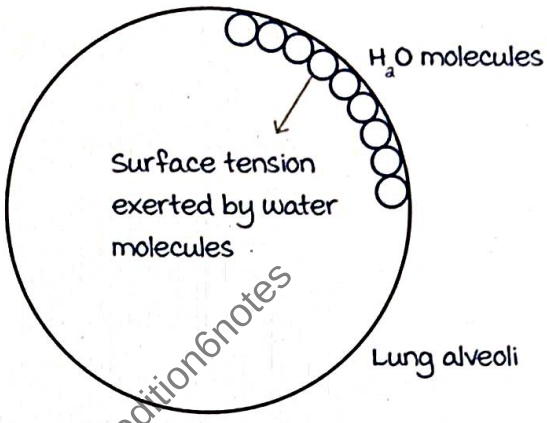
00:42:30

- Primary function : Decrease surface tension.

  On the surface of the alveoli, the water molecules present exert a force, i.e. surface tension.

  The surface tension acts inwards, trying to collapse the alveoli.

- Prevents collapse of the alveoli.
- Ensures stability of alveoli.
- Increases area of alveoli.



Laplace law :

Tension (T) = pressure (P) x radius (R).

For a spherical structure, like alveoli :

$2T = P \times R$.

In the alveoli :

2(surface tension) = (collapsing pressure) x (radius of alveoli).

Surfactants stabilize the alveoli from collapsing by :

Decreasing the surface tension.

Increasing the radius.

Area= πr^2.

Increase in the area of alveoli.

Decreasing the collapsing pressure.

- SP- A and SP- D contributes to lung immunity.

Active space

Regulation of surfactant synthesis 00:49:26

Factors that increase the surfactant production :

- Steroids.

  Cortisol increases surfactant production.

  In preterm babies, lung is immature. Betamethasone (preferred)/Dexamethasone (drug forms of cortisol) used to enhance lung maturity.

- Thyroid hormones T3, T4.

Factors that decrease surfactant production :

Never physiological, always pathological.

- High levels of insulin : Hyperinsulinism.

  Blocks cortisol action.

  Seen in infants of diabetic mother : Hyaline membrane disease (HMD)/Respiratory Distress Syndrome (RDS).

  Treatment : Drug forms of Surfactant.

  Lucinactant, Beractant.

MCQs :

Q. Cystic fibrosis transmembrane conductance regulator (CFTR) regulates ?

A. Sodium channel.

B. Potassium channel.

C. Calcium channel.

D. Chloride channel.

Q. All of the agents causes bronchoconstriction except?

A. Acetylcholine.

B. Histamine.

C. Nitric oxide.

D. Leukotrienes.

Q. Which of the following agents helps in prevention of Hyaline membrane disease?

A. Paracetamol.

B. Amikacin.

C. Betamethasone.

D. Insulin.

MECHANICS OF BREATHING

Boyle's law 00:00:58

Pressure (P) of a gas is inversely proportional to volume of that gas (V).

$P \propto \frac{1}{V}$

In physiology, V = Tidal volume (500 ml of air).
To change the tidal volume there needs to be a change in three important pressures.

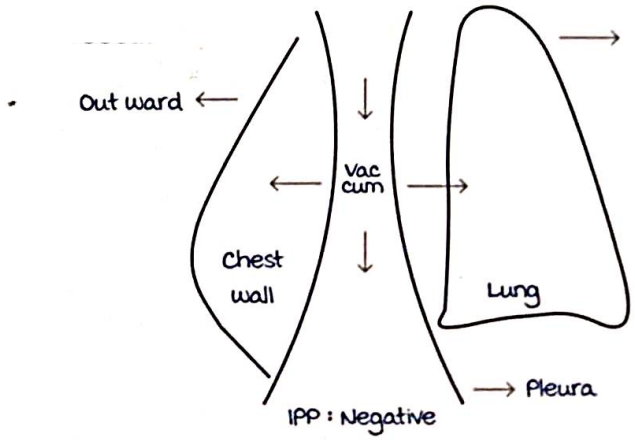
Intrapleural pressure (IPP) 00:03:20

At rest, IPP is negative = −2.5 mmHg or −3.4 cm H_2O.
(1 mmHg = 1.36 cmH_2O)
IPP becomes positive only during forceful expiration.

During inspiration :
Volume increases so → IPP decrease to −6 mmHg or −8 cmH_2O by Boyle's law.
So IPP becomes more negative during inspiration.

During expiration :
Volume decreases → so IPP increases to −2.5mm Hg.

Why is IPP negative during rest?



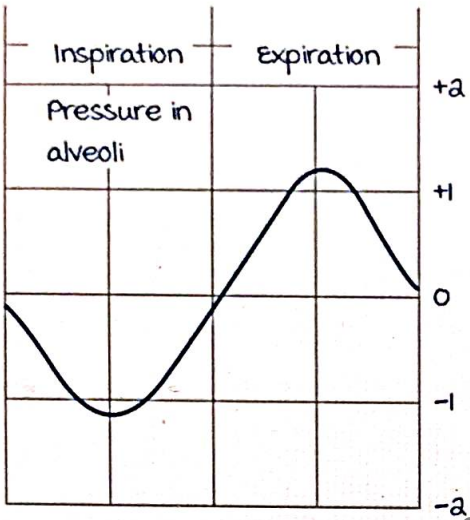
Normal tendency of the chest wall is to move out.
Normal tendency of the lung is to move inwards.

Active space

Pleura is present between lung and chest wall.
Hence pleura is stretched by two opposing forces →
Vacuum is created in between → Intrapleural pressure is negative.

Alveolar Pressure (AP)

00:10:46



Alveolar pressure changes

Resting alveolar pressure is zero.

According to Boyles law ,
During inspiration :
.Volume increases → Alveolar pressure decreases by 1mmHg.
At the end of inspiration, alveolar pressure = 0.

During expiration :
Volume decreases → Alveolar pressure increases by 1mmHg.
At the end of expiration, alveolar pressure = 0.

Transpulmonary pressure

00:15:16

Transpulmonary pressure (TP) = Alveolar pressure (AP) - Pleural pressure (IP).
At rest, TP = AP- IP.
TP = 0 - (-2.5).
TP = +2.5 mm Hg.
It is a distending pressure that keeps our alveoli distended.

Active space

Muscles of respiration

Inspiration

Active process.

Diaphragm (major) + accessory muscles :

External intercostal muscles.

Scalene muscle.

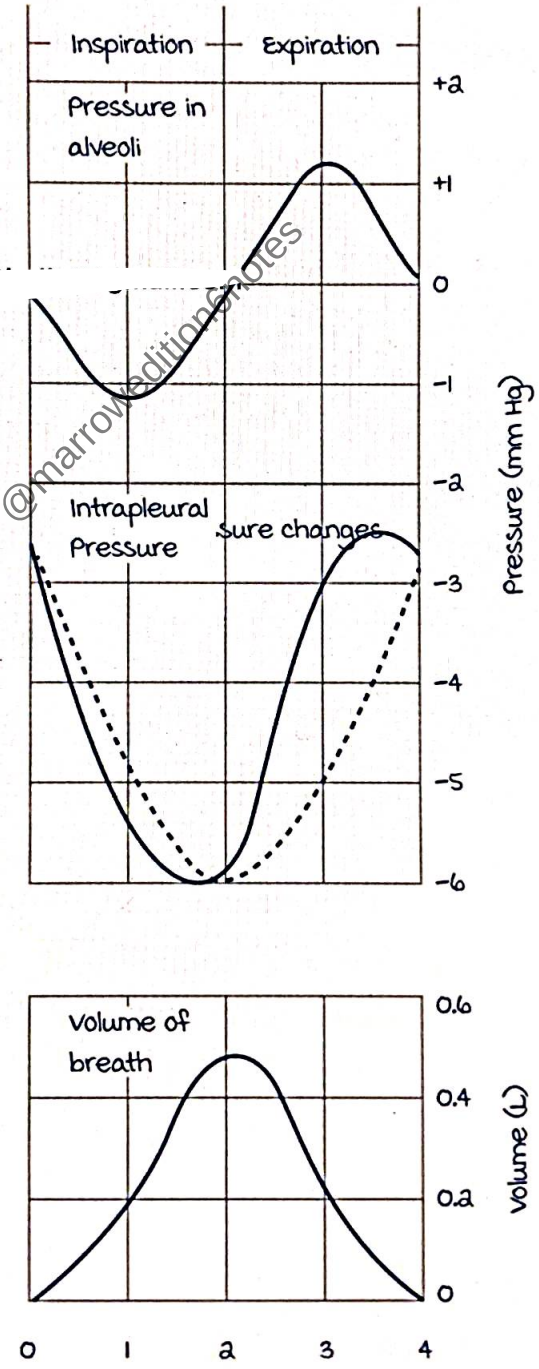
Sternocleidomastoid.

Expiration

Passive process

Required for forceful expiration (exercise) :

1. Rectus abdominus.
2. Transverse abdominus.
3. Internal intercostals.



Active space

Compliance

00:21:00

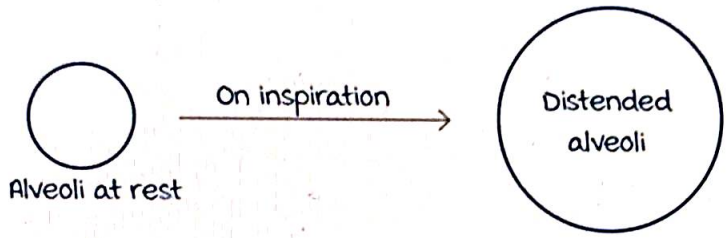
Distension of lung is also called compliance.

Lung is considered like a spring : High amount of distension.

2 opposing forces of compliance :

- Surface tension : Exerted by water molecules on surface of alveoli (major) → acts inward.
- Elastic recoil (Elastance).

$$\text{Compliance } \alpha \frac{1}{\text{Elastance}}$$



Emphysema :

Decrease in elastance → Increased compliance → Over distension of lung.

Chest radiograph : Hyperinflation of lung

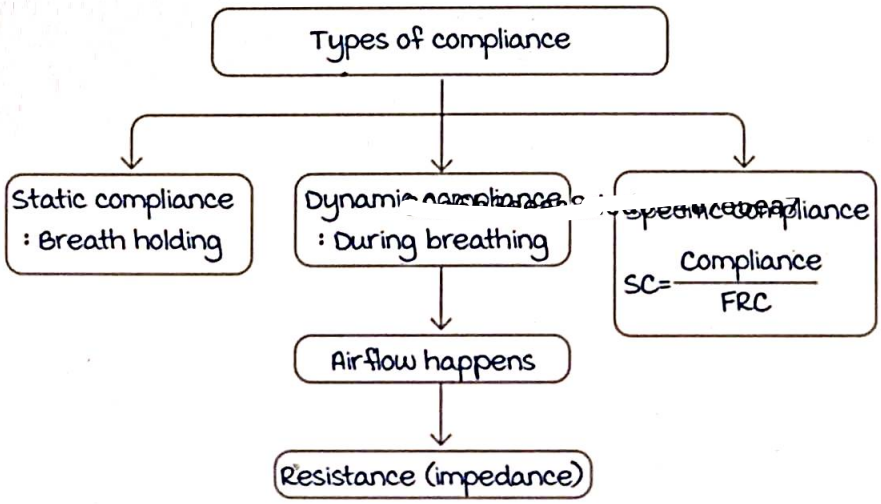
When lung is stiff→Less distensible→Compliance decreases.

E.g. in restrictive lung diseases like

- Pulmonary fibrosis.
- Interstitial lung diseases.

Normal compliance of lung = 200 ml/cmH2O

$$\text{Complaince (C)} = \frac{\text{Change in volume}}{\text{Change in pressure}}$$



Compliance curve

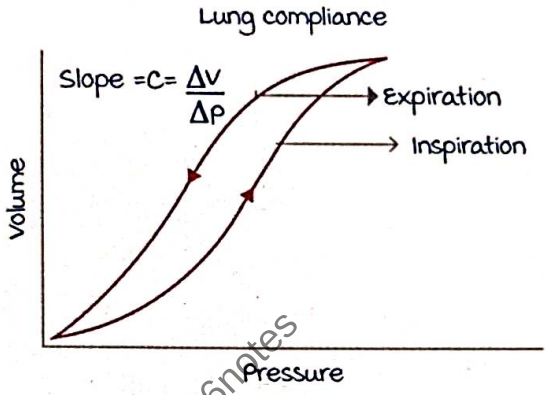
00:32:38

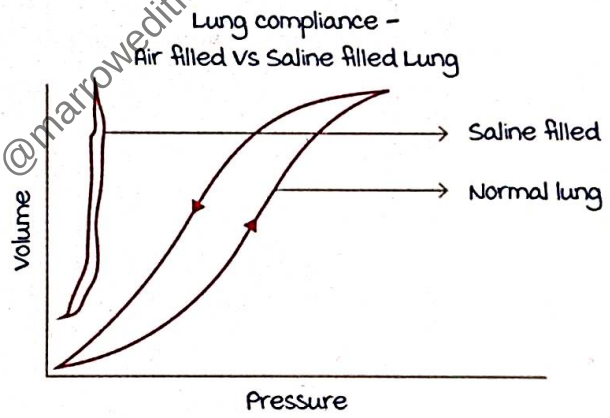
Relationship between inspiration and expiration :

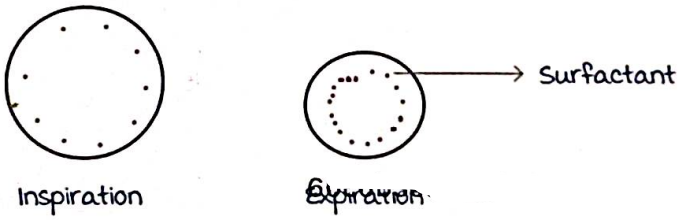
Hysteresis : Direction of inspiration is opposite to the direction of expiration.

Hysteresis is due to surface tension forces which is modulated by surfactant.

As change in volume is more during expiration, Compliance is greatest during expiration.







Compliance of air filled lung : Hysteresis is present.

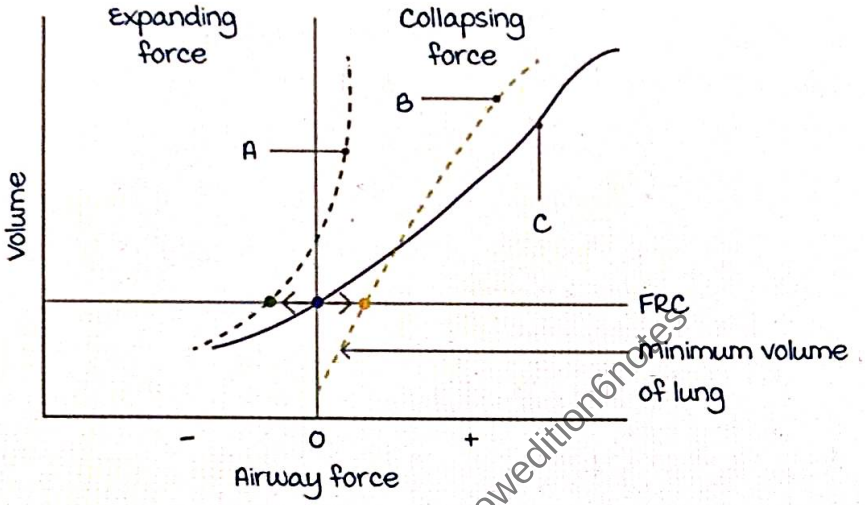
Active space

In saline washed lung : No hysteresis (No air fluid interface as saline removes surface tension forces).

During inspiration surface molecules are wide apart, so less reduction in surface tension .
During expiration they are closer, so more reduction in surface tension.

Reasons for hysteresis :

1. Surface tension forces.
2. Surfactant concentration.



Compliance curve with 3 compliances :

A : Compliance of chest wall.

B : Compliance of lung.

C : Total compliance.

2 opposing forces in thorax balances each other at an equilibrium volume refered as functional residual capacity (FRC).

At one point, the lung undergoes complete collapse (eg : pneumothorax), but it still encloses a volume called minimal volume of lung.

Work of breathing 00:49:00

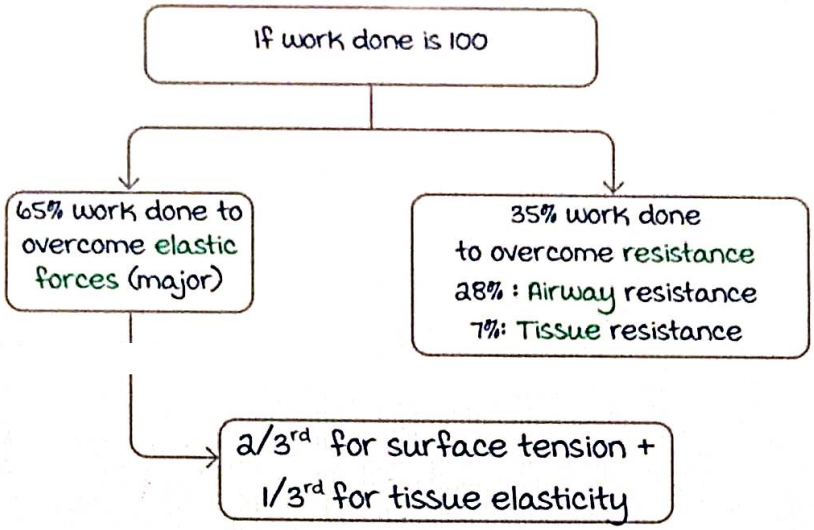
Work is done to move air in and out of lung.

work = Force x displacement.

↓ ↓

Pressure changes Volume changes

Normal work done by lung = 0.5 kg m/min.



Q. When elastic fibers of lung are replaced by stiff collagen fibers what will happen to lung compliance?

A. Increase.
B. Decrease.
C. No Change.
D. None of the above.

Q. The intrapleural pressure is negative both during inspiration and expiration because ?

A. Intrapulmonary pressure is always negative.
B. Thoracic cage and lung are elastic structure.
C. Transpulmonary pressure determines the negativity.
D. Surfactant prevents the lungs to collapse.

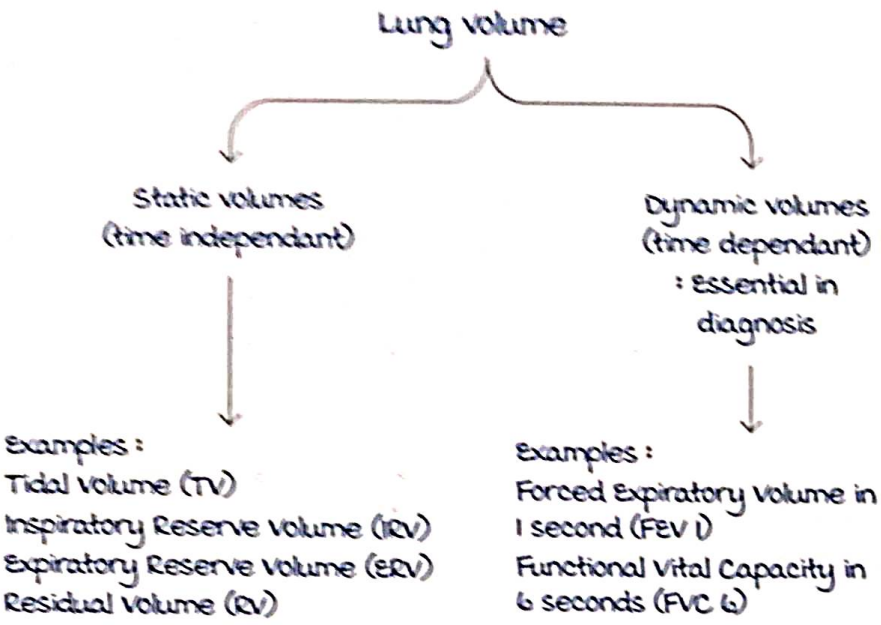
Q. Muscles that aid in active expiration are all except

A. Internal intercostals.
B. Rectus abdominis.
C. Sternocleidomastoid.
D. Transverse abdominis.

Active space

LUNG VOLUMES AND CAPACITIES

Introduction :



Static lung volumes

00:04:00

Time independent volume measurements.

Tidal Volume (TV) :

- About 500 mL
- The volume of air that moves in and out of lungs during normal breathing.

Inspiratory Reserve Volume (IRV) :

- Around 2-3 L.
- The volume of air taken in by maximal inspiratory effort over and beyond normal TV.

Expiratory Reserve Volume (ERV) :

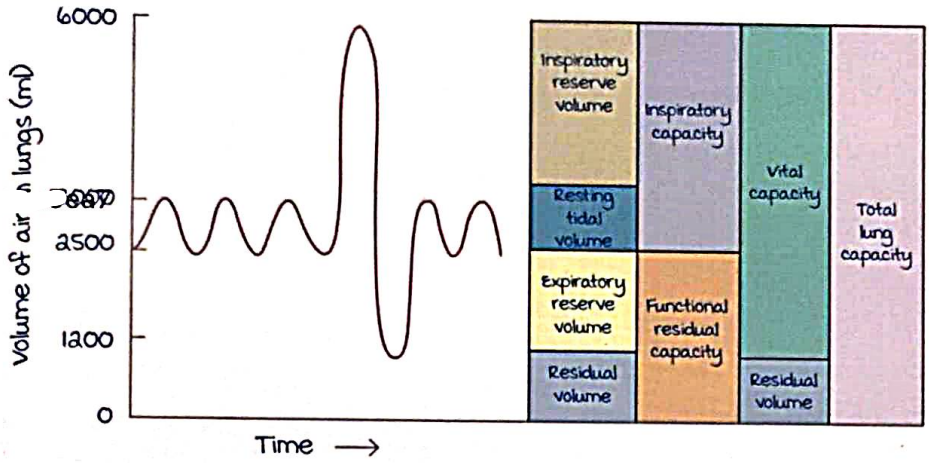
- Around 1.3 L.
- The volume of air moved out by maximal expiratory effort over and beyond the TV.

Residual Volume (RV) :

- Around 1.2 L.
- The volume of air remaining in the lungs even after maximal expiration.

Lung Capacities

00:10:39



Inspiratory Capacity (IC) = TV + IRV.

Functional Residual Capacity (FRC) = ERV + RV.

Around 2.5 L.

Vital Capacity (VC) = TV + IRV + ERV.

Around 3.8–4.5 L.

Total lung Capacity (TC) = TV + IRV + ERV + RV.

Around 5–6 L.

From the above, we can infer that FRC is around 50% of TLC

FRC is the volume of the lung at the midpoint (equilibrium point).

Hence, FRC is also known as equilibrium volume.

FRC is volume of air left at the end of normal expiration.

Miscellaneous static volumes :

Closing Volume (CV) :

The volume of air that is present in the alveoli in most dependant region of lung. Such alveoli begins to close near the end of expiration, entrapping some air.

Closing Capacity (CC) = CV + RV.

Methods to record FRC

00:16:49

RV cannot be measured by routine spirometry.

Hence, FRC and TLC cannot be measured by routine spirometry either.

Other methods used to record FRC which include :

- Helium dilution method (only of historical significance).
- Nitrogen washout method (only of historical significance).
- Body plethysmography (the most widely used clinical method).

Principle of body plethysmography :

Subject placed in an enclosed chamber → Breathes air in the chamber → volume changes in the lung are measured → pressure changes in the mouth are measured by special transducer.

According to Boyle's law, pressure exerted by a gas is inversely proportional to its volume.

During inspiration : $P \propto (1/V)$.

	Volume	Pressure
Lungs	Increases	Decreases
Chamber	Decreases	Increases

Opposite holds true for expiration.

FRC can be calculated using the formula :

$$P_{m^i} \times V_{L^i} = P_{m^f} \times (V_{L^i} + \delta V)$$

Where,

P_{m^i} : Initial pressure at the mouth.

V_{L^i} : Initial volume at the lung (FRC).

P_{m^f} : Final pressure at the mouth.

V_{L^f} : Final volume at the lung.

δV : Change in Volume.

Q. Patient in a body plethysmograph breathes normally through a mouthpiece. At the end of a normal expiration, a valve in the mouthpiece is closed. The inspiratory effort lowers the pressure at the mouth by 10 mmHg and expands the gas in the lungs by 50 ml. What is the patient's FRC measured with this technique?

Active space

Explanation :

Initial pressure in the mouth is the atmospheric pressure unless stated otherwise.

$$P_{m^i} = \text{Atmospheric Pressure} \sim 760 \text{ mmHg}$$

$$P_{m^i} \times V_{L^i} = P_{m^f} \times (V_{L^i} + \delta V)$$

Using this equation,

$P_{m^i} = 760$ mmHg

$V_{L^i} = FRC$

$P_{m^f} = (760 - 10)$ mm of Hg

$= 750$ mm of Hg

$\delta V = 50$ ml

$$P_{m^i} \times V_{L^i} = P_{m^f} \times (V_{L^i} + \delta V)$$

$$760 \times FRC = 750 \times (FRC + 50)$$

$$760\ FRC = 750\ FRC + 750 * 50$$

$$10\ FRC = 37500$$

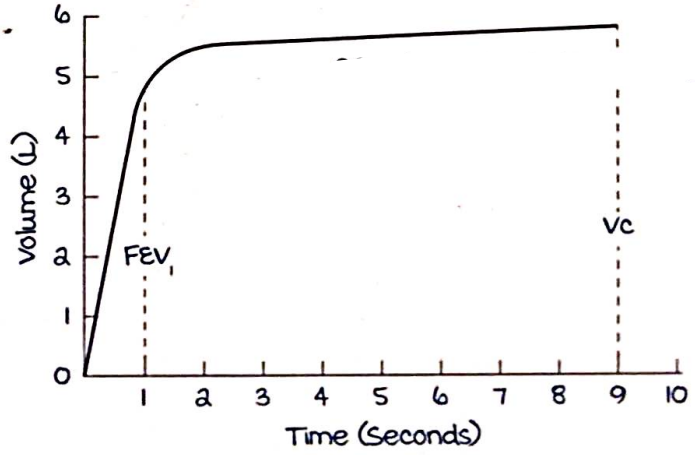
$$FRC = 3750 \text{ ml} = 3.75 \text{ L.}$$

Dynamic lung volumes & capacities 00:32:49

Time-dependant measurements. Essential for diagnosis.

Ask subject to take deep inspiration → fast and forceful expiration for 6 seconds. Ex : Forced Vital Capacity in 6 seconds (FVC_6).

Important is fast, forceful expiration in first second → Forced Expiratory Volume in the first second (FEV_1).



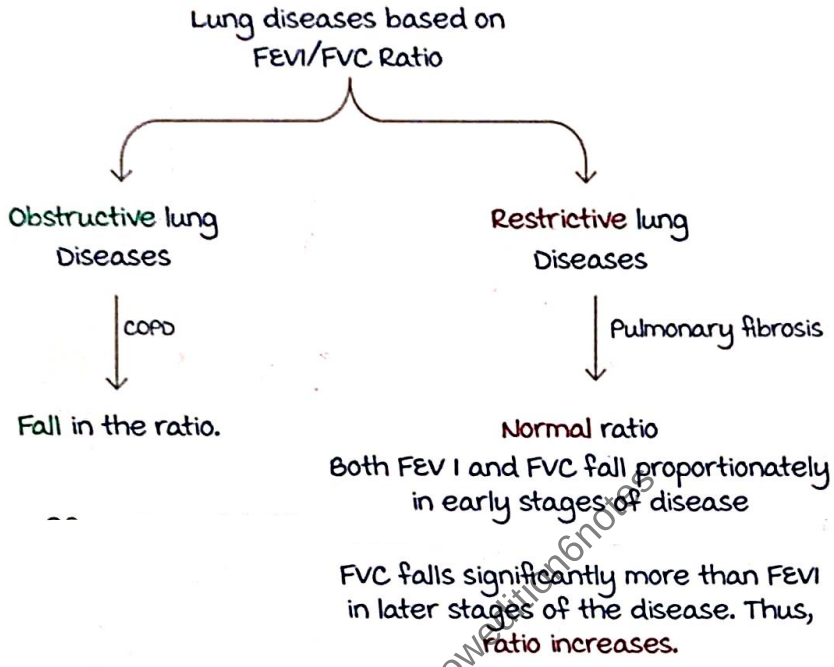
Active space

Significance of FEV_1 : Healthy individual expires (70-80) % of air in the first second.

FEV_1/FVC Ratio :

Also known as Tiffeneau-Pinelli's Index.

Normal value is 70-80 % .



Flow-Volume graph 00:41:48

Essential for diagnosing lung disorders.

Graph is plotted after subject takes deep inspiration & expires fast & forcefully.

Airway - expiration relationship :

Effort dependant : Large airways.

Effort independent : Medium and small airways which are affected in COPD.

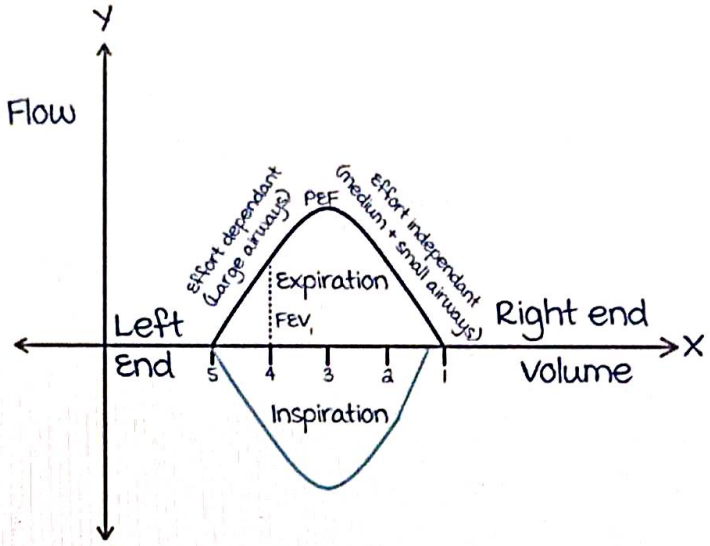
Left end = TLC = 5L.

Right end = RV = 1.2L

PEF : Peak Expiratory Flow Rate.

FVC = TLC − RV = 3.8L (5L − 1.2L)

FEV_1 : Volume corresponding to the first second.



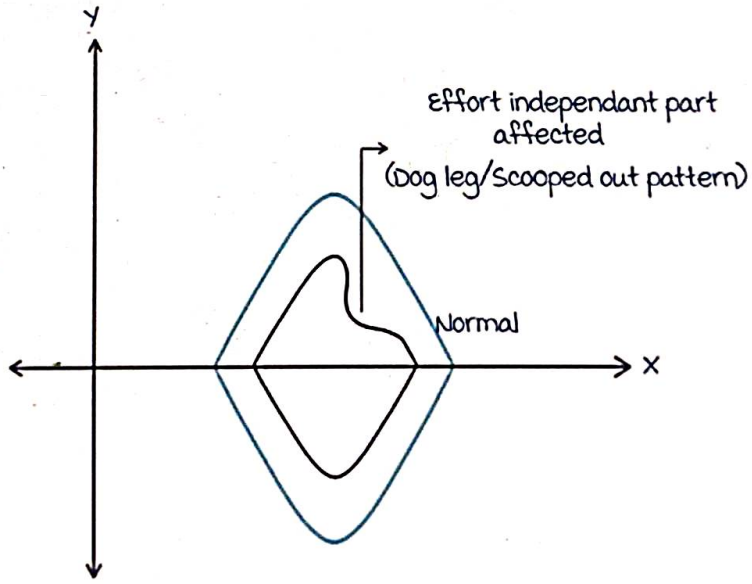
Variations in the graph :

1. COPD

Inspiration : Normal.

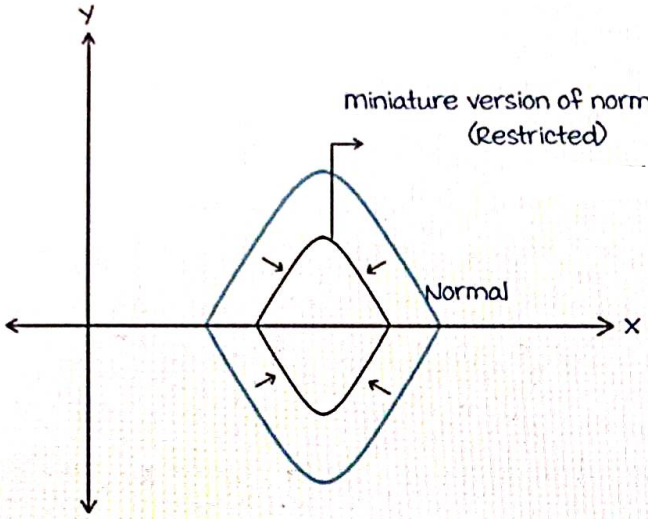
Effort dependent part : Normal.

Effort independent part affected : Dog leg pattern or scooped out pattern.

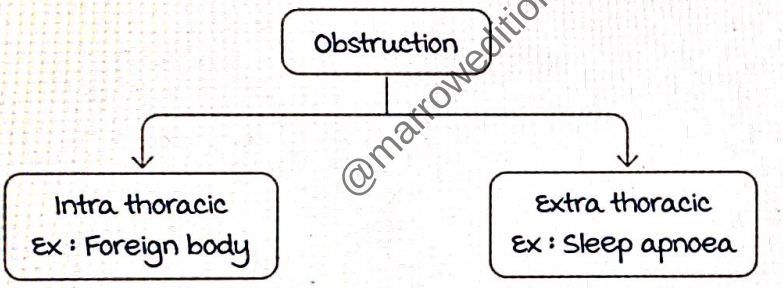


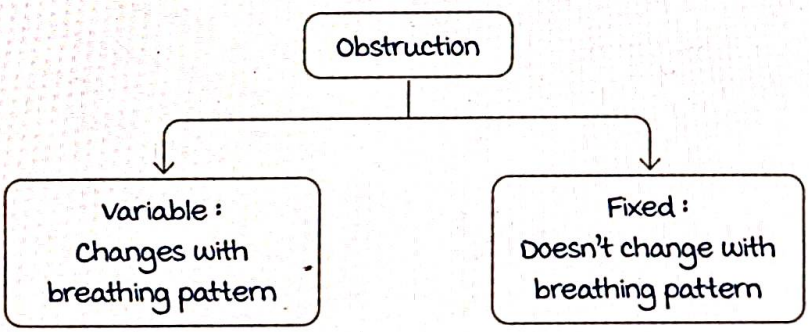
2. Pulmonary fibrosis :

Graph appears like a miniature version of the normal graph. Lung expansion is restricted. Seen in restrictive lung diseases.



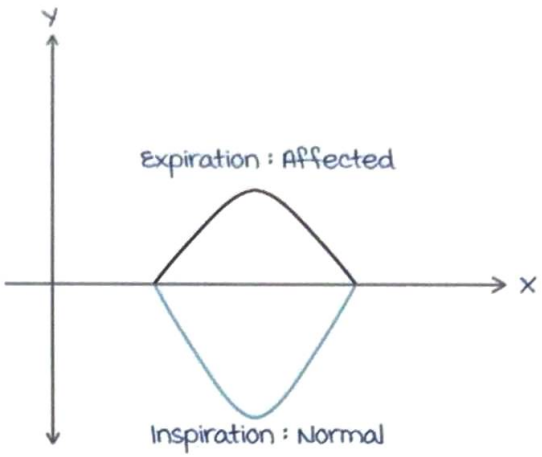
Other obstructions can also be diagnosed using the graph.



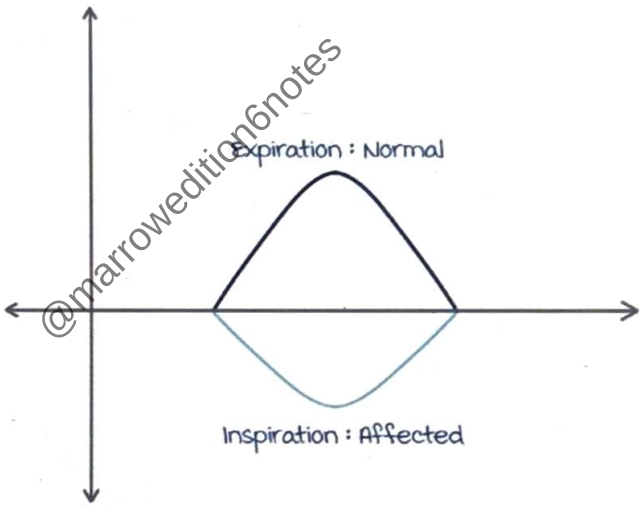


Active space

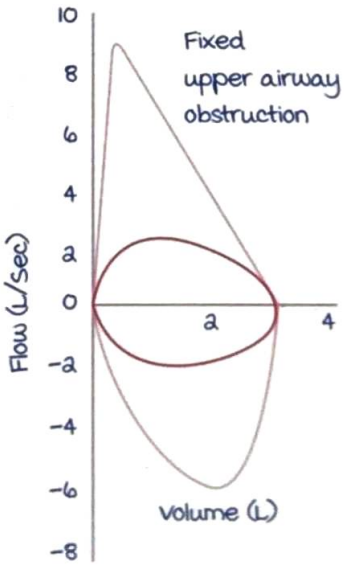
Inspiration normal, expiration affected : Variable intrathoracic obstruction.



Inspiration affected, expiration normal : Variable ~~extrathoracic obstruction~~.



Both inspiration and expiration affected : Fixed obstruction.



Active space

Clinical scenarios

00:58:58

Q. A 50-year-old white male presenting to the Emergency Department with acute onset shortness of breath. He had similar symptoms approximately 2 months ago with an acute, Chronic Obstructive Pulmonary Disease (COPD) exacerbation requiring hospitalization. What changes in pulmonary function testing is expected in him?

A. Increase in FEV1/FVC ratio.

B. No change in FEV1/FVC ratio.

C. Fall in FEV1/FVC ratio.

D. Increase in FEV1.

Q. What is the air remaining in lung after normal expiration is called?

A. Tidal volume.

B. Residual volume.

C. Functional residual capacity.

D. Vital capacity.

Q. Regarding pulmonary function test all are true, except ?

A. Total lung volume increases in emphysema.

B. Compliance decreases in interstitial lung disease.

C. Compliance is total lung distensibility.

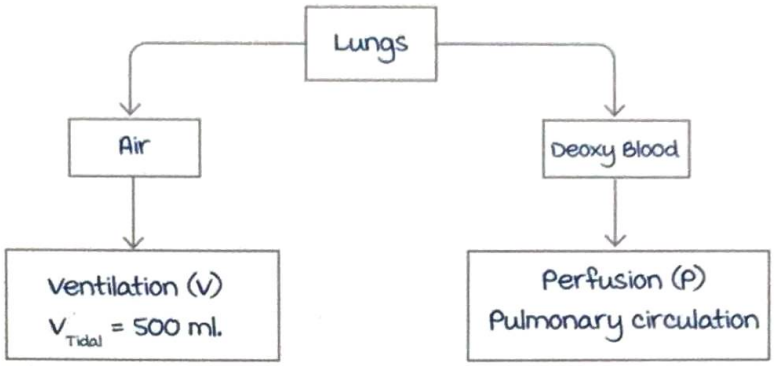
D. FEV_1 is forced expiratory rate at one minute.

TLC depends on lung distensibility/lung compliance.

Explanation : FEV_1 is the Forced Expiratory Rate after one second of forceful expiration.

Active space

ALVEOLAR VENTILATION AND PULMONARY CIRCULATION



Ventilation

00:02:33

Air we breathe is the environmental air.

Composition of environmental air :

Total pressure aka Atmospheric pressure (760 mmHg).

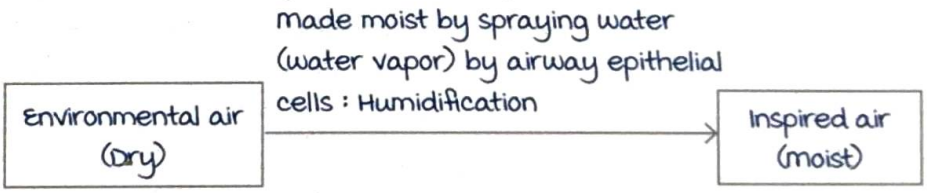
- Nitrogen : 79 %.
- Oxygen : 21% (Fractional concentration of Oxygen : 0.21)
- Carbon dioxide : Nil/negligible.

Partial pressure (PP) :

Pressure exerted by individual gases in the environment.

PP of oxygen (PO_a) : 160 mmHg (21% of 760 mmHg).

In environmental air, PO_a of oxygen : 160 mmHg.



In common cold, humidification does not happen due to inflammed airway epithelium. Patient breathes dry air.

Inspired air :

- Also called humidified air.
- Water vapor pressure (PH_aO : 47 mmHg). Dilutes O_a
- PP of inspired oxygen (Pio_a) : 150 mmHg due to dilution.

Active space

Alveolar air 00:10:28

Inspired air moves to alveoli (exchange airways).

- PO_a in alveolar air (P_AO_a) : 104 mmHg.
- P_AO_a calculated by alveolar gas equation :
  $P_AO_a = PiO_a - (P_ACO_a/RER)$.
  PiO_a : Partial pressure of oxygen in inspired air.
  P_ACO_a : Partial pressure of CO_a in alveolar air. Used interchangably with P_aCO_a : Partial pressure of CO_a in blood.
- Respiratory exchange ratio (RER) : Volume of CO_a produced/Volume of O_a consumed $\frac{VCO_a}{VO_a} = 0.8$
- PiO_a (Inspired air) = $FiO_a (P_B - PH_aO)$.
  FiO_a : Fractional concentration of oxygen = 0.21
  P_B : Atmospheric/barometric pressure = 760 mmHg.
  PH_aO : Water vapour pressure = 47 mmHg.

Q. A 62 year old man with severe respiratory distress is placed on ventilator with an FiO_2 of 0.5. His arterial blood gas sample reveals a PO_2 of 160 mmHg and a PCO_a of 40 mmHg. Calculate the alveolar oxygen tension, at a barometric pressure of 747 mmHg and a respiratory exchange ratio (R) of 0.8 ?

Here, $P_AO_a = 0.5 (747 - 47) - 40/0.8$
$= 350 - 50 = 300$ mmHg.

$$P_AO_a = P_IO_a - \frac{P_{ACO_a}}{RER}$$

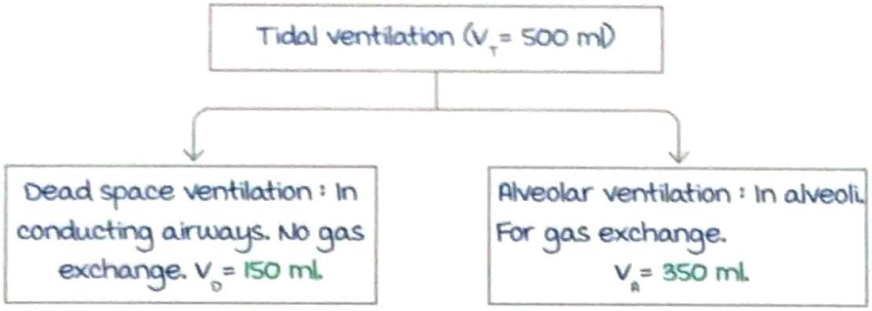
Alveolar arterial oxygen gradient : $P_{A-a}O_a$ gradient
$300 - 160 = 140$ mmHg.

- Expired air P_EO_a = 120 mmHg (16% oxygen).
  Therefore, mouth to mouth respiration provides 16% O_a.

Minute ventilation 00:23:33

Tidal volume x respiratory rate/minute = 500 x 12 = 6 L/min.

Active space



Dead space ventilation :

3 types :

1. Anatomical dead space (ADS) :
   In conducting airways (trachea, bronchi) ADS = 150 ml.
2. Alveolar dead space (AlvDS) :
   Always pathological, absent in healthy individuals.
3. Physiological dead space (PDS) :
   PDS = ADS + AlvDS. Also called as Total dead space.
   In healthy individuals, ADS = PDS = 150ml (since alveolar dead space is zero).

Measurement

00:30:37

- Anatomical dead space :
  By single breath nitrogen method.
  Also called fowler's method.
- Physiological dead space :
  measured using Bohr's equation.
  $V_D = V_T [(P_ACO_a - P_ECO_a)/P_ACO_a]$.
  V_D : Dead space.
  V_T : Tidal volume.
  P_ACO_a : Partial pressure of CO_a in alveolar air.
  P_ECO_a : Partial pressure of CO_a expired air.

Q. If tidal volume is 500 ml, P_ECO_a is 30 mmHg and P_ACO_a is 45 mmHg, calculate the dead space ?

So, $V_D = 500 \times (45 - 30)/45$

$V_D = 500 \times 0.33$

$V_D = 167$ ml

- V_D/V_T ratio normally is 0.3 (150/500) = Bohr's equation.
  Dead space/tidal volume = $(P_ACO_a - P_ECO_a)/P_ACO_a$.

Active space

- Alveolar ventilation (V_A) : Useful ventilation (gas exchange)

  V_A/min = 350 ml x Respiratory rate/minute

  350 x 12 = 4 litres/min.

  V_A/min = (T_V – DS) x Respiratory rate/minute.

  = (500–150) x 12 = 4litres/minute.

Blood perfusion

00:38:42

Pulmonary circulation/min : 5L/min (Entire right heart output : Deoxygenated blood).

Pulmonary circulation is highly distensible (high compliance) low pressure circulation.

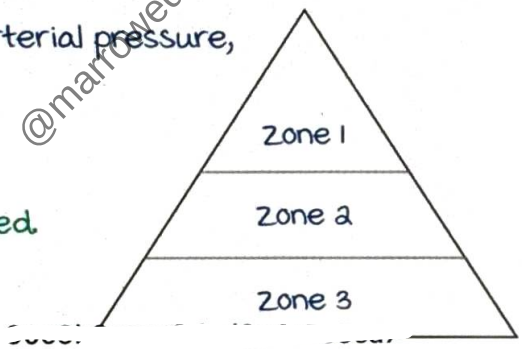
Components :

- Pulmonary artery : Carries deoxygenated blood to lung.
- Pulmonary capillaries : Oxygenation.
- Pulmonary veins : Carries oxygenated blood to heart.

Pulmonary blood flow happens in zones.

3 zones of lung :

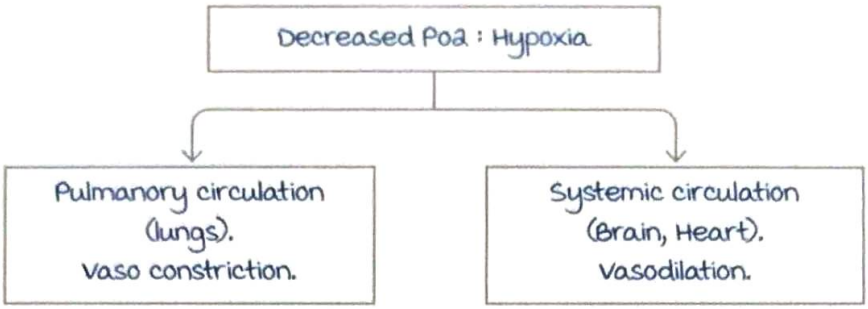
P_A: Alveolar pressure, P_a: Arterial pressure, P_v: Venous pressure.



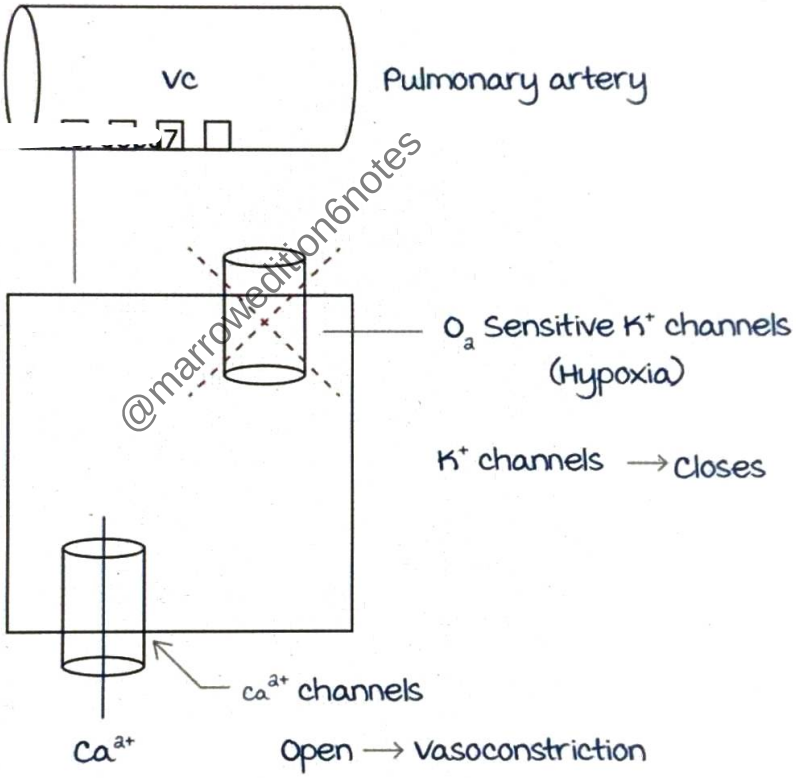
- Zone 1 : $P_A > P_a > P_v$.
  Blood vessels compressed.
  Apex of lung.
  Zone of no blood flow.
- Zone 2 : $P_a > P_A > P_v$.
  Intermittent flow (waterfall effect).
  Middle region of lung.
- Zone 3 : $P_a > P_v > P_A$.
  Continuous flow (maximum blood flow).
  Base of the lung.

Unique features of pulmonary circulation

00:46:22



Hypoxia induced vasoconstriction :
Mechanism seen only in lungs because O_a sensitive potassium channels are specific for lungs.



O_a sensitive potassium channels in response to hypoxia closes → Accumulation of K^+ (positive charge) → Deoplarization → Ca^{a+} channel opens → Influx of Ca^{a+} → Vasoconstriction of blood vessel.

MCQs :

Q. Ratio that is used to find out the proportion of ventilation remains in dead spaces is?

A. FEV1/FVC ratio.

B. RV/TLC ratio.

C. Vt/Vd ratio.

D. Vd/Vt ratio.

Q. All of the following statements are true regarding pulmonary circulation except ?

A. Low resistance.

B. Low pressure.

C. Low compliance.

D. Hypoxia inducing vasoconstriction.

Q. Hypoxia inhibits which current in pulmonary vascular smooth muscles ?

A. Sodium.

B. Calcium.

C. Potassium.

D. Chloride.

Active space

VENTILATION PERFUSION RATIO

Ventilation perfusion mismatch will lead to diseases.

Normal V/Q ratios

00:01:24

$$V/Q \text{ ratio} : \frac{\text{Ventilation (V)}}{\text{Perfusion (Q)}} = \frac{4L/min}{5L/min} = 0.8 \text{ (normal V/Q ratio).}$$

Normal V/Q ratios :

- Apex of lung : 3.2 (highest ratio).
  - Alveoli are big.
  - Less compliant.
  - Fall in perfusion > Ventilation.
  - Less gas exchange (high PaO_2, low PCO_2).
  - Mycobacterium tuberculosis flourishes in this area.
- Middle of lung : 0.8.
- Base of lung : 0.6 (lowest ratio).
  - Small alveoli.
  - Highly compliant.
  - Increase in perfusion is more than ventilation
  - Region of maximum blood flow.

Ventilation perfusion mismatch

00:09:48

- If Q=0, then V/Q = infinity :
  - No blood flow or perfusion.
  - Wasted ventilation : Only air flow is present in the absence of blood flow.
  - There is no gas exchange.
  - V/Q = Infinity is seen in :
    - Physiological : Anatomical dead space.
    - Pathological : Pulmonary embolism.

- If V = 0, then V/Q = 0

  No air flow or ventilation.

  Wasted perfusion : Only blood flow is present in the absence of air flow.

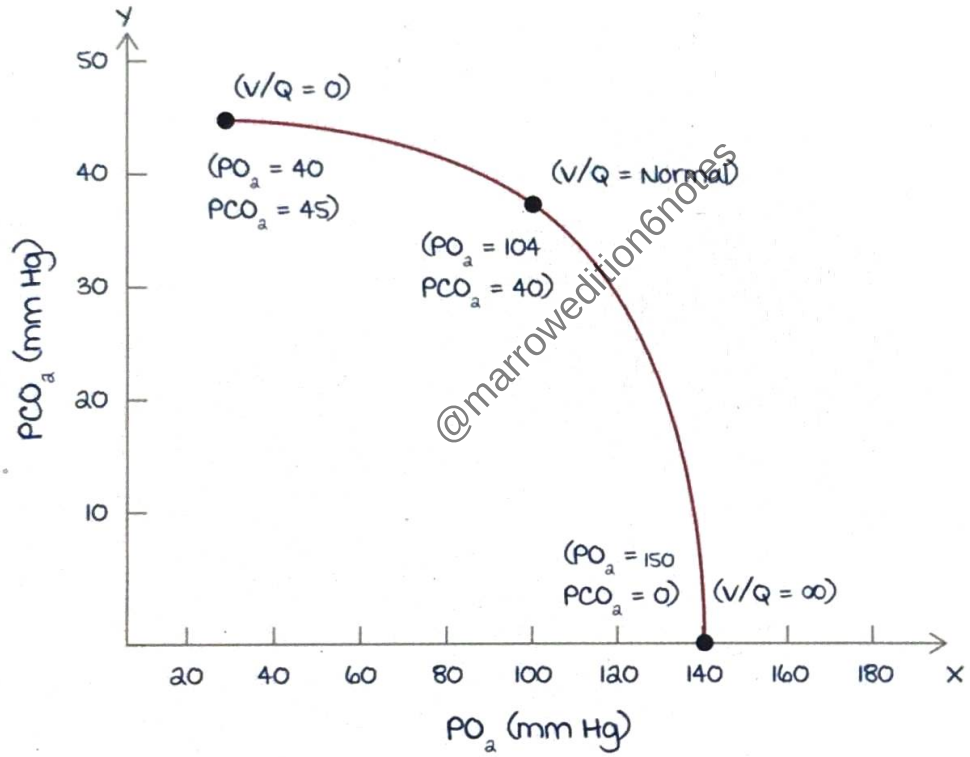
  No gas exchange.

  Seen in

  Physiological : Shunt blood : 2% of cardiac output.

  Pathological : Foreign body obstruction of airways (obstructed airways collapse).

Ventilation perfusion diagram: O2-CO2 diagram 00:16:28



- From the point of normal towards left :

  PO_a is falling, PCO_a is rising.

  V/Q ratio falls.

- From the point of normal towards right :

  PO_a is rising, PCO_a is falling.

  V/Q ratio increases.

Q. Pathological causes of non uniform ventilation are all except ?

A. Collapse of lung (emphysema).
B. Foreign body obstruction.
C. Compression of airways by tumour.
D. Pulmonary embolism.

Q. Oxygenation of shunt blood doesn't occur because ?

A. There is no perfusion.
B. There is no ventilation.
C. There is high perfusion.
D. There is high ventilation.

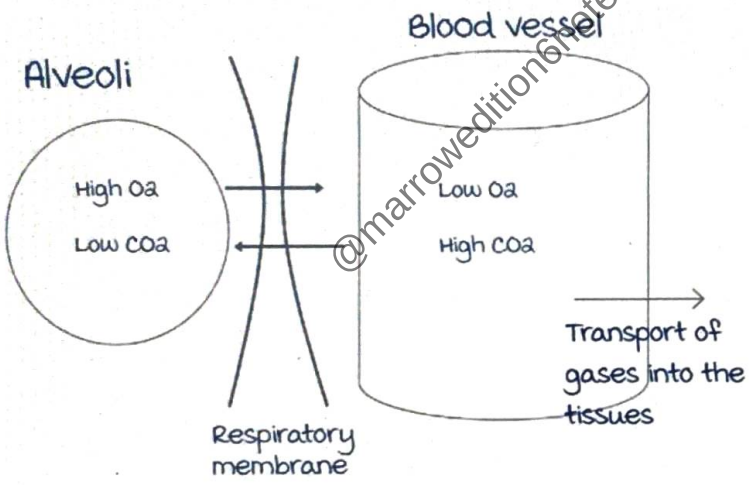
Q. Alveoli at the apex of the lung are ?

A. more compliant.
B. more ventilation.
C. more gas exchange.
D. Larger.

DIFFUSION AND TRANSPORT OF GASES

Diffusion is the process of gases moving from higher concentration to lower concentration.
The gases must cross a barrier in between the alveoli and blood vessel in the lung, which is in the form of a membrane called respiratory membrane.
Blood in the blood vessel stays for around 0.75 seconds, therefore, the entire process of diffusion must takes place in between this 0.75 second time gap.

Following diffusion oxygen needs to be transported to the tissues, therefore the need for transport of gases.



Diffusion of gases

It is a passive process, no need for ATP.
It is the simplest of all the transport processes, hence called simple diffusion.
According to Fick's law, Diffusion (D) α Concentration gradient
i.e., gases move from high concentration to low concentration.
The area of the respiratory membrane is very important, as it is the available surface area for diffusion,
therefore, D α Area.

$$D \propto \frac{1}{\text{membrane thickness}}$$

$$D \propto \frac{\text{Solubility (Lipid)}}{\text{Size of particle.}}$$

When there is decrease in membrane surface area, there will be decrease in diffusion.
Seen in patients with α_1-Antitrypsin deficiency, due to which they will have trypsin overactivity.
Trypsin is a protease i.e., it destroys the respiratory membrane causing a decrease in surface area leading to a decrease in diffusion of gases leading to emphysema.

When there is an increase in membrane surface thickness, there will be decrease in diffusion.
Seen in pulmonary fibrosis, where the pulmonary membrane is fibrotic and thicker.

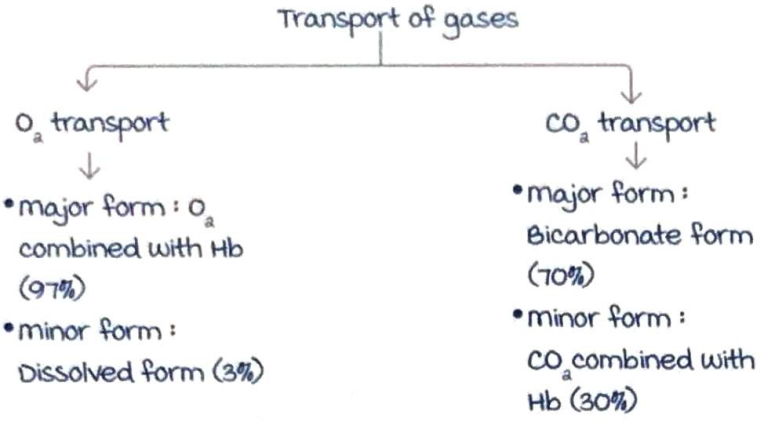
Diffusion is measured using the DLCO test (Diffusion ~~Capacity of lung for Carbon~~ monoxide).
Carbon monoxide is the preferred gas due to its very high affinity to Hb (210 times more affinity) causing faster diffusion as compared to O_a and CO_a.
Normal DLCO = 25 ml/min/mmHg.

Increase in DLCO may be caused by pathological increase in RBC, leading to more CO binding with Hb as seen in polycythemia.
Increase in DLCO may also be due to physiological causes like in exercise which increases diffusion of CO.

Decrease in DLCO is seen in emphysema due to decrease in area.
Decrease in DLCO is also seen in pulmonary fibrosis due to increase in thickness of respiratory membrane.
Decrease in DLCO is also seen in anemia, as RBC's are less in number leading to decreased CO binding with Hb.
Comparing diffusion of O_a and CO_a, $O_a <<< CO_a$.
This is due to increased solubility of CO_a, 20 times more compared to O_a.

Active space

Transport of gases 00:17:26



O_2 transport :

As the major form of O_2 transport is combined with Hb, 1 g of Hb can transport 1.34 ml of O_2.

A representative adult male, for 15g of Hb will transport 15 x 1.34 ml = 20.1 ml of O_2/100 ml of blood.

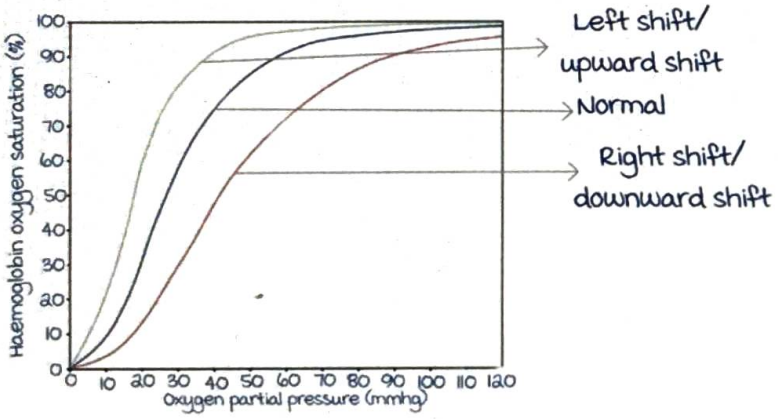
Dissolved form of O_2 transport is extremely important as it determines partial pressure of O_2.

Through this form we transport 0.3 ml of O_2/100ml of blood.

Presence of Hemoglobin, increase O_2 transport by 70 times.

Oxygen dissociation curve/ODC 00:23:17

O_2-Hb relationship can be studied with a curve called Oxygen Dissociation Curve (ODC).



ODC is the curve plotted between partial pressure of oxygen on x-axis v/s hemoglobin oxygen saturation on y-axis.

PO_2 = 100 mmHg : Plateau i.e., at this PO_2 no more Hb available to combine with O_2.

O_2-Hb saturation is 50% at PO_2 = 27 mmHg, this is called the P_{50} value.

Active space

P_{50} value = 27 mmHg means it is the PO_2 at which 50% of Hb is saturated.

In left shift there is a decrease in P_{50} value, whereas in right shift there is an increase in P_{50} value.

The normal ODC curve is 's'/sigmoid shaped.

This is because :

1 molecule of Hb carries 4 molecules of O_2.

The first O_2 molecule finds difficulty in binding with Hb, this is because this form of Hb exists as T-Hb (Tight Hb). The first O_2 therefore binds by breaking salt bridges thus, converting T-Hb into R-Hb (Relaxed Hb). This makes it easier for the other three O_2 molecules to come bind to Hb. This process is called cooperative binding kinetics, the first O_2 cooperates the binding of the remaining 3 molecules.

Cooperative binding is the suggested reason why the ODC is sigmoid in shape.

ODC : Right shift/left shift

00:32:18

O_2 → Hb → O_2

Binding of O_2	Release of O_2
High affinity	Low affinity
Loading of O_2	Unloading of O_2
In the lungs.	In the tissues.
Left shift of ODC.	Right shift of ODC.

Haldane effect & Bohr's effect

00:35:21

Loading of O_2 —(Lungs)→ Hb → Unloading of CO_2

Haldane effect is the loading of O_2 to Hb leading to unloading of carbon dioxide, happening in the lungs.

Bohr's effect is the release of O_2 at the level of tissues.

Right shift of ODC

00:37:28

Right shift indicates release of O_2 at the level of tissues.

Seen in :

Active space

- Hypoxia : Low level of O_a.
  ↓
- Hypercarbia : High levels of CO_a.
  ↓
- Acidosis : Fall in pH/increase in H^+ ions.
- Any tissue undergoing hypoxia will have anaerobic glycolysis. Important intermediate product of glycolysis is 2,3 diphosphoglycerate/2,3 DPG.
  Rise in levels of 2,3 DPG is the most important cause for right shift.
- Prolonged hypoxia at high altitudes can lead to right shift.
- Release of O_a, especially during exercise.

Increase in 2,3 DPG & acidosis cause right shift, however chronic/long standing acidosis inhibits glycolytic enzymes causing a fall in 2,3 DPG.

Left shift of ODC 00:43:10

Left shift : loading of O_a.

Seen in :

- Hypocarbia : Fall in CO_a.
  ↓
- Alkalosis : Increase in pH, fall in H^+ ions.
- Fetal Hb/HbF : Left shift is a high affinity state, fetal Hb has a very high affinity to O_a and low affinity to 2,3 DPG.
- Carbon monoxide.
- Stored blood before blood transfusion, there is inhibition of glycolysis and fall in 2,3 DPG.
  This can be circumvented by storing blood in CPDA/Citrate Phosphate Dextrose Adenine, as blood stored in CPDA has shown to have less fall in 2,3 DPG.

Myoglobin (Mg) 00:47:56

It is a closely related protein to Hb, exclusively for storage.

It is seen in muscles.

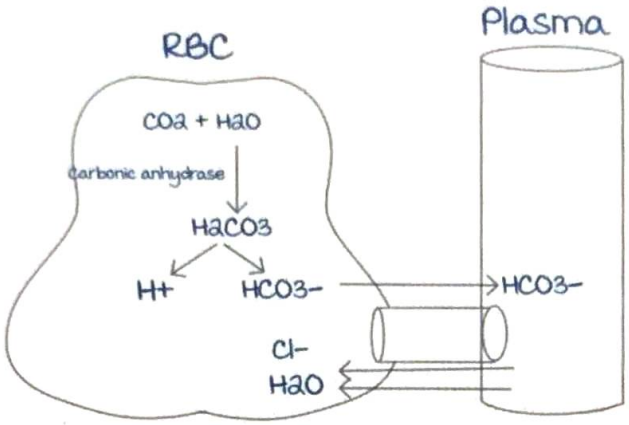
1 molecule of Mg carries 1 molecule of O_a (Ratio is 1 : 1).

The O_a-Mg ODC curve is rectangular hyperbola as there is no need for cooperative binding.

CO_2 Transport

00:49:33

70% of CO_2 transport is in the form of bicarbonate ion.



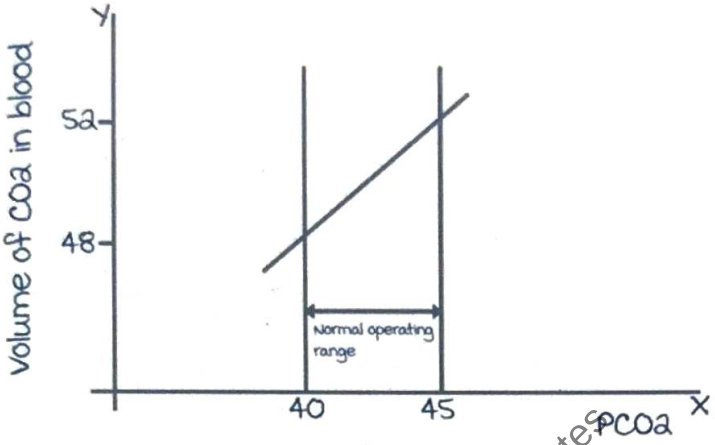
CO_2 in RBC combines with a molecule water to form carbonic acid. It is catalyzed by carbonic anhydrase/CA enzyme.
The carbonic acid will split into H^+ ion and bicarbonate ion.
The bicarbonate ion is moved into plasma by the RBC, from where it gets transported.
To maintain neutrality in the RBC as one negative ion is expelled, there must be entry of one negative ion inside : Cl^- ion. This is called as Chloride shift/Hamburger phenomenon.
This happens in RBC because of an important channel protein $Cl^- - HCO3^-$ Exchanger/Anion exchanger (AE).
The chloride moved inside is osmotically active, drags a water molecule inside and causes RBC to swell. This occurs in the venous blood, therefore PCV of venous blood = 3% more.
So, one side bicarbonate is moved.
The H^+ ions on the other side are buffered by Hb.
Hence RBC has an excellent buffer : Hb.

30% of CO_2 is transported combined with Hb, CO_2–Hb/ Carbaminohemoglobin.
Carboxyhemoglobin is Carbon monoxide combined with Hb (CO-Hb).

CO_2 dissociation curve

00:56:52

PCO_a in the venous blood is 45 mmHg.
This corresponds to CO_a value of : 52 ml CO_a/dl of blood.
PCO_a in the arterial blood is 40mmHg.
This corresponds to CO_a level of 48 ml CO_a/dl of blood.
Therefore 52-48 ml = 4 ml is the amount of CO_a usually transported.



Q. Conditions that increase diffusion capacity (DLCO) except ?
A. Polycythemia.
B. Alveolar haemorrhage.
C. Exercise.
D. Emphysema.

Q. Which of the following binds with β chains of hemoglobin causing more O_a to be released at tissues ?
A. Citrate.
B. Acetate.
C. 2,3 DPG.
D. Acetoacetate.

Q. When oxygen binds with hemoglobin, carbon dioxide is released at lungs. This is ?
A. Bohr's effect.
B. Haldane's effect.
C. Hamburger phenomenon.
D. Boyle's Law.

Active space

NEURAL REGULATION OF RESPIRATION

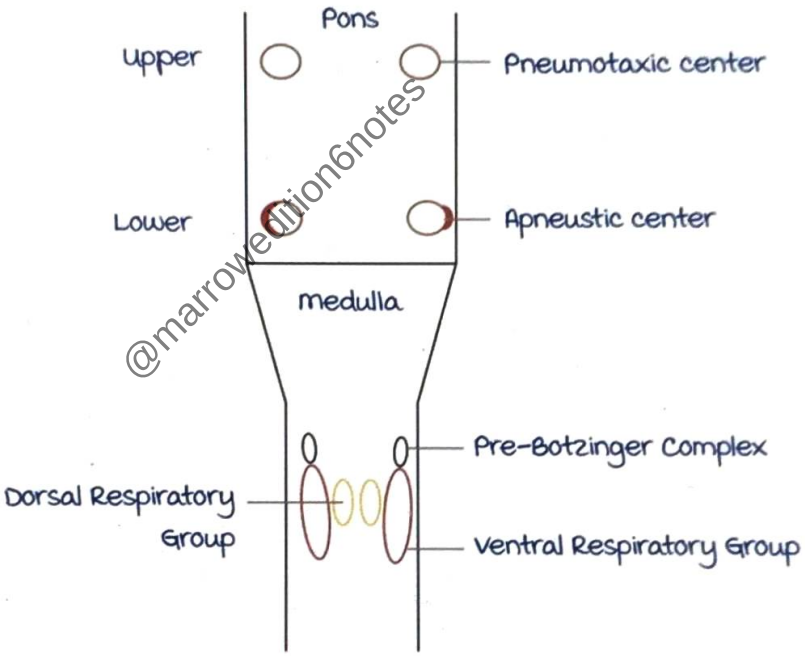
Regulation of respiration 00:00:33

Neural control (regulating areas in brain) :

- Pons : 2 groups of respiratory neurons.
- Medulla : 3 groups of respiratory neurons.

Chemical control :

- Changes in oxygen, carbon dioxide and H^+ vaules regulate respiration.
- Chemoreceptors mediated regulation.



Neural centers :

Pons :

1. Upper part of pons : Pneumotaxic center.
2. Lower part of pons : Apneustic center.

Medulla :

1. Dorsal respiratory group.
2. Ventral respiratory group.
3. Pre Botzinger complex (pacemakers for respiration : Located in ventral part above VRG).

Functions :

Pons :

1. Pneumotaxic center :
   Limits inspiration by inhibiting apneustic center.
   Increases respiratory rate (secondary effect).
2. Apneustic center :
   Prolong inspiration (increases depth of inspiration).

Medulla :

1. Pre Botzinger complex : Pacemaker (involuntary).
   Side effect of opioids : Respiratory depression by inhibiting pre Botzinger complex.

Mnemonic : DIVE

2. Dorsal respiratory group controls Inspiration.
   Generates ramp signal → Smooth rise in tidal volume (during inspiration)
3. Ventral respiratory group controls Expiration.
   Expiration is a passive process at rest.
   Therefore, needed only during forceful expiration (active process mainly during exercise).
   Extra-respiratory drive during exercise : Over-drive phenomenon.

Integration of neural areas

00:12:40

Inspiration :

Pre Botzinger complex → Signal from medulla to spinal cord → Activates phrenic nerve (C3, C4, C5) → Diaphragmatic contraction → Initiation of inspiration.
Death is inevitable if this circuit is disrupted (seen in hanging/critical injuries to medulla).

Maintenance of insipiration :
Apneustic center → Activates dorsal respiratory group → Generates ramp signal → Smooth increase in tidal volume → Tidal volume reaches 500 ml → Maintenance of inspiration.

Active space

Termination of inspiration :

1. Pneumotaxic center → Inhibits apneustic center → Termination of inspiration (central source of inhibition).

2. Tidal volume reaches 500 ml → Stretches lung → Activates vagal afferents → Inhibits apneustic center. (peripheral source of inhibiton)

Complete inhibition of apneustic center occurs if both the sources are present.
Partial termination occurs if only one source is present.
If apneustic centre is inhibited, dorsal respiratory group is automatically inhibited.

Expiration

00:21:15

Passive process at rest.
Forceful expiration (exercise) needs ventral respiratory group.

- Medulla : Initiates respiration (presence of pacemaker).
- Pons : Regularizes respiration.

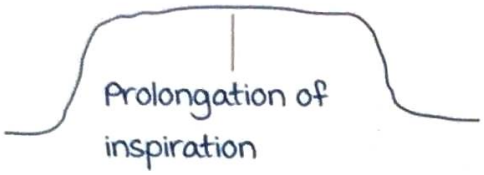
Lesions :

1. Lesion below medulla :
   - Death is inevitable.
   - Circuit between pre Botzinger complex and phrenic nerve is cut.
   - Involuntary respiration is very essential during sleep. Absence of pre Botzinger complex → Respiration becomes voluntary → If they sleep, they die (Ondine's curse).
   - Treatment : Provide mechanical ventilation during sleep.

2. Lesion at ponto-medullary junction :
   - Initiation is normal, regularization of respiration does not happen → Irregular respirations.

3. Lesion at mid pons with cut vagus nerve :
   - Apneustic center (a source of inhibitions) : Pneumotaxic center and vagus nerve.

Lesion at mid pons → Pneumotaxic center cannot inhibit apneustic center.
Vagus nerve cut → No inhibition to apneustic center.
This leads to constant stimulation to apneustic center → Prolongation of inspiration (apneustic spasm).



Pulmonary reflexes 00:30:55

Normal tidal volume : 500 ml (lungs stretch).
Maximum tidal volume : 1500 ml (lungs overstretch causing lung injury. This is protected by a reflex).

Hering Bruer reflex (protective reflex) :

- Hering Bruer inflation reflex : Overstretch lung injury prevented by this reflex.
  Hyperinflation → Hering Bruer reflex activated → Prolonged inspiration stops → Lung injury prevented → Expiration commences.
  This reflex stops inspiration, decreases duration of inspiration & increases expiratory duration.
- Hering Bruer deflation reflex :
  Prolonged expiration stopped → Inspiration continues.
  Prolonged expiration can cause lung collapse.
  Prevents lung collapse.
  Hering Bruer reflex is conveyed through myelinated vagal fibers (slow adapting).

Head's paradoxical reflex :

- Prolonged inspiration → Overstretch/Hyperinflation → Increases further inspiration (paradoxical).
  Opposite to Hering Bruer reflex.

Active space

- Newborn's first breath : Intrauterine life → Lung filled with fluid. At birth, fluid replaced with air → Inspiration prolongs to replace entire fluid → Head's paradoxical reflex.

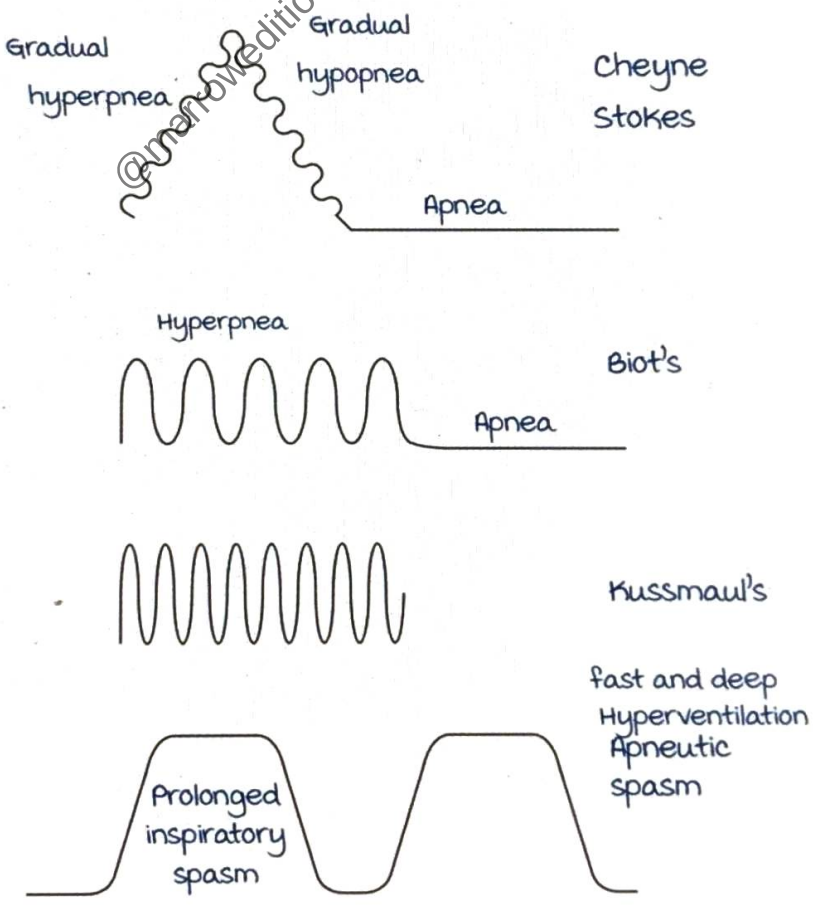
J-reflex :

- Pulmonary edema : C/o breathlessness.
- Pulmonary edema → Fluid comes out of pulmonary capillaries → Activates J-receptors (juxta position) → J-reflex → Apnea → Breathlessness → Hypotension → Bradycardia.
  - J-receptors were discovered by A.S Paintal (AIIMS physiologist).
  - Conveyed through unmyelinated vagal C-fibers.

Altered breathing patterns

00:43:04

Also called periodic breathing.



1. Cheyne Stokes respiration :
   Gradual hyperpnea - mode of hyperventilation (CO_2

washout) → Absence of respiratory centre stimulus → Gradual hypopnea → Apnea (CO_2 buildup) → stimulation of respitaory centre → next cycle of respiration.

Seen in :

- Normal (sleep).
- Congestive heart failure.
- Uremia.

2. Biot's/ataxic breathing:
   Hyperpnea → Apnea.
   Seen in :
   - Damage to medulla.
   - Meningitis.

3. Acidotic breathing/Kussmaul's breathing :
   Respiration is fast and deep (hyperventilation).
   Stimulated by acid.
   Seen in Diabetes.

4. Lesion at mid pons with cut vagus nerve :
   Prolonged inspiratory spasm (apneustic spasm).

MCQs

00:49:38

Q. Which of the following inhibit respiration by decreasing the activity of Pre Botzinger Complex?

A. Glutamate.
B. Norepinephrine.
C. Epinephrine.
D. Opioids.

Q. Which of the following reflexes prevents overdistension of lung alveoli at larger tidal volumes?

A. Hering Bruer deflation reflex.
B. Bezold Jarisch reflex.
C. Bainbridge reflex.
D. Hering Bruer inflation reflex.

Q. Which of the following reflex is activated by increase in the interstitial fluid volume of alveolar wall?

A. Hering Bruer Inflation reflex.

B. Cushing's reflex.

C. J reflex.

D. Mass reflex.

CHEMICAL REGULATION OF RESPIRATION

Chemicals 00:00:24

Changes in chemicals needed : Oxygen, carbon dioxide, H^+ ions.

Receptors : Chemoreceptors.

Brain (ventral surface of medulla, along floor of 4th ventricle) : Central chemoreceptors.
Neck (carotid + aortic bodies) : Peripheral chemoreceptors.

Central chemoreceptors :

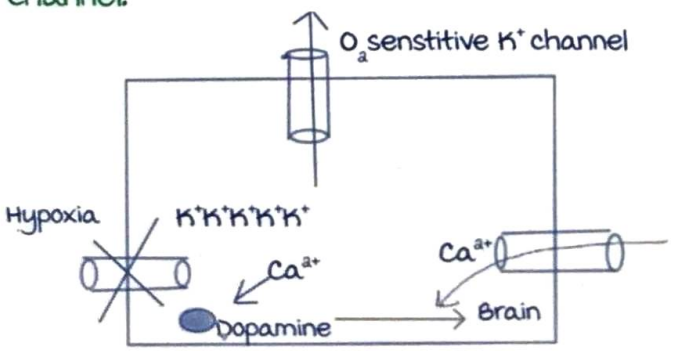
Exclusively sensitive to CO_a levels in blood (hypercarbia).
most important regulatory factor for respiration : CO_a.
CO_a can easily cross blood-brain-barrier but H^+ cannot.
$CO_a + H_aO \xrightarrow{\text{Carbonic anhydrase}}$ Carbonic acid $\rightarrow HCO3^- + H^+$.
H^+ in CSF stimulate central chemoreceptors directly.

Peripheral chemoreceptors 00:08:44

- Carotid bodies.
- Aortic bodies.

most sensitive to fall in oxygen levels (Hypoxia).
Oxygen sensor (glomus cells) seen in peripheral chemoreceptors.

- Glomus cell has an oxygen sensitive potassium channel.



	Central chemoreceptors	Peripheral chemoreceptors
Sensitive to	CO_a changes	O_a changes
Stimulus	Increase in H^+ ions/ decreased pH (acidosis)	Increase in H^+ ions/ decreased pH (acidosis)
	Decrease in blood pressure	Decrease in blood pressure

Hypoxia + hypercarbia + acidosis → Asphyxia → Chemoreceptors stimulated (central + peripheral) → Chemoreflex → Hyperventilation → CO_a washout → CO_a + H^+ fall and increased O_a (through increased intake of air).

Hypoxia

00:18:14

Types of hypoxia :

1. Hypoxic hypoxia.
2. Anemic hypoxia.
3. Stagnant hypoxia.
4. ~~Histotoxic hypoxia.~~

Hypoxic hypoxia :

- Fall in partial pressure of O_a: Determined by dissolved form.
- Fall in partial pressure of O_a → Fall in dissolved form → Peripheral chemoreceptors stimulated.
- Rx : O_a therapy highly beneficial.

Anemic hypoxia :

- Seen in anemic patients, carbon monoxide poisoning.
- PO_a normal (dissolved form is normal).
- Reduction in oxygen content (fall in hemoglobin).
- Peripheral chemoreceptors not stimulated.
- Increase in oxygen extraction from the available hemoglobin → Fall in mixed venous blood oxygen levels.

Stagnant hypoxia :

- Commonly seen in ischemic states (ischemic hypoxia).
- Ischemia → Tissue undergoes stagnation → Increased oxygen utilization → Arterio-venous oxygen difference increased.
- Stagnation → more amount of reduced hemoglobin → Cyanosis.

Histotoxic hypoxia :

- Commonly seen in cyanide poisoning.
- Cyanide → Inhibits cytochrome oxidase enzyme → Defective oxygen utilization → Carotid bodies unable to sense oxygen levels → Powerful signal for stimulating peripheral chemoreceptors.
- Peripheral chemoreceptors maximally stimulated in histotoxic hypoxia.
- Defective oxygen utilization → Arterio-venous oxygen difference decreased.

Chemical regulation of respiration 00:32:36

Central respiratory depression :

- Oxygen therapy not useful.
- Central respiratory depression → Hypoxic drive to breathing (most important stimulator) → Do not give oxygen therapy (abolishes the hypoxic drive).

MCQs :

Q. Peripheral chemoreceptors stimulation releases which neurotransmitter?

A. GABA.

B. Glycine.

C. Nitric Oxide.

D. Dopamine.

Active space

Q. Central chemoreceptors are mainly stimulated by ?

A. PO_a.

B. PCO_a.

C. H^+ ions.

D. Acetoacetate.

Q. Oxygen carrying capacity of arterial blood is reduced in

A. Cyanide poisoning.

B. Organophosphate poisoning.

C. Amikacin overdose.

D. Carbon monoxide poisoning.

ENVIRONMENTAL PHYSIOLOGY

Introduction

00:00:43

1. High altitude.
2. Deep sea physiology.
3. Space physiology.

We live at sea level :

Barometric pressure : 760 mmHg (1 atmospheric pressure).

Composition : 21 % of oxygen.

Partial pressure of O_a : 160 mmHg (in environmental air).

High altitude :

Composition of air : 21 % oxygen.

Atmospheric or barometric pressure : Low.

Therefore, hypoxia seen predominantly.

People get acclimatized to this environment with some compensatory changes :

1. Earliest :
   - Hypoxia → Peripheral chemoreceptors stimulated → Chemoreflex → Hyperventilation (respiratory rate + depth of respiration increased) → CO_a washout → Respiratory alkalosis.
   - Respiratory alkalosis → Albumin binds to calcium more than H^+ → Bound form of calcium rises → Fall in free calcium levels → Hypocalcemia → Tetany.
   - Respiratory alkalosis → Kidney increases bicarbonate ion excretion (to prevent hypocalcemia).
2. Hypoxia :
   - Hypoxia → Erythropoietin release → Increase in RBC count → more hemoglobin available.
   - Hypoxia → VEGF (Vascular Endothelial Growth Factor) → New blood vessels are formed + increase in vascularity (angiogenesis).

- Hypoxia → Increased diffusion of gases → Increased diffusion capacity.
- Hypoxia → Increased cytochrome oxidase activity → Increased oxygen utilization → Cellular acclimatization.
- Hypoxia → Enhanced release of oxygen to tissues (right shift in oxygen hemoglobin dissociation curve).

High altitude illness 00:13:12

High altitude illness (seen in people without the above compensatory mechanisms) :

1. AMS (Acute Mountain Sickness) :
   - Within 6 to 12 hours of ascent to high altitude.
   - Features : Nausea, vomiting, confusion.
   - May become severe → Edema (lung, brain).
     HAPE : High Altitude Pulmonary Edema.
     HACE : High Altitude Cerebral Edema.
   - Treatment :
     Descent to lower altitude.
     Oxygen therapy.
     Calcium channel blockers like Nifedipine.
     Dexamethasone (for edema).
2. Chronic mountain sickness (Monge's disease) :
   - Excessive erythrocytosis.
   - Pulmonary hypertension.
   - Corpulmonale (if untreated).
   - Treatment : Venesection, Acetazolamide.

Deep sea physiology 00:18:11

Seen in :

- Divers.
- Caisson workers.
- Military operations.
- Recreational (scuba diving).

Deep sea is a state of high barometric pressure → Gases are in compressed state.

Ascend rapidly → Decompression → Gases gets released suddenly → Bubbles → Decompression sickness.

Deep sea (10 m) : 2 atmospheric pressures.
(At sea level → 1 atmospheric pressure + every 10 m → 1 atmospheric pressure increases).

Decompression sickness :

Seen in anyone moving from high pressure to low pressure (divers, pilots, mountaineers).

Also called diver's disease/caisson's disease.

Features:

- Nitrogen gas bubbles clinically seen.
- Nitrogen easily crosses blood brain barrier : Nitrogen narcosis (euphoria).
- Nitrogen in joints : Bends.
- Nitrogen in lungs : Chokes.
- Nitrogen in blood vessels → Obstruction → Air embolism → Death.

Treatment :

- Hyperbaric chamber.
- Ascend slowly (slow decompression of gases).

Space physiology 00:27:46

Gravitational forces (G forces) :

1. Positive G :

   Huge gravitational force acting from head to foot → Venous pooling in lower limbs → Decreased cardiac output → Cerebral perfusion decreases → Blackout (unconsciousness).

2. Negative G :

   Huge gravitational force from foot to head → Increased venous return → Increased cardiac output

→ Increased blood flow to brain → Congestion, particularly in the eye → Red out in eye.

3. Zero gravity/micro gravity : Loss of calcium and phosphate from bone → Loss of bone mass.
   - Loss of muscle mass.
   - Decrease in RBC number.
   - Decreased work capacity.

Clinical scenarios

00:33:37

Q. Which of the following happens during respiratory alkalosis in high altitude?

A. Decrease in protein bound calcium and increase in free calcium.

B. Decrease in protein bound calcium and free calcium.

C. Increase in protein bound calcium and free calcium.

D. Increase in protein bound calcium and decrease in free calcium.

Q. Which gas is responsible for the narcosis seen in decompression sickness ?

A. Oxygen.

B. CO_2.

C. Nitrogen.

D. Carbon monoxide.

Q. Features of positive G are all except ?

A. Venous pooling in lower limbs.

B. Cerebral perfusion increases.

C. Unconsciousness.

D. Blackout of vision.

Active space

CARDIAC ACTION POTENTIALS

Cardiac action potentials 00:01:59

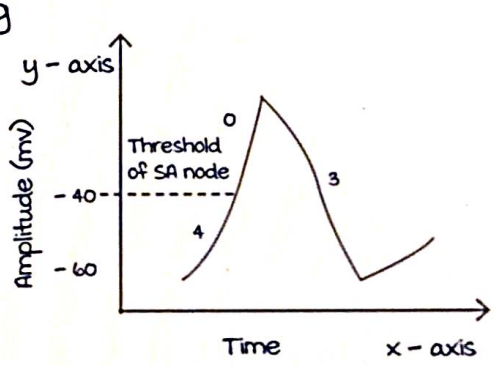
Sino Atrial nodal (SA node) action potential :
Exclusively for heart rate generation.
Known as the dominant pacemaker of the heart.
This property of generation of heart rate is called chronotropy phenomenon (chrono = time).
Sympathetic nervous system acts on it to increase the heart rate (positively chronotropic).
Parasympathetic nervous system acts on it to decrease the heart rate (negatively chronotropic).
All pacemakers have restless membrane potential (SA node membrane potential oscillates from -60 mv to -40 mv).

Ventricular action potential :
It is related to the contractility of the ventricles of the heart.
This property of contractility is called inotropy.
Ventricles have the stable Resting membrane Potential (RMP) of -90 mv.

SA nodal action potential 00:07:50

Phase 4 : Pre-potential phase (-60 mv to -40 mv).

- Ca^{a+} influx through T (Transient) type Ca^{a+} channels.
  (2 types of calcium channels are present in the heart.
  One is fast acting and the other is long acting.
  Fast acting channel is called transient calcium channel)
- Na^{+} funny currents causing Na^{+} influx.
- Decrease in K^{+} efflux.



Phase 0 : Depolarisation phase.
Action potential begins when

thereshold level/firing level is reached, which is -40mv for SA node.
Ca^{2+} influx through L type (Long duration) Ca^{2+} channels causes depolarisation which is unique to SA node.
majority other depolarisation is because of Na^+ influx.

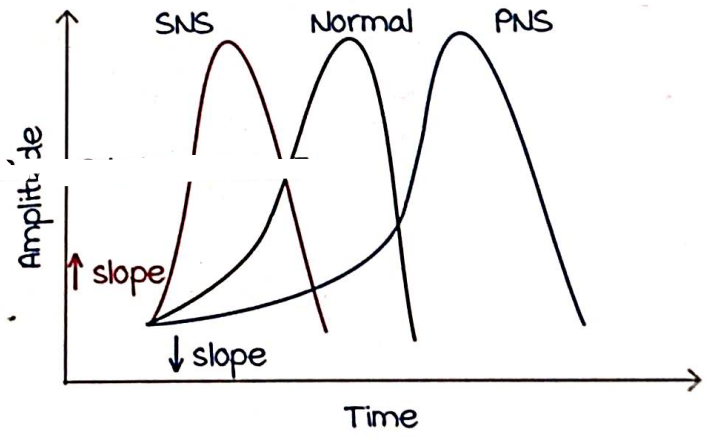
Phase 3 : Repolarisation phase (regaining polarity).
Due to K^+ efflux (universal).
At the end of repolarisation, there is decrease in K^+ efflux and pre-potential phase begins again.

Phases are named in accordance with ventricular action potential.
Threshold of SA node/firing level of SA node : -40 mv.
Threshold of nerve : -55 mv.

Effects of autonomic nervous system 00:16:54

Sympathetic and parasympathetic nervous systems act at pre-potential phase to change the heart rate :

- Sympathetic nervous system increases the heart rate by increasing the slope of the pre-potential phase.
- Parasympathetic nervous system decreases the heart rate by decreasing the slope of the pre-potential phase.



Funny currents/ I_f 00:19:49

Also called as Hyperpolarisation Cyclic Nucleotide channels (HCN channels).
These are the special type of Na^+ channels present in :

- Eye : For vision.

- SA node of the heart : Sinus rhythm generation.

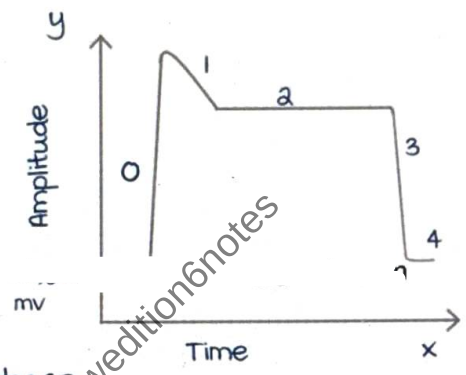
In patients with pathological increase in HR (arrhythmia),
Rx : I_f channel blocker (decreases HR) : Ivabradine.
Side effect of Ivabradine : Decreases visual acuity (due to blockade of the I_f channels in eye).

Ventricular action potential

00:23:13

It is a stable resting membrane potential. There is no pre-potential phase.

Phase 0 : Early depolarisation phase due to Na^+ influx.
Phase 1 : Early repolarisation phase due to K^+ efflux.
Phase 2 : Plateau phase.
Due to K^+ efflux. To balance the efflux, Ca^{2+} influx via L type Ca^{2+} channels.
At the end of plateau phase Ca^{2+} channels close.



Phase 3 : Late repolarisation phase.
Due to continued K^+ efflux.
Phase 4 : Maintenance of RMP by Na^+-K^+ ATPase pump.
Na^+ is pumped out and K^+ is pumped inside the cells.

Comparison of ventricular action potential and SA node action potential

00:30:38

	Ventricular AP	SA node AP
RMP	4	4 (restless)
Depolarisation phase	0	0
Repolarisation phase	3 (late)	3

Conduction system of the heart

00:32:14

SA nodal action potential takes 0.22 seconds to reach the base of the ventricles.
This property of conduction of impulse is called dromotrophy.
Components :

- SA node.

- AV node.
- His bundle.
- Purkinje fibers.

SA node :

Dominant pacemaker of the heart.
It has got the highest rate of impulse generation capacity compared to the other pacemaker cells of the heart.
So it is called the dominant pacemaker of the heart.

SA node firing rate is 100 impulses per minute but the normal resting HR is 72 bpm.
This is because the SA node firing is inhibited by the parasympathetic nervous system even at rest (resting vagal tone).

Atropine (anticholinergic, blocks PNS) → HR increases to 150 bpm due to sole effect of the sympathetic nervous system.
In heart transplant patients (denervated heart), there is no action of parasympathetic or the sympathetic nervous system on the heart.
Thus, these patients have resting HR of 100 bpm (i.e. equal to SA nodal firing rate).

AV node :

Physiological conduction delay happens in AV node for about 0.10 seconds.
This delay is required for the proper ventricular relaxation when the atria are contracting.
Also known as the Gatekeeper of the heart.

Purkinje fibers (from His bundle) :

Innervate all the ventricular myocardial cells.
Impulse conduction velocity is the highest (4 m/sec) in purkinje fibers because of the presence of highest number of gap Junctions (GJ) in them.
The number of gap junctions is lowest in AV node. Therefore, the conduction velocity is lowest in AV node (0.04 m/sec).

Gap junctions

00:46:17

Impulses are conducted rapidly to all cells of the ventricular myocardium due to presence of gap junctions.
This leads to the contraction of all the ventricular myocardial cells at the same time.
This phenomenon is called synchronised contraction a.k.a functional syncytium.
Cardiac gap junctions are formed by special group of proteins called as connexins.
In cardiac muscle histology, gap junctions are found in intercalated disc region.

MCQ's :

1. A 56 year old man with heart disease is prescribed a drug that inhibits depolarisation of the sinoatrial (SA) node. This drug acts on which channels ?
   A. Sodium channels
   B. Potassium channels
   C. Chloride channels
   D. Calcium channels

2. A patient is given a drug that shortens the duration of phase 4 of SA node potential. which of the following chages will be seen ?
   A. Decrease in frequency of atrial contractions
   B. Decrease in frequency of ventricular contractions
   C. Increase in frequency of atrial & ventricular contractions
   D. Increase in frequency of ventricular contractions

3. Gate Keeper of heart is
   A. SA node (Dominant pacemaker)
   B. AV node
   C. His Bundle
   D. Purkinje fibers

Active space

ECG & JVP

Introduction

00:00:19

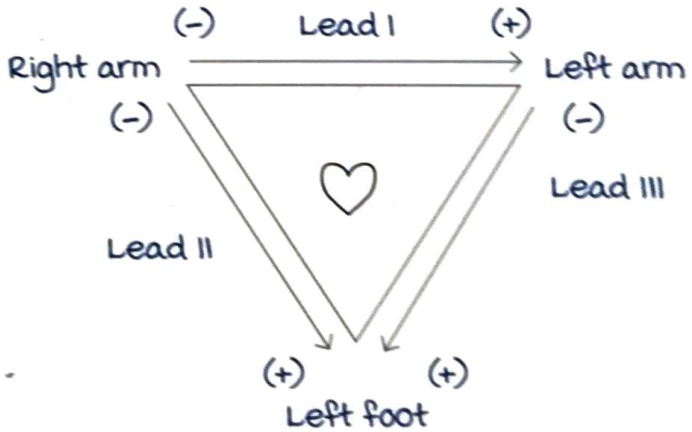
Einthoven received Nobel prize concerned with ECG.

12 lead ECG		
3 limb leads	3 augmented leads	6 chest leads
Lead I, 2, 3	avR, avL, avF	V1, V2, V3, V4, V5, V6

Every lead has a negative end and a positive end which measures potential difference that reduce deflections represented in the form of waves.

Significance of limb leads (Einthoven leads) :

He considered human body into triangle called Einthoven triangle.



To prevent electrical shock, grounding is needed. So right foot is grounded.

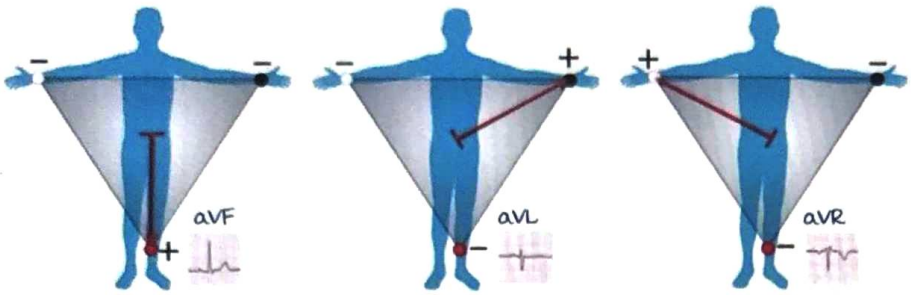
Einthoven's law : Potential in lead I + lead III = lead II.

Active space

Augmented leads

00:08:38

Augmented unipolar leads



Also called Goldberger leads.

Here, because of small modification, potential in these leads is increased by 1.5 times

aVR	aVL	aVF
Right arm is (+)	Left arm is (+)	Left foot is (+)
Left arm & left foot are (–)	Right arm & left foot are (–)	right arm & left arm are (–)

ECG leads and surfaces

00:12:39

II, III, aVF : Inferior surface leads.

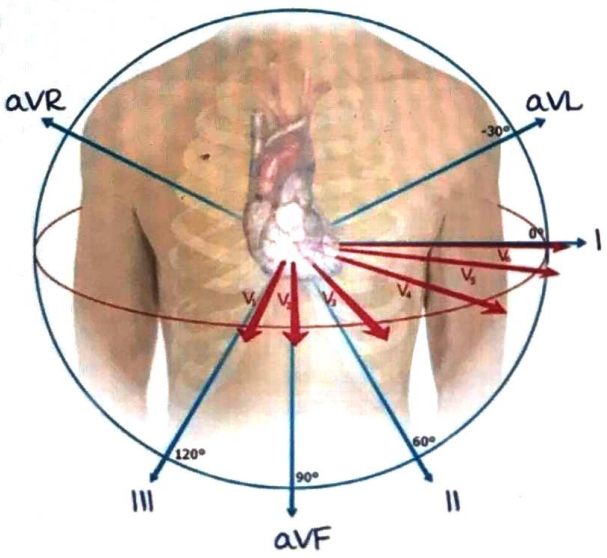
V_1, V_2 : Septal leads.

V_3, V_4 : Anterior surface leads.

V_1, V_2, V_3, V_4 : Antero septal leads

V_5, V_6, lead I, aVL : Lateral surfaces.

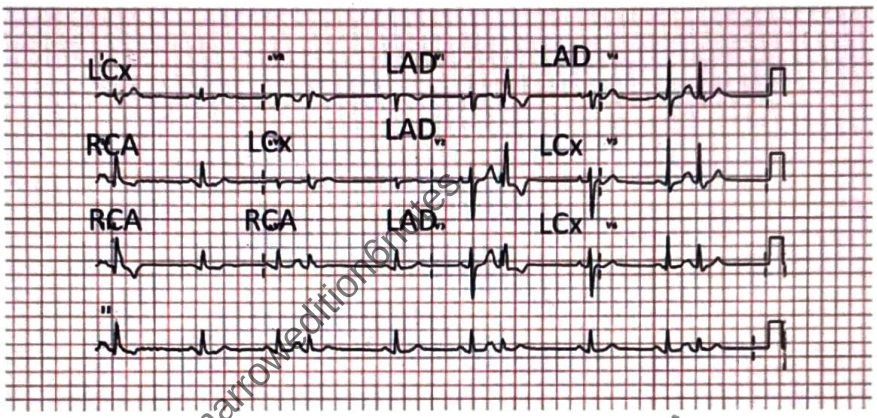
ECG leads and surfaces



ECG : Poor man's echcardiogram.

Surface distribution	Supplied by
II, III, aVF : Inferior surfaces	Right coronary artery (RCA)
V1, V2 : Septal leads V3, V4 : Anterior surface leads	Left anterior descending (LAD) Most commonly affected, so called Widow makers artery.
V5, V6, I, aVL : Lateral surfaces	Left circumflex artery (LCA)

ECG Leads and coronary artery territories



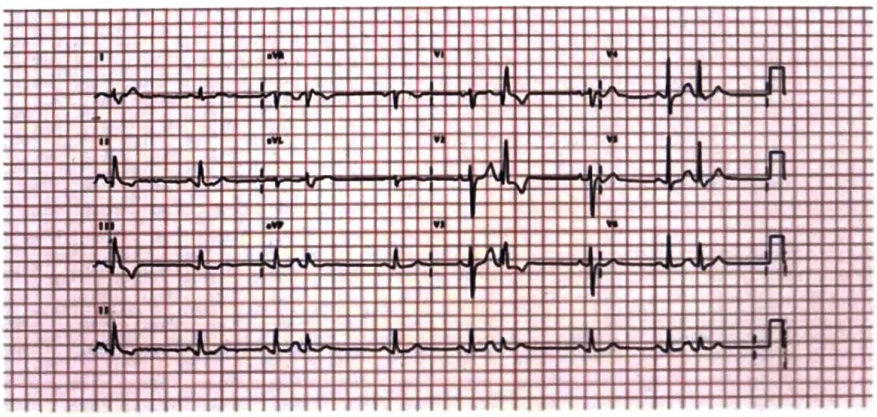
The ECG paper

00:18:46

Used to calculate :

- Duration.
- Amplitude of wave.

The ECG paper



One large square has 25 small squares.

Each small square time is 0.04 seconds, amplitude is 0.1 mV.

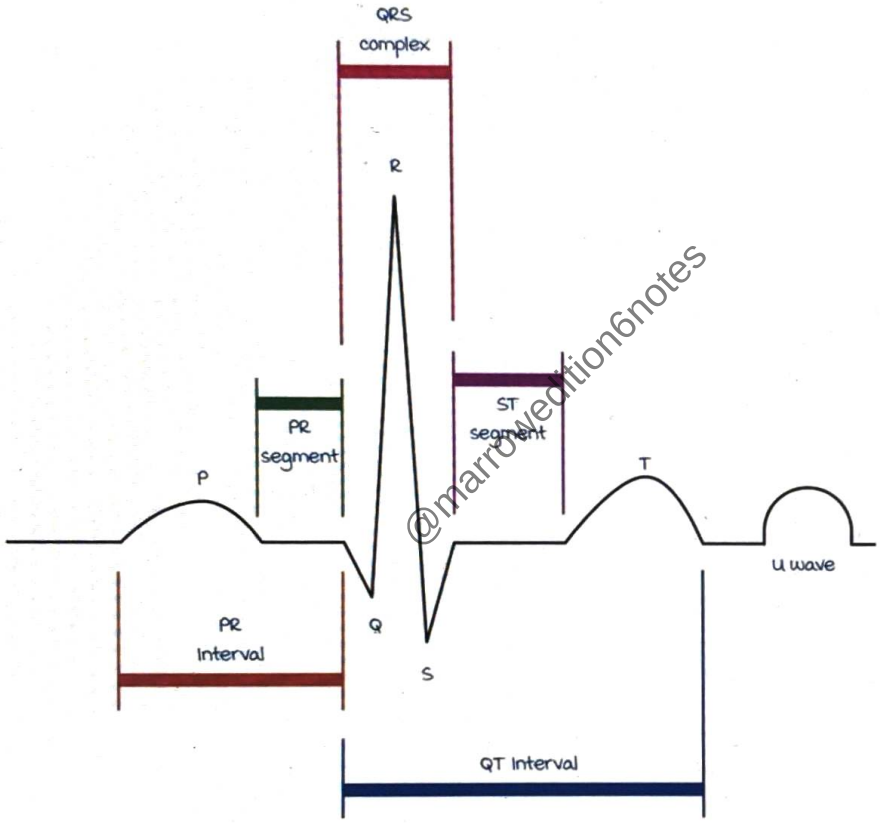
Now, one large square time is 0.04 × 5 = 0.20 seconds and amplitude is 0.1 × 5 = 0.5 mV

Rhythm of life/ ECG waves :

- P wave : Due to atrial depolarisation.
- QRS complex : Ventricular depolarization.
- T wave : Ventricular repolarisation.
- U wave : Late repolarisation.

Causes of U wave : Purkinje fibre repolarisation.
Papillary muscle repolarisation.

Straight lines (segments) in ECG : Aka iso electric points.



PR segment : End of P wave to onset of QRS complex, there is no current flow.

AV node delay is 0.10 seconds.

ST segment (J Point) : End of QRS complex to onset of T wave, there is no current flow.

Also called joining point (J point) in ECG as it connects the end of QRS (ventricular depolarisation) to start of T wave (ventricular repolarisation hasn't yet started).

Ideally, there will be no current flow in healthy person, but if there is flow, its pathological called as injury current due to myocardial infarction which can be ST elevation or ST depression.

Intervals in ECG

00:34:09

Combination of wave and segment.

PR interval : Before the onset of P wave to onset of QRS complex.

It includes P wave and PR segment. It is a combination of atrial depolarization followed by AV nodal delay.

- Normal PR interval : 0.12 – 0.20 seconds.
- Prolonged PR interval : >20s. Cardiac conduction defects & heart blocks.

RR interval : Interval between two successive R waves. Used for heart rate calculation.

$$\text{Heart rate} = \frac{1500}{\text{Number of small squares between a successive R waves}}$$

Prolonged RR : Decreased heart rate due to effect of PNS or vagal stimulation.

qT interval : Onset of QRS complex till the end of T wave.

It includes QRS Complex + ST segment + T wave. It is a combination of ventricular depolarisation and ventricular repolarisation & is called total ventricular activity.

Normal QT Interval : 0.40 seconds.

qT interval changes according to heart rate of the individual therefore qTc (corrected qt) is used.

$$qTc = \frac{qT}{\sqrt{RR}}$$ This is called Bazet's formula.

Active space

Direction of depolarization and repolarization 00:44:18

The direction of depolarisation and repolarisation are totally opposite in whole heart.

Depolarisation	Repolarisation
Starts from left ⟶ right side. Always starts in septum to endocardium, to epicardium.	Starts from right ⟶ left. Always starts in epicardium to endocardium to septum.

The first part of heart to undergo depolarisation is the last part to undergo repolarisation.
In individual myocardial cells, the direction of depolarisation and repolarisation are same.

Cardiac axis 00:48:19

Related to direction of overall electrical activity.

Mean QRS axis : Usually around +59 degrees.

Normal cardiac axis : -30 to +110 degrees.

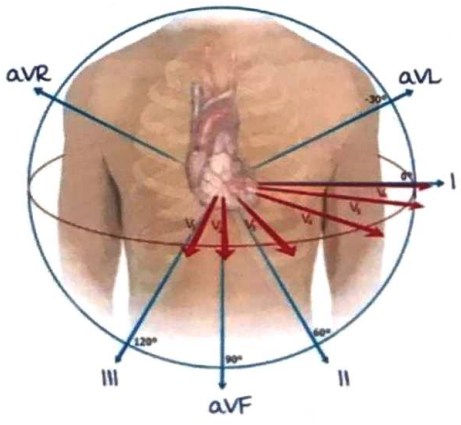
Leads that are close to mean QRS axis will always show positive deflection.

Maximal positive deflection is seen in lead II.

Leads that are away from mean QRS axis will show negative deflection.

Maximal negative deflection is seen in aVR. aVR looks into the cavity of heart.

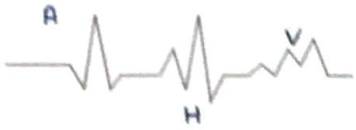
- Cardiac axis



His bundle electrocardiography 00:53:40

Always taken along with normal ECG.

Three waves A, H, V waves.



Three intervals :

- PA interval : Between P wave (ECG) to A wave (His bundle ECG)
- AH interval : Between A wave (AV nodal activity) to H wave (His bundle activity)
- HV interval : Between H wave (His bundle activity) to V wave (ventricular depolarisation)

Prolonged intervals indicate cardiac conduction block.

Primary purpose of His bundle in ECG is diagnosing cardiac conduction blocks.

Jugular venous pressure waveforms 00:58:09

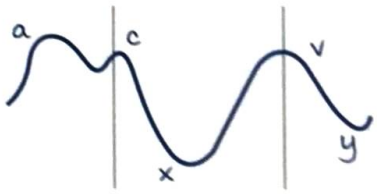
Preferred vein is internal jugular vein.

Totally 5 waves.

3 positive waves :
- a wave
- c wave
- v wave

2 negative waves :
- x wave
- y wave

JVP waveforms



Wave	Sign	Cause
a	Positive	Right atrial contraction
c	Positive	Right ventricular contraction leads to bulging of tricuspid valve into right atrium
x descent	Negative	Right atrial relaxation
v	Positive	Right atrial filling with venous blood

Y descent	Negative	Right atrial emptying into right ventricle

MCQ :

Q. Einthoven's law states that :

A. The sum of the potentials in leads I and II equals the potential in lead III.

B. The sum of the potentials in leads I and III equals the potential in lead II.

C. The sum of the potentials in leads II and III equals the potential in lead I.

D. The difference of the potentials in leads I and II equals the potential in lead II.

Q. Which of the following denotes AV nodal delay?

A. RR interval.

B. QT interval.

C. PR segment.

D. ST segment.

Q. Due to rapid emptying of right atrium once tricuspid valve opens, which wave is seen in JVP?

A. a wave.

B. c wave.

C. x descent.

D. Y descent.

CARDIAC CYCLE

Cardiac cycle 00:00:26

Normal duration of cardiac cycle : 0.8 second for a heart rate of 72/min.

Cardiac cycle has two phases :

- Atrial systole : 0.1 sec (short).
- Atrial diastole : 0.7 sec (long).
- Ventricular systole : 0.3 sec (short).
- Ventricular diastole : 0.5 sec (long).

$$\frac{\text{diastole}}{\text{heart rate}}$$

Cardiac cycle α

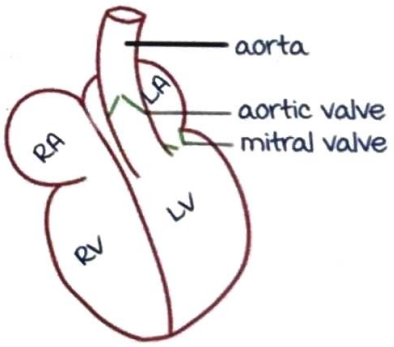
During exercise, cardiac cycle is 0.3 second for a heart rate of 200/min.

Ventricular systole : 0.12 second
Ventricular diastole : 0.18 second (compromised more).
Ventricular filling is compromised.

Ventricular systole 00:05:40

Duration : 0.3 second duration.

Has 3 phases.



- Isovolumic contraction :
  Mitral valve closes.
  First heart sound (S1) heard.
  LV contracts against closed mitral and aortic valves.
  No change in volume.
  Pressure increases.
  Ends at opening of aortic valve.
- Rapid ejection phase : 2/3rd of ventricular volume is ejected.
- Slow ejection phase : Close to remaining 1/3rd of blood is ejected.

At the end of systole, some volume of blood remains in the ventricle : End systolic volume (50 ml).

Ventricular diastole 00:12:55

Duration : 0.5 sec

Has 5 phases :

- Protodiastole :
  Closure of aortic valve : First event of diastole.
  Second heart sound (S2) is heard.
- Isovolumic relaxation : Volume remains the same as the ventricle is relaxing (pressure falls).
- Rapid filling phase.
- Slow filling phase.

  } 80% filling happens (passive filling).
- Filling due to active atrial contraction.
  20% of the remaining blood.
  Also called atrial kick.
  Ventricular filling is both active and passive.
  Slow filling phase is also called diastasis.

Heart sounds 00:18:34

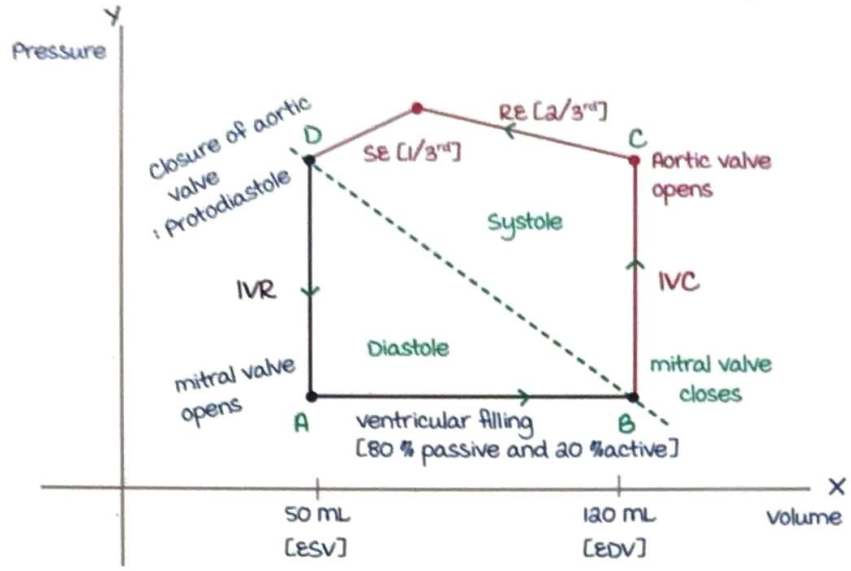
S1	1st heart sound	Closure of mitral and tricuspid valves
S2	2nd heart sound	Closure of aortic and pulmonary valves
S3	3rd heart sound	Heard during 3rd phase of diastole : rapid filling phase. In children and during exercise, the rapid filling phase is enhanced → rapid filling blood causes vibration of ventricular wall → S3 is heard.
S4	4th heart sound	Always pathological. If atrial contribution of ventricular filling is >20% (normal 20%) : Forceful atrial contraction. Seen in stiff ventricles : • Restrictive cardiomyopathy. • Long standing hypertension.

Pressure-volume graph

00:23:32

Volume can either increase, decrease or remain constant in the cardiac cycle.

Pressure can increase or decrease in the cardiac cycle.



Graph helps to understand the phases in cardiac cycle.

In the graph :

A : Opening of mitral valve.

B : Closing of mitral valve.

C : Opening of aortic valve.

D : Closing of aortic valve.

ESV : End systolic volume.

EDV : End diastolic volume.

IVR : Isovolumic ~~relaxation (pressure decreases)~~

IVC : Isovolumic contraction (pressure increases)

RE : Rapid ejection.

SE : Slow ejection.

S2 in the graph : point D.

S1 in the graph : point B.

Derivations from pressure-volume graph

00:32:07

From the diagram :

Stroke volume (SV) = EDV - ESV.

= 120 - 50 = 70 ml.

Ejection fraction (EF) = $\frac{SV}{EDV} \times 100$

Normal EF : 55-60%.

$$EDV = \frac{ESV}{1 - EF}$$

$$ESV = EDV\,(1 - EF).$$

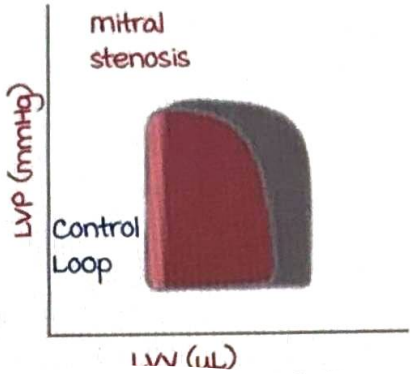
Clinical importance of pressure – volume graph :

Normal loop is shown in grey color.

Loop showing the pathology : Red.

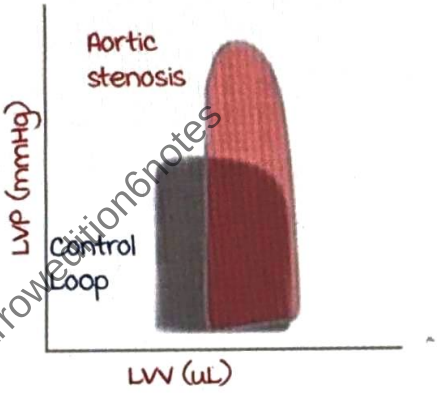
In mitral stenosis :

- EDV decreases.
- Stroke volume decreases.
  Less blood flows into LV in mitral stenosis.
- Left shift of the loop is seen.



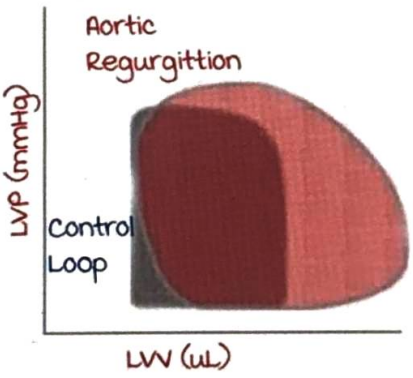
In aortic stenosis :

- ESV increases.
  Blood remains in the LV, due to stenosed aortic valve.
- LV pressure rises tremendously (contraction against stenosed valve)



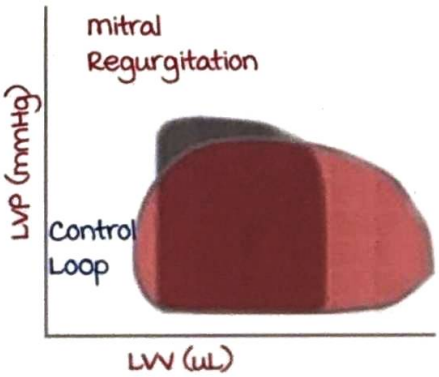
In aortic regurgitation :

- Isovolumic contraction and isovolumic relaxation are not straight lines (both valves should remain closed to have a straight line)
- EDV increases.
  Some amount of blood comes back to LV from the aorta.
- Width of graph increases.
- Height of graph increases.



In mitral regurgitation :

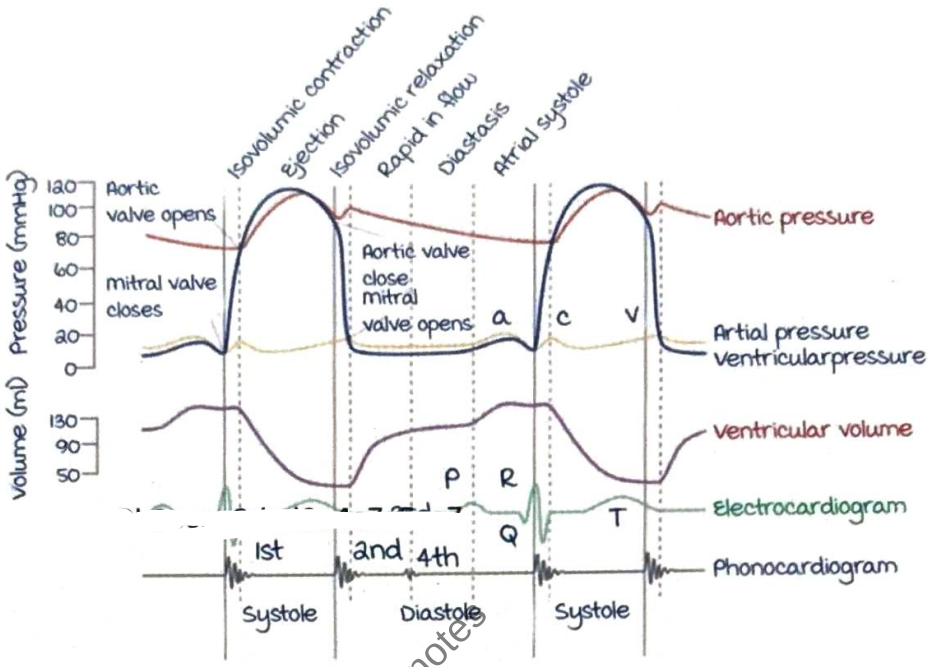
- Isovolumic contraction and relaxation are not straight lines.
- EDV increases.
- Width of the graph increases.



- Height of the graph decreases
  (helps to differentiate from aortic regurgitation)

Wiggers diagram

00:43:28



Pressure and volume changes along with ECG, phonocardiogram and JVP wave forms.
Phonocardiogram : Recording of heart sounds.

Pressure changes :
Ventricular pressure changes are huge waves.
Atrial pressure changes are smaller when compared to ventricular pressure changes.
Aortic pressure is within the limits of 120-80 mm of Hg.

Volume changes :
In ventricular contraction : Isovolumic contraction shows no change in volume (straight line).
Blood is ejected out, so ventricular volume decreases.
In ventricular diastole, isovolumic relaxation shows no change in volume. Blood fills, so the volume increases in diastole.

Heart sounds and ECG correlation

00:50:06

Heart sound	ECG correlation
S1	R wave

S2	End of T wave
S3	Rapid filling in cardiac cycle
S4	P wave

Clinical terminologies relevant to cardiac cycle :

Electromechanical systole (QS2) :
Between QRS complex in the ECG and closure of aortic valve (S2).
Dicrotic notch : Closure of aortic valve seen as a notch in the aortic pressure curve.

Left ventricular ejection time (LVET) :
From carotid artery pressure rise to closure of aortic valve.
Carotid artery pressure rise is studied with carotid artery pressure transducer.

Pre-ejection period :

PEP = QS2 – LVET.

Decrease in LVET : Decrease in EF.

$\frac{PRP}{LVET}$ ratio = 0.35.

If the ratio increases : Fall in EF.
The ratio always negatively correlates with EF.

MCQs :

Q. In aortic pressure curve, dicrotic notch is due to ?
A. Opening of aortic valve.
B. Closure of aortic valve.
C. Closure of pulmonary valve.
D. Opening of mitral valve.

Q. If the ventricle is not properly relaxing (stiff ventricle), atrium contracts forcefully to fill ventricles. This causes ?
A. First heart sound.
B. Second heart sound.
C. Third heart sound.
D. Fourth heart sound.

Active space

Q. If the carotid transducer is not functioning then which of the following readings could not be obtained?

A. QS.

B. QS, and LVET.

C. QSa, and PEP.

D. LVET and PEP.

CARDIAC OUTPUT

Cardiac output (CO)

00:00:24

Normal : Average of 5 L/min.

CO = Heart rate (HR) x stroke volume (SV).

HR α CO.

Heart rate is under the control of autonomic nervous system.

Sympathetic stimulation increases HR → Increases CO.

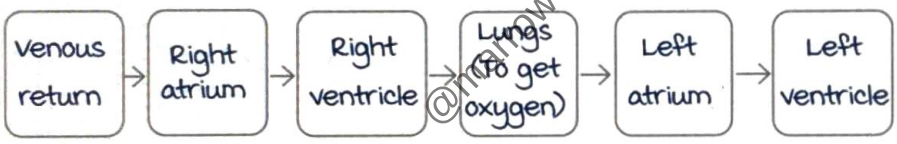
Parasympathetic stimulation decreases HR → Decreases CO.

SV α CO.

Stroke volume depends on (mnemonic : CAP)

- Contractility of the ventricles.
- Afterload.
- Preload.

Preload :



Factors aiding venous return :

- Calf muscle contraction.
- One way valve in veins.
- Deep fascia that supports veins (prevents collapse).

The volume of blood in the LV is the end diastolic volume (EDV), which is otherwise called preload.

It is the load given to heart.

Contractility of ventricles :

Increase in EDV increases the contractility of healthy ventricles, within physiological limits : Frank-Starling Law.

↑ Force of contraction causes ↑ SV, which in turn ↑ CO.

Contractility of ventricles & Preload α CO.

Active space

Afterload

00:10:10

Load that comes after the ventricles.

EDV is pumped by ventricles into the aorta against aortic pressure/total peripheral resistance.

Heart & kidneys work as 2 parellel circuits. If one of the kidneys is damaged/removed, total peripheral resistance increases thereby, decreasing CO.

Afterload $1/\alpha$ CO.

Preload is volume based while afterload is pressure based.

Parameters to assess factors regulating stroke volume :

Factor	Parameter
Preload	End diastolic volume (EDV)
Afterload	Aortic pressure/total peripheral resistance
Contractility (Inotropy)	Ejection fraction (EF). In heart failure, EF decreases. To increase EF, positive inotropic agents like Digitalis or Dobutamine are given.

Measurement of CO

00:17:52

Fick's principle :

Amount of oxygen consumption of an organ is arteriovenous oxygen difference times blood flow.

Amount of oxygen consumption = (arterial O_a – venous O_a) x blood flow.

Blood flow is taken as cardiac output.

$$CO = \frac{\text{amount of oxygen consumption}}{\text{arteriovenous oxygen difference}} = \frac{\text{amount of oxygen consumption}}{\text{arterial O2 – venous O2}}$$

- Echocardiography : most commonly clinically used.
- Thermodilution or dye dilution method.

Distribution of cardiac output :

Liver receives the highest blood flow : 1500ml.

Brain receives only half of blood flow to liver.

Coronary blood flow is 250mL/min ~ 5% of cardiac output.

Active space

For per 100gm of tissue :

Highest : Kidney.

Lowest : Resting skeletal muscle.

Highest oxygen extraction/A-V oxygen difference : Heart.

Highest O_2 consumption : Liver.

Per 100gm : Heart (10ml/100g/min)

Maximum fraction of cardiac output and O_2 consumption : liver.

Distribution of cardiac output

Region	Blood flow		Arterio-venous Oxygen difference (ml/L)/O_2 extraction	O_2 consumption		Precentage of total	
	ml/min	ml/100g/min		ml/min	ml/100g/min	cardic output	O_2 consumption
Liver	1500	57.7	34	51	2.0	30	20.4
Kidney	1260	420	14	18	6.0	23.3	7.2
Brain	750	54	6.2	46	3.3	13.9	18.4
Skin	462	13.8	25	12	0.3	8.6	4.8
Skeletal	840	2.7	60	25	0.3	15.6	20
Heart	250	84	84	29	9.7	4.7	11.6

Cardiac index ratio (CIR) 00:26:59

Expressing cardiac output per m^2 body surface area.

Normal : 3.2 L/min/m^2 of body surface area.

Coronary circulation (blood flow to heart) :

5% of CO goes to heart (250 mL/min).

Heart receives its blood flow only during diastole.

The coronary arteries are compressed during systole.

Area most susceptible to ischemia : Sub-endocardial region.

Heart has the highest oxygen extraction/A-V O_2 difference.

Oxygen consumption per 100g/min : 10 ml/100g/min.

The oxygen consumption is exclusively for myocardium :

Myocardial oxygen consumption/myocardial oxygen demand.

Myocardial oxygen consumption is directly proportional to heart rate, duration of systole & systolic blood pressure.

Regulation of coronary blood flow 00:33:18

Nervous control has a minor role.

Local factors play a major role : Accumulation of substances.

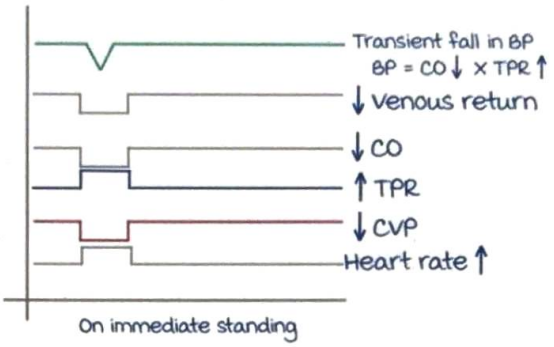
- Adenosine.
- Nitric oxide.
- H^+ ions.
- Local products of metabolism.

} Increase coronary blood flow.

Postural variation :

on immediate standing.

- Transient fall in blood pressure, corrected by baro reflex.
- Venous return decreases due to gravity.
- Cardiac output decreases.
- Total peripheral resistance increases.
- Central venous pressure (CVP) decreases.
- Heart rate increases.



Shock 00:40:02

Decrease in cardiac output causes decrease in blood flow to organs to meet the demands.

Types of shock :

1. Hypovolemic shock.
2. Neurogenic shock.
3. Cardiogenic shock.
4. Anaphylactic shock.
5. Septic shock.

Hypovolemic shock : Most common & most commonly due to hemorrhage.

Stages	Features of hypovolemic shock
Non-progressive stage	Compensations done by the body.
Progressive stage	Death can occur without treatment.
Irreversible stage	Death is inevitable.

Non-progressive stage :
Compensations occur.

- Sympathetic activation by norepinephrine.
  Increases HR, CO and BP.
  In the kidneys, constriction of afferent arterioles.
  This diverts blood to vital organs like heart and brain.
- Increase in antidiuretic hormone. Water conservation leads to increase in blood volume.

Progressive stage :
Decrease in coronary blood flow causes cardiac deterioration, which further decreases coronary blood flow.
A positive feedback is established causing further cardiac deterioration.
Clot formation in small blood vessels causes decreased blood flow to heart that decreases CO.

Irreversible stage :
Loss of energy source especially in heart. Decrease in ATP, creatine phosphate. Adenosine regeneration is very slow (2% of original value per hour).

Neurogenic shock 00:49:44

Commonly seen during anaesthesia : General or spinal anaesthesia.
Causes sympathetic inhibition → Fall in peripheral vascular resistance → Extensive vasodilation causing shock.

Cardiogenic shock :
Cardiac disorders decreasing CO, causes shock.

Anaphylactic shock :
Major mediator : Histamine.
Histamine increases capillary permeability (fluid loss) & excessive vasodilation → Decrease in CO & shock.

Septic shock (bacterial infection) :
Infection increases body temperature, which increases blood flow and CO (only shock with increase in CO).

MCQs :

Q. Which is the clinically useful variable used to assess cardiac muscle contractility ?

A. Preload.
B. Afterload.
C. Aortic pressure.
D. Ejection Fraction.

Q. Cardiac output decreases during ?

A. Pregnancy.
B. Exercise.
C. Standing from lying down.
D. Anxiety.

Q. The peak left coronary flow occurs during ?

A. Isovolumic contraction.
B. Rapid ejection.
C. Slow ejection.
D. Isovolumic relaxation.

HEMATOPOIESIS AND BLOOD GROUPS

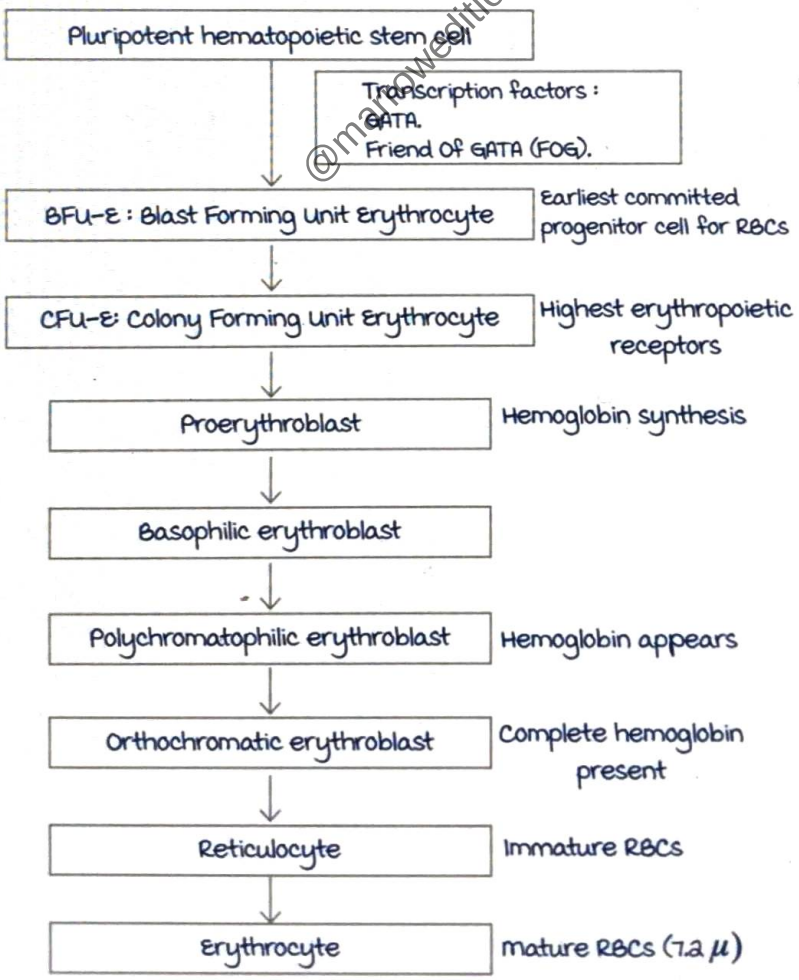
Hematopoiesis

00:02:28

Location of hematopoiesis during different periods of life :

Age	Location
Intrauterine Life (3 weeks to 3 months)	Yolk Sac
Intrauterine life (3 months to 5 months)	Liver and spleen
6 months till 20 years of age	Red bone marrow of long and flat bones
After 20 years of age	Red bone marrow of flat bones (iliac crest)

Erythropoiesis .



Active space

Pluripotent hematopoietic stem cell (PHSC) is the starting point for all RBCs. For PHSC to develop into an RBC, certain transcription factors are needed like, GATA & friend of GATA.

PHSC along with the transcription factor forms the Burst Forming Unit Erythrocyte (BFU).
BFU : Earliest committed progenitor cells for RBC.
BFU develops into colony forming unit (CFU).

CFU cells : Highest erythropoietic receptors which regulate erythropoiesis. Later on develops into
Proerythroblast (Hb synthesis begins) → Basophilic erythroblast → Polychromatophilic erythroblast (Hb appears) → Orthochromatic erythroblast (full Hb appears) → Reticulocyte (immature RBCs) → Erythrocyte (mature RBCs).

Regulation of Erythropoiesis :
Erythropoietin is the major regulator of erythropoiesis.
80% of erythropoietin is from interstitial cells of the Kidney.

Erythropoietin is produced from :

1. Kidneys.
2. Liver.
3. Brain.

Major stimulus for erythropoietin : Hypoxia.

Erythropoietin increases RBCs number by acting on Janus Kinase 2 receptor. This is part of JAK_2 STAT pathway.

If there is a gain of function mutation, that is if the erythropoietin becomes over active, there will be a tremendous increase in RBC production. This is called as Polycythemia Vera.

When Po_2 is normal/normoxia, a transcription factor known as Hypoxia Inducible Factor (HIF) is not in need. Therefore during normoxia, HIF is combined with Von Hippel Lindau (VHL) Factor to form a complex that undergoes degradation.

Normoxia : HIF + VHL complex → Degradation.
Hypoxia : HIF is separated from VHL factor.

Individual HIF : Increases erythropoietin production.

Drug forms of erythropoietin :

- Recombinant erythropoietin : Used in cases of anemia of chronic diseases or in patient undergoing dialysis.
  1. Epoetin alfa.
  2. Darbepoetin alfa.

Increase in RBC is caused by :

- Erythropoietin.
- Growth Hormone.
- T_3.
- Cortisol.
- Testosterone (reason why males have more RBC).

Estrogen is known to decrease RBC levels in females.

Leucopoiesis 00:18:03

Granulocytes :

- Neutrophils.
- Eosinophils.
- Basophils.

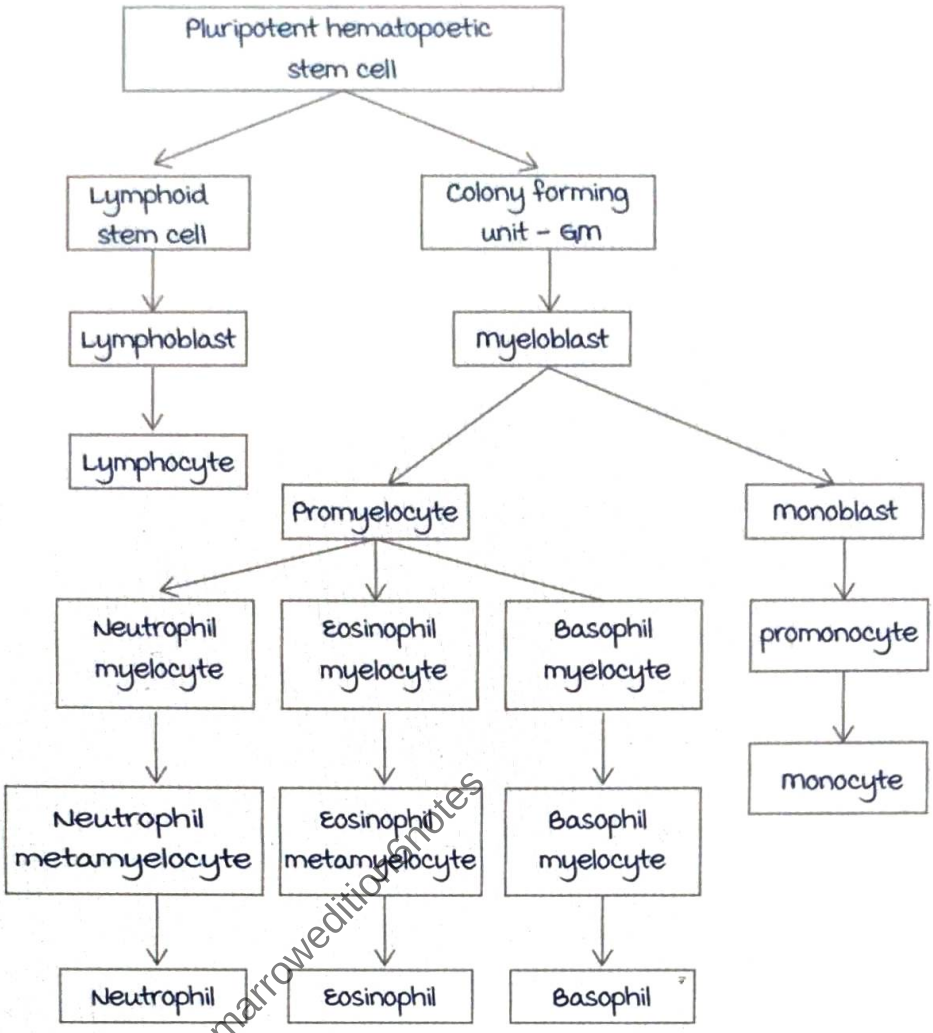
Agranulocytes :

- Lymphocytes.
- Monocytes.

Lymphocytes have a different lineage compared to other white blood cells.

Lymphocytes develop from lymphoid stem cells whereas the rest 4 WBCs develop from GM - CFU (granulocyte monocyte colony forming unit).

Leucopoeisis



Regulation of Leucopoiesis :
Colony stimulating factors such as G-CSF (Granulocyte Colony Stimulating Factor) and GM-CSF (Granulocyte monocyte Colony Stimulating factor) are responsible for leucopoiesis.

Drug form of G-CSF : Filgrastim.
Drug form of GM-CSF : Sargramostim.

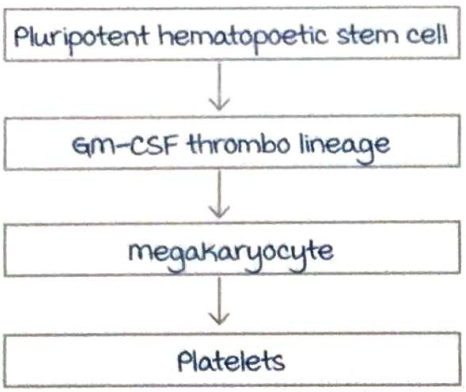
IL 5 is needed for eosinophil development.
IL 3 & 4 is needed for basophil development.

Thrombopoiesis

00:23:47

Thrombopoietin is responsible for increase in platelet production. The drug form of thrombopoietin is called as eltrombopag.

Thrombopoeisis



IL 11 is also needed to increase platelets as well, its drug form is known as Oprelvekin.

Blood groups

00:25:56

ABO System : most important blood grouping system, invented by Karl Landsteiner.

This system classifies blood based on RBC antigens and sugars.

Antigens : Agglutinogen.
Antibody : Agglutinin.

All RBCs have a very important common H antigen present on them. On this H antigen, an A or B antigen and N-Acetyl Galactosamine (NAG) or Galatose (G) sugar is present.

A blood group : H antigen + A antigen + NAG sugar present.
B blood group : H antigen + B antigen + G sugar present.
O blood group : H antigen only.

In AB blood group, both A and B antigen is present and both these antigens express themselves, this is called as co-dominance.

Bombay blood group : No H antigen, no A or B antigen.

	Antigen found on RBC	Antibody found in the plasma
A group	A	Anti-B
B group	B	Anti-A
O group	No antigen	Anti-A, Anti-B
AB group	A, B	No antibody

O blood group has no antigens, therefore they can serve as Universal donors.

AB blood group has no antibodies, therefore they can receive any blood and are called as Universal recipients.

Blood group antigens can be found in blood, semen, amniotic fluid, saliva.
Similar to our blood group antigens, they are also found in intestinal bacteria and food substances we intake.

Rh System

00:34:51

Antigens present are C, D and E. Among which D is the most important one.
Rh +ve : D antigen present.
Rh -ve : D antigen absent.

Rh incompatibility :
If an Rh -ve mother is carrying Rh +ve fetus, at the time of delivery, the fetal blood entering the maternal circulation can cause antibody development and the next Rh +ve child's RBCs can be attacked by the maternal antibodies causing hemolysis. This is called as erythroblastosis fetalis.
The hemolysis results in unconjugated bilirubin crossing the blood brain barrier and affecting the basal ganglia causing Kernicterus.
Treatment :
Anti Rh antibodies to the mother.
KELL system of blood grouping :
If Kell system is absent in an individual, the person is

susceptible to mcleod phenotype.

In such individuals :

- Acanthocytes are seen (RBC with spikes).
- Cardiac defects are seen.

P-system of blood grouping :

Auto-antibodies against the P-system can lead to a clinical state called as Paroxysmal cold hemoglobinuria.

The P system also serves as a receptor for the entry of Parvovirus B-19 and E.coli.

Duffy system :

Serves as a receptor for Plasmodium Vivax.

Q. Mutation in JAK2 of erythropoietin receptor can lead to?

A. Anemia of chronic diseases.

B. Paroxysmal Nocturnal hemoglobinuria.

C. Sickle cell anemia.

D. Polycythemia vera.

Q. Recombinant form of IL-11 commonly used in cancer chemotherapy induced thrombocytopenia is?

A. Romiplostim.

B. Eltrombopag.

C. Oprelvekin.

D. Darbepoetin.

Q. Inheritance of ABO blood group system is

A. Autosomal dominant.

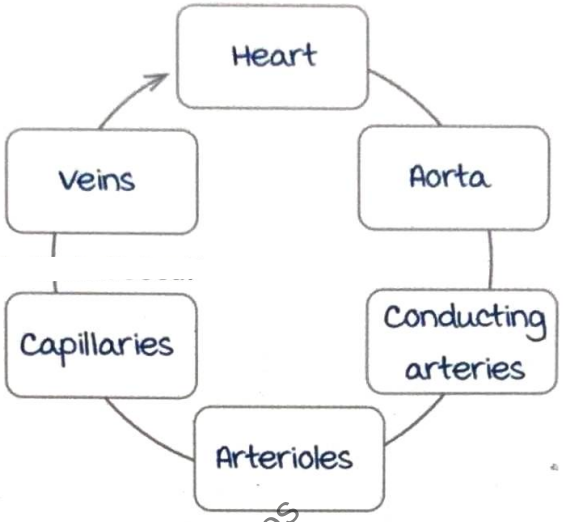
B. Autosomal recessive.

C. X linked recessive.

D. Autosomal codominant.

CHARACTERISTICS OF BLOOD VESSELS

Organization of the blood vessels 00:00:44



Conducting arteries take blood from center to periphery.
Eg : brachial artery, ulnar, radial arteries.

Aorta 00:02:28

Elasticity/windkessel effect is the exclusive property of large & elastic vessels like aorta.
When stretched they undergo elastic recoil.
It is this property that maintains the blood pressure between 120 mmHg (systolic) and 80 mmHg (diastolic).
Aorta is stretched during systole & undergoes elastic recoil during diastole.

Proteins responsible for aortic elasticity are :

- Elastin.
- Fibrillin (supportive protein).

If elastin undergoes mutation, presents with supravalvular aortic stenosis (William's syndrome).
If fibrillin undergoes mutation, presents with dilatation of aortic root (marfan's syndrome).

Importance :
Aorta is very close to heart.
Blood vessel with highest blood flow velocity.
Blood flow velocity α 1/cross sectional area of blood vessel.
Therefore, aorta has lowest cross sectional area.

Arterioles 00:08:54

Exclusively known for presence of smooth muscles.
These smooth muscles undergo :

- Contraction/vasoconstriction under influence of agents like Norepinephrine, leading to decrease in blood flow and an increase in resistance.
- Relaxation/vasodilation under agents like Nitric oxide leading to increase in blood flow due to widened lumen and a decrease in resistance.

Functions of arterioles :

1. Called resistance vessels.
2. Regulation of blood flow.

Capillaries 00:12:17

They arise from arterioles.
Also known as exchange vessels, as they facilitate exchange of nutrients and gases with the interstitial space.
After which, blood will flow into the veins.
5% of total blood volume is within the capillaries at any given time.
Pre-capillary sphincter :
Located between arterioles and capillaries.
Undergoes vasomotion (intermittent contraction & relaxation) to allow blood flow from arterioles to capillaries.
Capillaries have the largest cross sectional area.
They have the lowest blood flow velocity.

Starling forces 00:15:4

These are the forces that facilitate exchange between capillaries and interstitial space.

Active space

There are 4 starling forces, namely

- Hydrostatic pressure (P) :
  In capillaries Pc : 25 mmHg.
  In interstitial space Pi : -2 mmHg.
  Pi is positive in skeletal muscle, liver and brain.
- Oncotic pressure/colloid oncotic pressure (π) :
  Exclusively due to protein (albumin).
  In capillaries πc : 25 mmHg.
  In interstitial space πi : 3 mmHg.

Filtration : Fluid moving out of capillaries into interstitial space.
Forces that favor filtration are : Pc & πi.
Reabsorption : Fluid taken back from interstitial space into capillaries.
Forces that favor reabsorption are : πc & Pi.
Net filtration pressure/NFP =
Forces favoring filtration − Forces favoring reabsorption
i.e., NFP = (Pc + πi) − (πc + Pi)

Filtration >>>> Reabsorption i.e. not everything filtered is reabsorbed back.
Therefore, there is an excess of filtered fluid but this does not lead to edema in healthy individuals, as lymphatic circulation brings it back into the capillaries.

Lymph flow/circulation 00:25:07

Increase in lymph flow may be due to :

1. Lymphatic pump in lymphatic circulation.
2. Muscle contraction.
3. Blood vessel pulsations.
4. Massaging.
5. Increase in hydrostatic pressure of capillaries (Pc).

Edema 00:27:46

Accumulation of fluid in the interstitial space.
Causes :

1. Fall in oncotic pressure in capillaries (πc) as seen in :
   - Liver diseases as the production of albumin is decreased e.g. liver cirrhosis.

- Kidney diseases where there is excess excretion of albumin e.g. nephrotic syndrome.

2. Increase in hydrostatic pressure of capillaries (Pc) as seen in :
   - Long standing hypertension (chronic increase Pc, overwhelmed lymphatics).
3. Lymphatic obstruction leading to decrease in lymph flow as seen in :
   - Microfilaria causing filariasis (lymphedema).

Veins

00:32:52

They are called capacitance vessels as they function as storage reservoirs of blood because of their ability to distend (compliance).

Compliance is the change in volume for the given change in pressure.

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Maximum compliance/maximum distension is for veins due to lowest pressure. Therefore, veins store 55% of total blood volume.

Clinical significance :

This reservoir function of pulmonary veins cause breathlessness /dyspnea upon lying down called Orthopnea in many individuals.

There are some specific circulations where there is no capillary between arteries and veins and they continue directly as shunt vessels/Arterio-Venous anastomosis (AV anastomosis).

No capillaries in AV anastomosis implies there is no exchange. So blood here is only for regulation of body temperature.

These are seen in skin, fingertips and ear lobes.

- Blood vessel with maximum diameter : Vena cava (SVC, IVC)
- Blood vessel with maximum thickness : Aorta.
- Blood vessel with maximum CSA : Capillaries.

- Blood vessel with maximum blood flow velocity : Aorta.
- Blood vessel with minimum blood flow velocity : Capillaries.
- Shunt vessels : AV anastomosis (temperature regulation).
- Blood vessel with maximum blood pressure : Aorta.
- Blood vessel with minimum blood pressure : Vena cava.
- Site of gas exchange : Capillaries.

MCQs :

1. Mutation in elastin characterised by supravalvular aortic stenosis is ?
   A. Marfans syndrome.
   B. Ebsteins anomaly.
   C. Turners syndrome.
   D. Williams syndrome.

2. Increased hydrostatic pressure leading to edema is seen in ?
   A. Congestive cardiac failure.
   B. Lymphatic filariasis.
   C. Liver cirrhosis.
   D. Right atrial myxoma.

3. Which vessels can store large amount of blood with very little increase in pressure?
   A. Aorta.
   B. Veins.
   C. Arterioles.
   D. Capillaries.

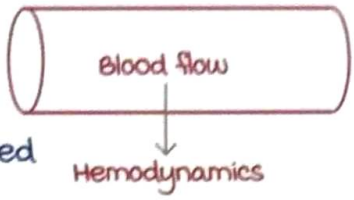
HEMODYNAMICS

Hemodynamics 00:00:50

Ohm's law :

Voltage = Current X Resistance

V = IR



Voltage changes in humans are related to pressure changes.

Pressure changes = Blood flow X Resistance.

3 important parameters :

- Blood flow.
- Resistance.
- Pressure changes.

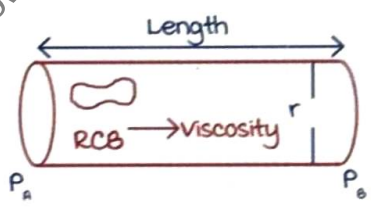
Poiseuille–Hagen law of blood flow :

Blood flow α Pressure difference ($P_A - P_B$).

Blood flow α Radius changes (r^4).

Blood flow α $\frac{1}{\text{Viscosity}}$

Blood flow α $\frac{1}{\text{Length of the vessel}}$



Clinical consideration :

In a patient with renal artery stenosis, radius is reduced to 1/2, blood flow also decreases by 16 times (i.e. 2^4 radius).

Length is doubled → Blood flow is 1/2 of original flow.

For regulation of blood flow, which of these 4 is most important?

Radius, because it changes to power of 4.

Resistance to blood flow 00:08:38

In case of vasoconstriction → Decrease in radius → Decrease in blood flow → Increase in resistance.

Resistance α $\frac{1}{\text{Radius}^4}$, called fourth power law.

Velocity of blood flow :

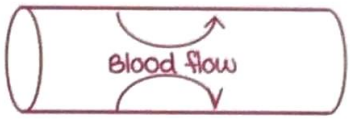
Velocity α $\frac{1}{\text{Cross sectional area of blood}}$

$\frac{1}{\text{Area}}$

Velocity α (Area = πr^2) i.e. Velocity is inversely proportional to square of radius.

Pressure :

Refers to blood pressure.



Lateral pressure exerted on the vessel wall by flow of blood is blood pressure.

Blood pressure is a form of Potential Energy (PE).

Blood is in movement → Kinetic Energy (KE).

Bernoulli's principle : At any one point in time,

PE + KE = Constant.

Blood pressure

00:14:26

SI unit : Pascal.

Preferred unit : mm Hg.

Systolic BP : On an average 120 mmHg.

Diastolic BP : On an average 80 mmHg.

Difference between SBP and DBP is called as Pulse pressure.

Mean arterial pressure :

Mean arterial pressure = DBP + $\frac{1}{3^{rd}}$ of pulse pressure.

(Or)

Mean arterial pressure = SBP + $\frac{2\,DBP}{3}$

Normal : 93–100 mmHg.

BP measurement :

Direct	Indirect
Commonly done in animals (for research purpose).	Most commonly used.
Intra-arterial BP.	Sphygmomanometer.
Values are usually high.	Usually underestimates BP (especially SBP by 10 mmHg).

Indirect method : Riva rocci cuff is used.

Dimensions :

Length → 80% arm circumference.

Width → 40% arm circumference.

False high BP :

- Small size cuff.
- Obesity.
- Thick calcified vessels.

While estimating BP : We hear Korotkoff sounds when the cuff is deflated.

Phase 1 : Tapping sound → Representation of SBP.

Phase 2 : Murmur like.

Phase 3 : Crisp and crystal clear.

Phase 4 : Muffled.

Phase 5 : Disappearance → Representation of DBP.

Auscultatory gap : Korotkoff sounds become inaudible between SBP & DBP and reappears as cuff deflation continues.

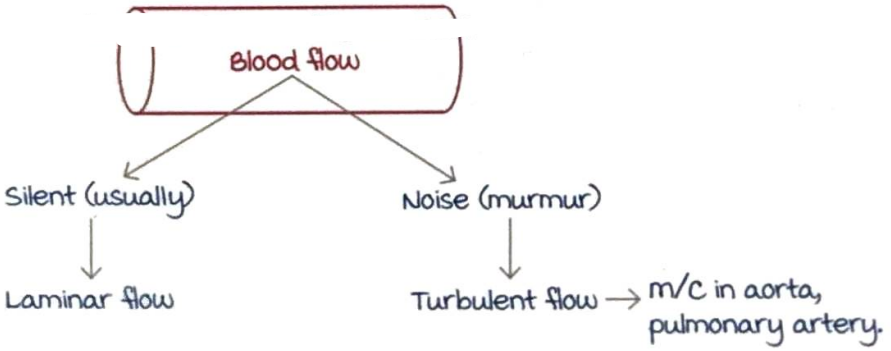
Due to this gap, we always underestimate SBP and overestimate DBP.

Blood pressure in various heart chambers 00:24:09

Heart chambers	Normal SBP	Normal DBP
Right atrium	5 mmHg	0
Right ventricle	25 mmHg	5 mmHg
Left atrium	12 mmHg	4 mmHg
Left ventricle	140 mmHg	4 mmHg

Pulmonary capillary wedge pressure : 4 – 12 mmHg.

Average : 10 mmHg.



Active space

Reynold's Number (RN)

00:30:08

Determines whether the flow is laminar or turbulent.

RN < 2000 : Laminar flow.

RN > 3000 : Turbulent flow.

RN between 2000 to 3000 : Transitional flow.

RN α Density of blood (directly related to diameter of cell wall and velocity of flow).

$$RN \alpha \frac{1}{\text{Viscosity}}$$

RBC determines viscosity :

Decrease in RBC → Decrease in viscosity → Increase in Reynold's number → Flow murmur.

This is particularly seen in anemia of pregnancy.

Laplace's law :

Tension is directly related to pressure and radius.

T α P & r.

Significance :

- Capillaries have less radius → Less tension on their walls → Capillaries don't rupture.
- Dilated heart → Increase in radius → more tension is generated for work to be done.
- Aortic aneurysms (dilation) → more the radius → Increase in tension across aortic wall → Aortic rupture.

MCQs :

Q. In laminar flow, if radius is reduced to half then ?

A. Blood flow increases four fold.

B. Blood flow decreases four fold.

C. Blood flow increased sixteen fold.

D. Blood flow decreased sixteen fold.

Q. Flow is laminar in small vessels because

A. Reynolds number is > 2000.

B. Total cross-sectional area of small.

C. Diameter of smaller vessels is more.

D. Effective velocity in small vessels is less.

Q. Rupture of aortic aneurysm can be explained using ?

A. Poiseuille- Hagen Law.

B. Laplace Law.

C. Fourth power Law.

D. Weber Fechner Law.

VASCULAR INJURY

Vascular injury

00:00:36

Gap in the endothelium is sealed with the help of :

- Platelets.
- Clotting factors.
- Endothelium.

Immediate response following an injury to blood vessel is Vasoconstriction : Limits blood loss. It is a transient phenomenon. Mediators responsible are endothelin and serotonin.

Platelets :

Platelet adhesion : Vascular injury → Collagen and VWF are exposed → Platelets adhere to vessel wall using GPI_b/IX receptors.

↓

Platelet aggregation : more platelets attach to themselves using $GPII_b/III_a$ receptors.

↓

Primary hemostatic plug develops and seals the gap initially.

↓

Definitive clot formation is required to seal the gap effectively. It requires clotting factors.

Clotting factors :

Factors	Deficient state
I. Fibrinogen	Afibrinogenemia
II. Prothrombin	Hypoprothrombinemia (usually secondary to vitamin K deficiency)
III. Tissue thromboplastin	-
IV. Calcium ion	-
V. Proaccelerin	Parahemophilia
VI. -	-

VII. Proconvertin	Hypoconvertinemia
VIII. Anti-hemophilic factor A	Hemophilia A
IX. Anti-hemophilic factor B (Christmas factor)	Hemophilia B (Christmas disease)
X. Stuart-Prower factor	-
XI. Anti-hemophilic factor C (PTA : Plasma thromboplastin antecedent)	PTA deficiency
XII. Hageman factor	Hageman triad
XIII. Fibrin stabilizing factor	-

Coagulation pathways 00:11:55

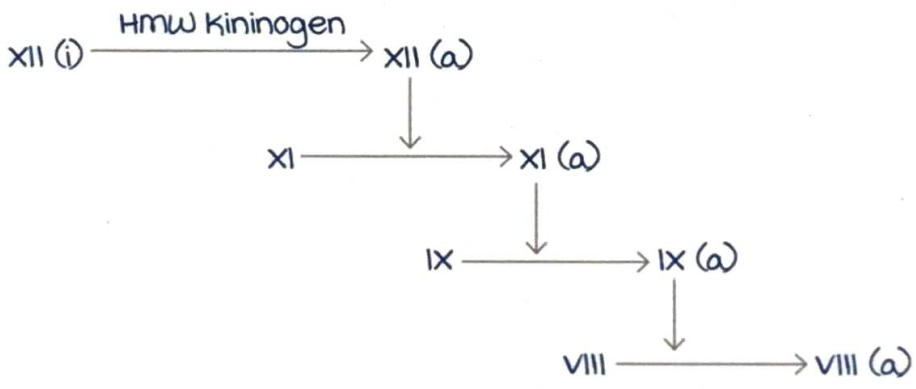
Once started, they amplify further (amplification at every step) : Cascade.
It is also called as coagulation cascade : Example for positive feedback mechanism.

When vessel wall is intact, clotting factors are in an inactive state.
Every single clotting factor needs to be activated for clot formation.

Pathways :

- Intrinsic pathway (contact activation) : Usually happens in laboratory when blood comes in contact with test tube/glass.
- Extrinsic pathway.
- Common pathway (intrinsic + extrinsic).

Intrinsic pathway :



i : Inactive

a : active

HMW : High molecular weight

Extrinsic pathway :

Tissue Thromboplastin

(III)

VII ⟶ VII (a)

Common pathway :

X ⟶ X (a)

V ⟶ V (a)

X(a), V(a) in the presence of Ca^{2+}, convert

Prothrombin ⟶ Thrombin

Fibrinogen ⟶ Fibrin (monomer)

XIII

Fibrin stabilization

(Definitive clot)

Vitamin K dependent clotting factors :

2, 7, 9 and 10 are vitamin K dependent.

Protein C & its co factor Protein S are also vitamin K dependent.

Applied : Warfarin inhibits gamma carboxylation. Affects vitamin K dependent clotting factors, thereby serving as an anticoagulant.

Tests to assess coagulation pathways 00:21:20

Prothrombin time (PT) : To assess extrinsic and common pathways.

Plasma clotting is produced by adding exogenous source of tissue thromboplastin.

Example : Brain extract and calcium.

Normal value : 11–16 seconds.

Prolonged PT : Defect in factors 7, 5, 10, fibrinogen, prothrombin.

Activated partial thromboplastin time (aPTT) : To assess intrinsic and common pathways.
Plasma clotting is produced by adding Kaolin that activates factor 12.
Cephalin is added that serves as a substitute for platelet phospholipids.
Finally, calcium is also added.

Normal value : 26–40 seconds.
Prolonged aPTT : Defect in factors 8, 9, 10, 11, 12, 5, fibrinogen and prothrombin.

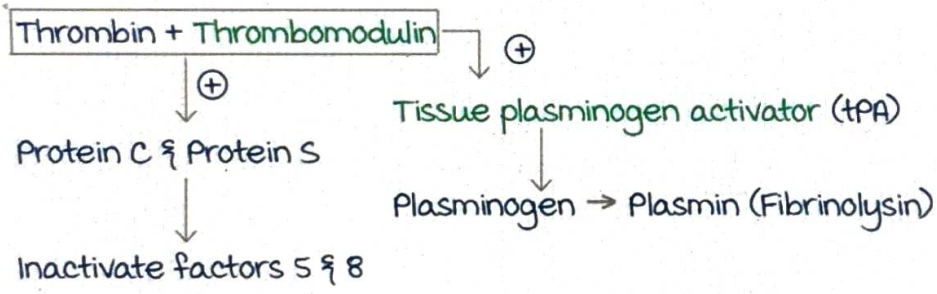
Platelet count :
Normal : 1.5–4 lakhs cells/cu mm.

Bleeding time :
Normal : 2–8 minutes.

Clotting time :
Normal : 2–6 minutes

Coagulation is always balanced by anticoagulation to maintain homeostasis.

Anticoagulation pathways :



Thrombin alone is a pro-coagulant.
Thrombomodulin is found throughout ciruclation except cerebral circulation.

2. Antithrombin 3 + Heparin inactivate factors 9, 10, 11 and 12.
3. TFPI (Tissue factor pathway inhibitor).

Regulators of anticoagulation :

- PAI (Plasminogen activator inhibitor).
- Alpha 2 antiplasmin.
- TAFI (Thrombin Activatable Fibrinolysis Inhibitor).

Coagulation-anticoagulation happens in healthy individuals also.

MCQs

00:34:04

Q. Protein C activation leads to which of the following?

A. Promotion of clotting.

B. Inactivation of factor 2.

C. Activation of factor 10.

D. Inactivation of factor 5, 8.

Q. Dicumarol therapy would decrease the plasma concentration of which of the following procoagulants?

A. Factor II (vitamin K dependent factor).

B. Factor III.

C. Factor XII.

D. Factor XIII.

Q. Which of the following is not involved in intrinsic pathway?

A. Factor XII.

B. Factor IX.

C. Factor XI.

D. Factor VII.

REGULATION OF BLOOD PRESSURE

Single most important factor that regulates cardiovascular system : Blood pressure.

Blood pressure : It is the lateral pressure exerted by the flowing blood on the blood vessel wall.

Short term regulation :

Occurs within seconds as they are exclusively under nervous control.

- Baro reflex.
- Chemo reflex.
- CNS ischemic response.

Intermediate mechanisms :

Acts within hours.

- Capillary fluid shift mechanism : If the blood pressure is low, the capillaries take in fluid from the interstitial space and rise the BP and vice versa.
- Stress relaxation : Vasodilation resulting in fall in BP.
- RAAS : Renin Angiotensin Aldosterone System.

Long term regulation :

Takes days.

- Kidneys : Pressure diuresis, excess pressure causes increase in urine output (Regulates BP by regulating body fluid volume).

Short term regulation

00:06:58

Baro reflex : Negative feedback system as increase in BP will trigger a quick decrease in BP.

Reflex arc components :

1. Receptor.
2. Sensory afferents.
3. Center.
4. Output.
5. Response.

Reflex arc of BP :

Baro receptor stretches due to increase in BP and acts as a sensor for high pressure. Baro receptors are exclusively abundant at the neck region.

1. Carotid Sinus.
2. Aortic Arch

	Carotid sinus	Aortic arch
Sensory afferents	Usually innervated by CN IX (glossopharyngeal nerve) via Herring's nerve.	Usually innervated by CN X (vagus nerve) via Cyan's nerve.

- CN IX and X innervate the sinuses, therefore they are known as sinus nerves and also buffer changes in our BP, therefore also called as buffer nerves. These nerves convey the sensory input of increase in BP. Baro receptors are activated only by increase in BP.
- Center for baro reflex lies in medulla.
- Outputs for medulla :
    1. Sympathetic nervous system (SNS).
    2. Parasympathetic nervous system (PNS) :

  In response to raised BP, sympathetic system inhibition & parasympathetic system activation occurs.
- Response : Decrease in BP and heart rate (because of parasympathetic activation).

Center

00:15:15

Center in medulla : Nucleus Tractus Solitarius (NTS).

NTS activates Caudal Ventrolateral Medulla (CVLM) with the help of a neurotransmitter Glutamate.

CVLM via GABA neurotransmitter inhibits Rostral Ventrolateral Medulla (RVLM) which is part of the sympathetic system.

- NTS $\xrightarrow{\text{glutamate}}$ Activate CVLM $\xrightarrow{\text{GABA}}$ Inhibit RVLM (SNS).

NTS also activates Nucleus Ambiguus (NA) which is part of parasympathetic nervous system

- NTS → Activate NA (PNS).

Baroreflex summary :

↑ BP : SNS inhibition & PNS activation, resulting in ↓ BP & ↓ HR.

i.e., Increase in BP causes a reflex decrease in HR.

BP α 1/HR : Marey's law in cardiovascular physiology.

Experiments on baroreceptors 00:20:00

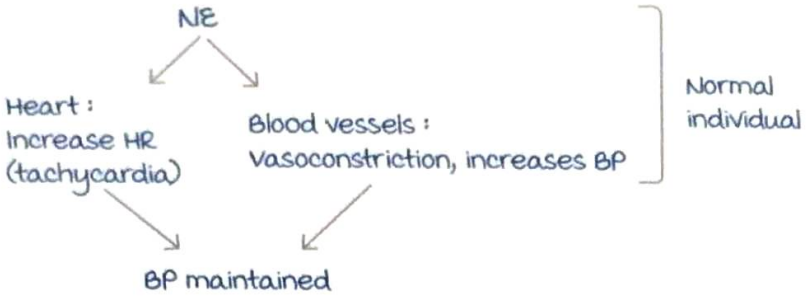
Points to remember for exams regarding experiments done on baroreceptors.

- Usually done in the carotid sinus baroreceptors.
- Carotid sinus is a dilation seen in internal carotid artery.
- Increase in BP activates baro receptors causing inhibition of SNS and activation of PNS.
- Decrease in BP inhibits baroreceptors and PNS but activates SNS.
- Occlusion of common carotid artery (CCA) :
  1. Causes ↓ blood flow to the internal carotid artery (ICA).
  2. Therefore, decreased pressure at the carotid sinus.
  3. Baroreceptor inhibition and sympathetic activation.
  4. Resulting in : ↑ BP & ↑ HR.
- Clamping above carotid sinus :
  1. Pressure builds up at carotid sinus.
  2. Baroreceptors activated and sympathetic inhibition occurs.
  3. Resulting in : ↓ BP & ↓ HR.
- Clamping below carotid sinus :
  1. Causes decreased pressure at the carotid sinus.
  2. Baro receptors are inhibited & SNS is activated.
  3. Effects : ↑ BP & ↑ HR.
  4. Similar to occlusion of CCA.

Clinical applications of baro reflex 00:26:54

- On immediate standing, a transient fall in BP occurs. This causes inhibition of baroreceptors, SNS gets activated. Norepinephrine is the SNS mediator, which targets the heart and blood vessels and increases the BP to normal levels in normal individuals.

But in patients with sympathetic under activity, they cannot maintain their BP, and this results in postural hypotension.



- Activating baro receptors to decrease HR for therapeutic purposes :
  In cases of Paroxysmal Supra Ventricular Tachyarrhythmia (PSVT), carotid sinus massaging is done to decrease the HR in the patient.

Baro receptors at sites other than carotid sinus & aortic arch?
Ans. Atrium.

Atrial baroreceptors are low pressure receptors, also called as volume sensing receptors. They are of 2 types :
Type A atrial baroreceptor : Activated during atrial systole.
Type B atrial baroreceptor : Activated during atrial diastole.

- Baroreceptors are considered the 1st line control for blood pressure monitoring.
- Baroreceptors monitor a pressure range of 70 – 150 mmHg of the Mean Arterial Pressure (MAP).
- Maximum pressure that baroreceptors respond to is 180 mmHg.
- If MAP falls less than 70 mmHg, then chemo reflex controls the BP.
- Chemo reflex is considered the 2nd line of control for BP. Chemo receptors operate at the range of 40 – 70 mmHg.

Chemo receptors :

- Direct effect : PNS activation : ↓ HR.
- Indirect effect : SNS activation : ↑ HR.

Therefore, chemoreflex effect on HR is variable.

If MAP falls <40 mmHg, leads to ↓ perfusion pressure → ↓ blood flow to brain → Brain undergoes ischemia.
CNS ischemic response acts as the last line of control for BP less than 40 mmHg.

CNS ischemic response activates the RVLM (part of SNS) → SNS activation occurs and BP can ↑ by up to 250 mmHg within seconds.
This is why CNS ischemic response is considered to be the most powerful BP control mechanism and used as a final measure to maintain the BP, hence also known as last ditch stand mechanism.

Short term regulation of BP is entirely nervous controlled.

1. Baroreflex : 70 – 150 mmHg.
2. Chemoreflex : 40 – 70 mmHg.
3. CNS ischemic response : <40 mmHg.

Fluctuations in BP recording due to nervous control mechanisms :

Mayer waves :
Fluctuations of BP due nervous control mechanisms while recording BP.

Traube Hering waves :
Fluctuations in BP corresponding to respiration

Other cardiac reflexes 00:45:39

Based on HR changes.

Bradycardic reflexes :

Bezold Jarisch reflex :

Profound hypotension & bradycardia seen in patients with myocardial infarction.
This is because infarcted tissue releases serotonin that activates the bradycardic reflex.

Cushing's reflex :

Seen in trauma patients with head injury, having elevated intracranial tension, always characterized by ↓ in HR and bradycardia.

Tachycardic reflex :

Bainbridge Reflex :

In patients of congestive cardiac failure, edema or fluid overload is seen, which ends up at the right atrium. The excess fluid stimulates the SA node and increases its firing and thereby increases HR.

Chemical control of BP

00:51:53

Vasoconstriction : ↑ BP and ↓ blood flow.

Vasodilation : ↓ BP and ↑ blood flow.

Vasoconstrictors :

1. Urotensin (most potent).
2. Endothelin.
3. Vasopressin.
4. Angiotensin.
5. Nor Epinephrine.

Endothelin (ET) :

ET 1 : Found in endothelial cells and acts as a vasoconstrictor.

- Endothelin is a very important vasoconstrictor, especially found in the lung. High levels of ET at lungs can cause Pulmonary Arterial Hypertension (PAH). Treatment for PAH is ET receptor blocker : Bosentan.

Endothelin Receptors : ET_A & ET_B.

ET_A : Causes vasoconstriction.

Vasopressin :

Vasoconstrictor that ↑ BP & ↓ blood flow. This helps minimize blood loss, in patients with esophageal varices. Can be treated with Terlipressin, a vasopressin analogue.

Angiotensis II :

Vasoconstrictor that acts in the RAAS system to increase BP.

Vasodilators :

Decreases BP & used for hypertension.

1. Calcitonin G-related peptide/CGRP (most potent).

2. Nitric oxide.
3. Natriuretic peptides :
    a. ANP.
    b. BNP.
    c. CNP.
4. Kinins : Bradykinins.

Nitric oxide : For vasodilation, it uses a 2nd messenger, cGMP.
Nesiritide is a BNP analogue that ↓ BP.

Q. Major neurotransmitter in afferents in nucleus tractus solitarius to regulate cardiovascular system ?

A. GABA.
B. Glutamate.
C. Glycine.
D. Norepinephrine.

Q. Endothelin receptor blockers are most commonly useful in treatment of ?

A. Congestive cardiac failure.
B. Right atrial myxoma.
C. Pulmonary arterial hypertension.
D. Mitral regurgitation.

Q. When a person stands from supine position, which of the following will happen ?

A. Inhibition of sympathetic nervous system.
B. Activation of parasympathetic nervous system.
C. Decrease in venous pooling.
D. Deactivation of baroreceptors.

Active space

GASTROINTESTINAL SECRETIONS

Gastrointestinal physiology :
Primary function of GI system is digestion and absorption of food. Enzymes for digestion are present in the GI secretions.

The movement of food is coordinated by gastrointestinal motility.

Regulation of GI system is done by :

- Gastrointestinal hormones.
- Enteric nervous system.

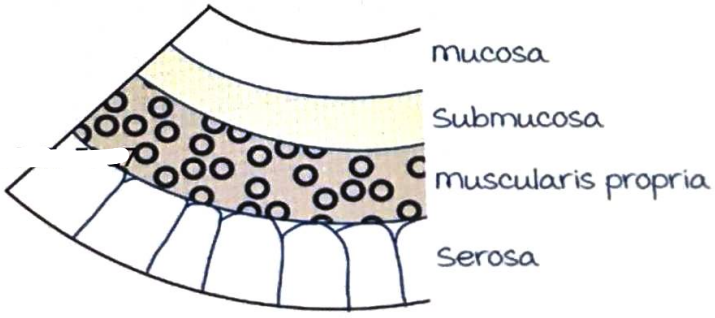
GI layers

00:03:24

From out to in : The 4 layers are :

- Serosa.
- Muscularis Propria : This layer consists of
1. Longitudinal group of muscles.
2. Circular group of muscles.
3. Myenteric plexus (Auerbach's Plexus) is seen in between these muscles. This plexus is exclusively concerned with motility.

- Submucosa :
  Has the meissner's (submucosal) plexus which plays an important role in GI secretions.
- Mucosa :
  Muscularis mucosa is the muscle present and has no role in GI motility. They contract to alter the available surface area of the GI tract.



GI secretions

00:08:44

Total secretion in the GIT is around : 9 L/day.
Around 8.8 L/day is absorbed back into the system and only 200 ml is lost in feces.

GI secretions :

- Saliva.
- Gastric secretion.
- Exocrine pancreatic secretion.
- Biliary secretion.
- Small intestinal secretion.

Maximum secretion per day is seen by :
Gastric secretion (2.5 L/day).
Most acidic secretion : Gastric secretion (pH : 1.5-3).
Most alkaline secretion : Brunner's gland secretion (pH : 8.9) and pancreatic secretion (pH : 8.3).

Saliva :
Around 1.5 L/day is produced.
pH of the saliva is 7, hypotonic.
Salivary glands :

- Major glands :
  1. Parotid glands (20%).
  2. Submandibular gland (70%).
  3. Sublingual gland (10%).
- Minor gland : Von Ebner's Gland.

Functions :

- Helps in digestion :
  1. Carbohydrate digestion :
     Done by salivary amylase enzyme (ptyalin) which is activated by Cl^- ions and inhibited by low pH.
  2. Fat digestion :
     Lingual lipase produced from Von Ebner's Gland.
  3. Protein :
     No enzymes present in the saliva for protein digestion.

Active space

- Lubrication : Important for deglutition and speech.
- Protection :
    1. Saliva confers protection because it has secretory immunoglobulin (IgA).
    2. Lactoferrin and lysozymes are considered to be anti-bacterial.

Saliva regulation :
Entirely under the control of autonomic nervous system (ANS).
ANS = Parasympathetic Nervous system (PNS) + Sympathetic Nervous System (SNS).
Both PNS and SNS increase the salivary secretion.
PNS : Thin, watery saliva is secreted under its influence.
SNS : Thick saliva is secreted under the influence of SNS.

Increase in saliva is seen in : Nausea and stimulating aroma.

Decrease in saliva is seen in :

- Fatigue.
- Dehydration.
- Sleep.
- Fear.

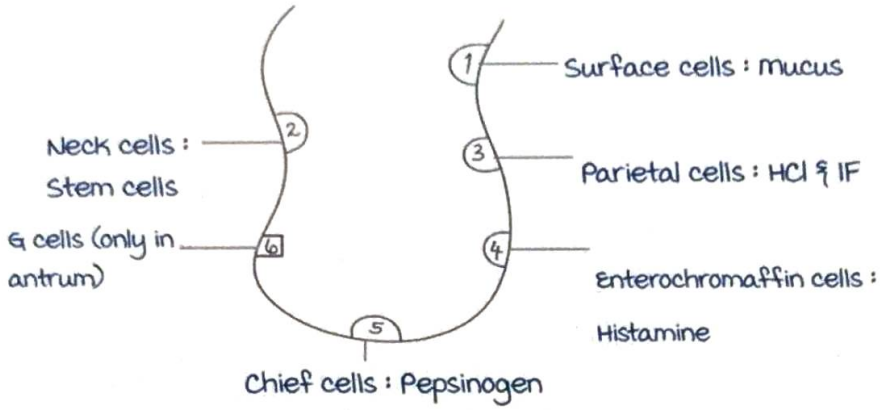
Salivary glands and their Innervation :
Cranial nerve 9 via otic ganglion innervates parotid gland.
Cranial nerve 7 through sub mandibular ganglion, innervates sub mandibular gland and sub lingual gland.

Gastric secretions 00:23:27

Source of gastric secretion : Gastric glands, which are flask shaped structures.

- Surface cells : Secrete mucus.
  Which helps in acid neutralization. The surface cells also produce trefoil peptides which have immune functions.
- Neck cells : Found at the necks of the gastric gland.
  These neck cells are considered to be stem cells for stomach regeneration.
- Parietal cells : Produces HCl and intrinsic factor of Castle (for B12 absorption).

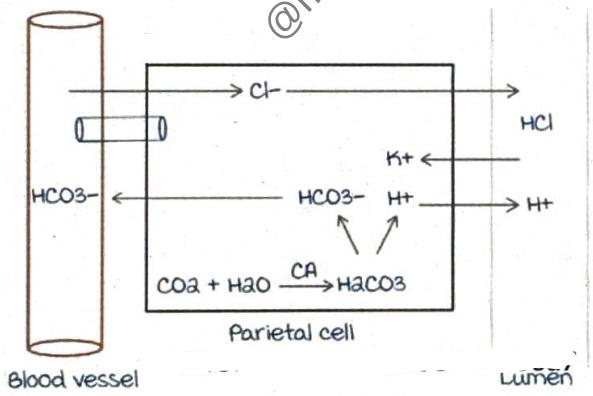
- Enterochromaffin like cells (ECL) : major source of histamine. Histamine also increases acid secretion (in cases of peptic ulcers, histamine blockers are used).
- Chief cells : Produces pepsinogen.
- G-Cells : Seen at the gastric antrum and produces gastrin.



In case of pernicious anemia, where there is damage to parietal cells by auto-antibodies :

- Achlorhydria is seen.
- Vit B12 deficiency causes anemia.

Parietal cells :



In the parietal cells, CO_2 reacts with a molecule of water in the presence of carbonic anhydrase to form carbonic acid. Carbonic acid splits into H^+ ion and bicarbonate ion.

The H^+ ion is thrown into the lumen in exchange for a K^+ ion via the H+ ATPase proton Pump.

HCO_3^- Cl^- exchanger, a channel protein, facilitates Cl^- ion entry into the parietal cell as a bicarbonate ion moves into the blood vessel.

The Cl^- ion then moves into the lumen and reacts with H^+ to form HCl for digestion.

Post prandial alkaline tide :
For every HCl in the lumen, a bicarbonate ion enters the blood vessel.

Agents that increase acid secretion :

- Histamine via H_a receptor.
- Gastrin via cholecystokinin-B receptor.
- Vagal stimulation via Ach which acts on M3 receptor.
- Stomach distention.
- Coffee intake.
- Alcohol.
- Calcium.

Agents to decrease acid secretion :

- Acid (excess acid inhibits its own production, in a negative feedback system).
- Somatostatin from the D-cells.
- Prostaglandins (PGE_a).
- CCK and secretin.
- Calcitonin.

Gastric protein digestion :

- Pepsin : Pepsinogen $\xrightarrow{HCl}$ Pepsin.
- Rennin : Found in cows.

Fat digestion in stomach via gastric lipase.
No enzymes for carbohydrates in gastric secretion.

Phases of gastric secretion :

- Cephalic phase : Occurs in the absence of food i.e by seeing, thinking or talking about food.
  20-30% of gastric production occurs via the sensory stimulation by food without swallowing it.
- Gastric phase : 60-70% of acid production happens due to food intake and is mediated by the hormone, gastrin.
- Intestinal Phase : 10% of acid production occurs.

Pancreatic secretions

00:42:46

Exocrine pancreatic secretion :

It is highly alkaline with a pH of 8.3 as it is bicarbonate rich.

This secretion is needed to counteract the highly acidic gastric secretion.

Pancreatic secretion is the single most important secretion for the digestion of food, it has all the enzymes to digest any food.

Carbohydrate digestion : Pancreatic amylase.

Fat digestion :

- Pancreatic lipase.
- Co-lipase.

Protein :

Protein digesting enzymes are stored as zymogens (inactive form of the enzyme) to prevent auto digestion of pancreas.

- Trypsinogen.
- Chymotrypsinogen.
- Procarboxypeptidase.

In acute pancreatitis, inflammatory processes can prematurely activate them in the pancreas which can cause complications.

Trypsinogen is activated by the removal of few amino acids in small interstine by enterokinase enzyme.

$$\text{Trypsinogen} \xrightarrow{\text{Entereokinase}} \text{Trypsin}$$

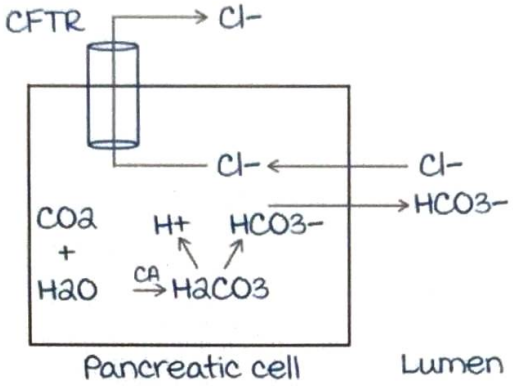
Regulation of pancreatic secretion :

- Cholecystokinin-Pancreozymin (CCK-PZ) :
  Pancreozymin makes the pancreatic secretion rich in enzymes.
  Cholecystokinin causes contraction of gallbladder.
- Secretin :
  Pancreatic secretion rich in bicarbonate ions, therefore makes it alkaline. This is used for acid neutralization.
  Secretin is also called as nature's antacid.

Bicarbonate ion from the pancreatic cell moves into the lumen in exchange for a chloride ion with the help of bicarbonate chloride exchanger.

The chloride entering the pancreatic cell is recycled back outside the pancreatic cell via CFTR (Cystic Fibrosis Transmembrane Regulator).

Therefore, chloride recycling occurs due to CFTR.



Bile

00:55:38

Liver bile is produced at the rate of 500 mL/day.

It contains around 97% water and is stored in gallbladder.

Concentration of bile occurs in the gallbladder (87% water).

Bile consists of :

- Bile acids :

  Primary Bile acids : Cholic acid, chenodeoxycholic acid.

  When these acids reach the intestine, they are converted into secondary bile acids by the intestinal flora.

  Secondary bile acids : Deoxycholic acid, lithocholic acid.

  Bile acids in the liver undergo the process of conjugation (glycine or taurine is added).

- Bile salts : Sodium salt form of conjugated bile acid.

  Example : Sodium glycocholic acid.

  Bile salts, at the terminal ileum are absorbed and recycled back to the liver via portal vein. This is known as enterohepatic circulation.

Enterohepatic circulation happens 6-8 times/day, this is done to avoid the energy intensive procedure of producing the bile salts.

- Bilirubin.
- Cholesterol.

Functions of bile :

- Concerned with the digestion and absorption of fats.
- It is an important mode of excretion for bile pigments and cholesterol.

Regulation of bile :

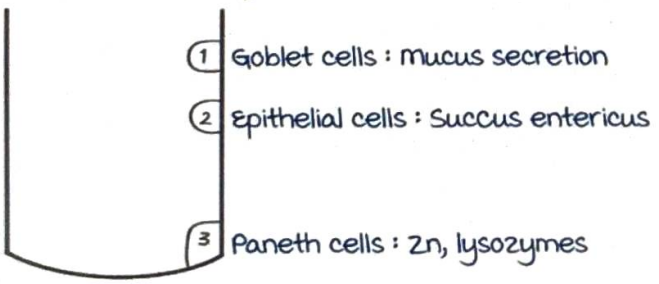
- Choleretics : Agents that increase bile synthesis.
    1. Bile salts.
    2. Secretin.
    3. Vagal stimulation.
- Cholagogue : Agents that release bile by contraction of gallbladder.
    1. Cholecystokinin.

Small intestinal secretions 01:06:38

Produced from the Crypt of Lieberkuhn.

Small Intestine :

- Goblet cells : Secrete mucus and plays role in acid neutralization.
- Epithelial cells : Source for succus entericus.
- Paneth Cells :
  Found at the base of the crypt and have a high concentration of zinc.
  Paneth cells also have defensins and lysozymes which are considered to be anti-bacterial in nature.



Maximum K^+ secretion is found : Saliva (mEq/day).

Highest potassium concentration : Colonic Secretions (mEq/L).

Active space

MCQs

Q. Which of the following agents decrease salivary secretion?

A. Bethanechol.
B. Organophosphates.
C. Pilocarpine.
D. Atropine.

Atropine block the PNS.

Q. Gastric acid secretion is decreased by ?

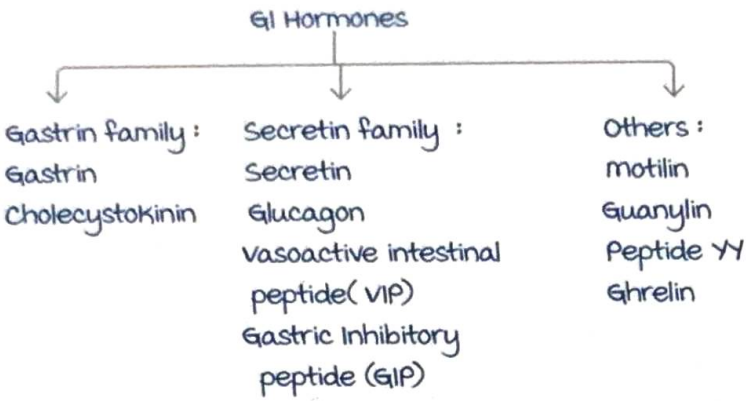
A. Secretin.
B. Vagal stimulation.
C. Proteins in gastric fluids.
D. Gastric antral distension.

Q. The channel that regulates the movement of chloride into lumen is called ?

A. Chloride-bicarbonate exchanger.
B. Na-K pump.
C. Na-H exchanger.
D. Cystic Fibrosis Transmembrane Regulator.

GI HORMONES

Classification of GI hormones 00:00:38



Sources of GI hormones : Entero endocrine cells.

- G cell : Gastrin.
- S cell : Secretin.
- I cell : Cholecystokinin.
- [illegible]
- K cell : GIP.

Gastrin 00:04:26

Produced from G cells in antrum.

Food → Antral distension → Stimulates G cells → Gastrin → Increases acid secretion.

Pepsinogen $\xrightarrow{HCl}$ Pepsin → Protein digestion → Amino acids → Stimulate G cells → Gastrin.

Factors that increase the gastrin levels :

- Antral distension.
- Protein digestion products.
- Vagal endings (GRP : Gastrin Releasing Peptide).
- Ca^{2+}.
- Epinephrine.

Factors that decrease gastrin levels :

- Excess acid.
- D cells : Somatostatin.
- GIP.
- Secretin.

Active space

Actions :

1. Increases acid production : Through CCK-B receptor.
2. Contraction of LES : Prevent gastro esophageal reflux.
3. Increases gastric motility.
4. Trophic action : Stimulates mucosal growth throughout GIT.
5. Increases pepsin secretion.

Cholecystokinin : Pancreozymin 00:12:20

Produced by I cells.
Protein digestion products/fats → Stimulate I cells → CCK-PZ.
Pacreozymin : Pancreatic secretion rich in digestive enzymes.

Cholecystokinin :

- Contraction of gall bladder and relaxation of sphincter of Oddi → Release of bile (cholagogue).
- Inhibits gastric emptying by contraction of pyloric sphincter.
- Stimulates small intestine and colon motility.
- Augments action of secretin.

CCK found in brain → Decreases food intake (satiety)/ anxiety/analgesia.

Acts through CCK-A receptor.
Trophic action : Stimulates growth of exocrine pancreas.

Secretin 00:18:48

First hormone discovered : 1902 by Bayliss and Starling.
Source : S cells.
Acidic chyme → Stimulates S cells → Secretin → Pancreatic secretion rich in HCO_3 : Neutralizes acid (nature's antacid).

Functions :

1. Pancreatic secretion rich in HCO_3^-.
2. Augments CCK.
3. In stomach :

- Decreases gastrin/acid production.
- Contraction of pyloric sphincter.

Active space

GIP and VIP

00:22:46

Stimulant : Carbohydrates → Stimulate K cells → Pancreas → Insulin release.

GI hormones causing insulin release : Incretins (GIP/GLP).

GIP also called Glucose dependent Insulinotrophic Peptide.

VIP : Relaxation of smooth muscle → Vasodilation.

Functions of VIP :

- Increases fluid and electrolyte secretion.
- Decreases acid production.
- Potentiates action of acetylcholine in salivary gland.

Other Hormones

00:27:40

Motilin :

From Mo cells → Increase motility in GI tract (especially during fasting : MMC).

Migratory motor complex (MMC) : Prepares GIT for meal.

Erthromycin stimulates motilin receptor :

- Increases GI motility.
- Used for treatment of gastroparesis.

Guanylin :

Increases Cl^- secretion in GIT.

Structure similar to E coli.

E coli can activate guanylin receptor → Increase Cl^- secretion (molecular mimicry).

Peptide YY : Its major stimulus is fats.

Functions :

- Inhibits ileal motility (Ileal brake phenomenon).
- Decreases gastric motility.
- Decreases acid secretions.

Ghrelin :

Source : Oxyntic gland region of stomach.

Function :

1. Increases food intake : Ghrelin → Hypothalamus → arcuate nucleus → (+) Neuropeptide Y → Increase food intake (hormone of hunger).
2. Instrumental in growth hormone release (first function to be discovered).

3. Increases gastric motility and gastric acid secretion.
4. Increases insulin secretion.
5. Promotes adipogenesis :
   - Ghrelin levels low in obesity.
   - High in anorexia nervosa.

MCQs :

1. A 47-year-old male presented with watery diarrhoea for 10 months. Esophagogastroduodenoscopy (OGD) showed prominent gastric folds and multiple duodenal ulcers. Which hormone excess will be noted in this condition ?

A. Ghrelin.
B. Peptide YY.
C. Somatostatin.
D. Gastrin.

Answer : D. Gastrin. Zollinger Ellison syndrome causing hypergastrinemia.

2. Which hormone contracts smooth muscle in the stomach and intestines in between meals ?

A. Secretin.
B. Cholecystokinin.
C. Motilin.
D. Gastrin.

Answer: C. Motilin.

3. A 55-year old man presented with 4 months history of watery diarrhea, severe generalized weakness, 5 kg of weight loss, a facial rash, and hypokalemia. Which hormone will be elevated in this condition ?

A. GLP.
B. GIP.
C. Somatostatin.
D. Vasoactive Intestinal Peptide (VIP).

Answer : D. Vasoactive Intestinal Peptide (VIP).

DIGESTION AND ABSORPTION

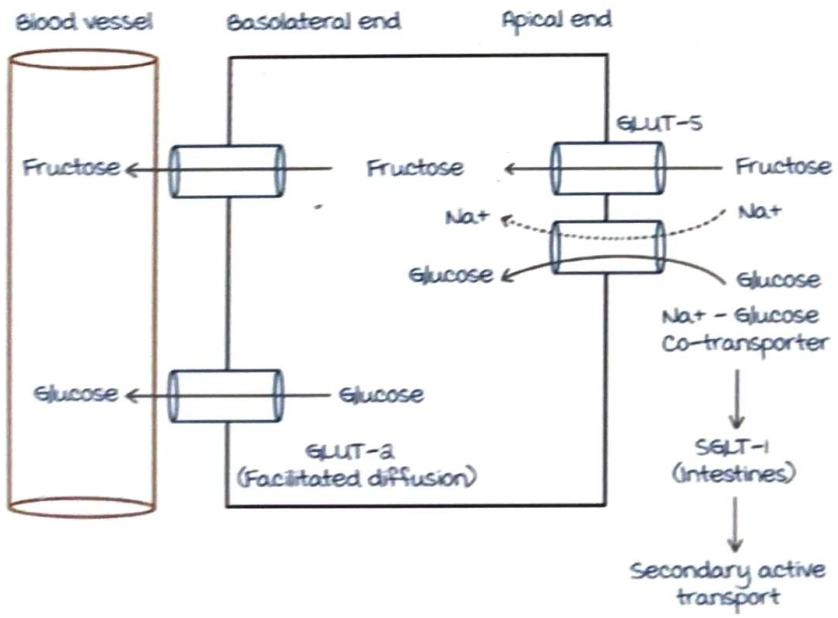
Carbohydrate digestion 00:01:20

Salivary amylase present in saliva :
Activated by chloride ions.
Deactivated by acid (low pH) in stomach.

Stomach : No enzymes for digestion.

Pancreatic amylase from exocrine pancreas :
95% carbohydrate digestion.

Pancreatic amylase acts at the level of 1,4 α linkages
↓
Disaccharides
↓
Disaccharidases - Lactase, Isomaltase & sucrase in the mucosal surface of small intestine (act at the level of 1,6 α linkages)
↓
monosaccharides (glucose & fructose)



Carbohydrate absorption :

Glucose is transported into the intestinal cell from the lumen by SGLT-1 along with Na^+ used in ORS.
From intestinal cell to blood vessel, glucose is transferred by GLUT-2 in the basolateral region.
Fructose absorption : Transported by GLUT-5 and is transported to the bloodstream via GLUT-2.

Lipid digestion

00:09:34

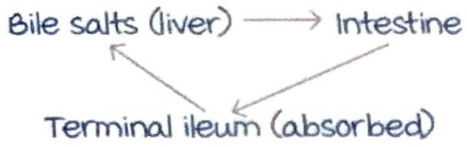
Diet : Triglycerides.
Mouth (saliva) : Lingual lipase (minor role).
Stomach : Gastric lipase (minor role).
Pancreas :

- Pancreatic lipase.
- Colipase.
- Cholesterol esterase.

Triglycerides
↓ Lipase, Colipase, C. esterase
Free fatty acids, cholesterol, fat soluble vitamins A,D,E,K
↓
Incorporated into micelles
(high concentration of free fatty acids)
↓
micelles come closer to mucosal cell & Free Fatty Acid (FFA) move into mucosal cells
↓
Passive diffusion (high to low concentration)
↓
In mucosal cell, FFA are re-esterified into triglycerides
↓
Chylomicrons are formed by triglycerides

Bile :
Emulsification of fats and incorporation into micelles.
Formation of bile salts is an energy dependent process.

Enterohepatic circulation : To reduce forming new bile salts.



Recycling of bile salts : 6 to 8 times/day.

Short chain fatty acid (SCFA) : Produced by bacteria in colon,

- Propionate.
- Butyrate.
- Acetate.

Functions :

- Trophic action (increase mucosal growth).
- Acid-base balance (during absorption H^+ is exchanged).
- Prevent inflammation.

Protein digestion 00:19:20

Diet : Polypeptides.
Mouth (saliva) : No enzymes.

Stomach : Pepsin.
Pancreas :

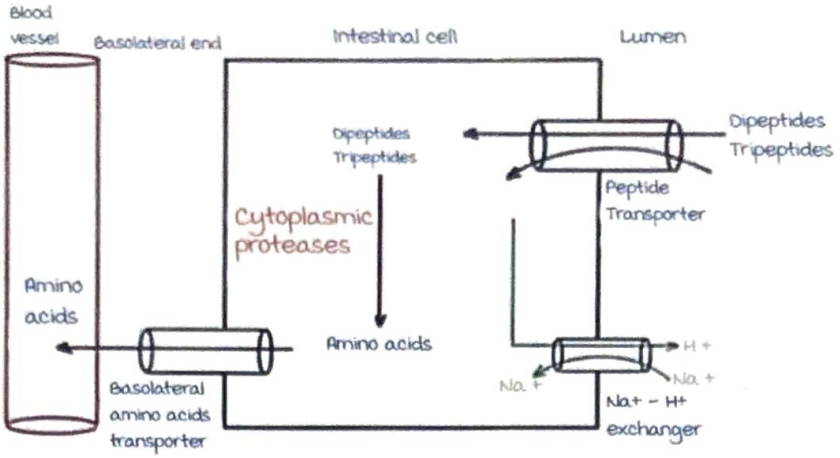
Trypsinogen.
Chymotrypsinogen.
Procarboxypeptidases.

These zymogens are in inactive form to prevent autodigestion of pancreas.

Trypsinogen is converted to trypsin in the presence of enterokinase in small intestine.

Chymotrypsinogen to chymotrypsin and formation of carboxypeptidases from procarboxypeptidase both are catalysed by trypsin.
Chymotrypsin and trypsin are endopeptidases : Acts on peptide bonds in the interior region.

Carboxypeptidases are exopeptidase : Acts on bonds in end region.



Peptidase :

Dipeptidase/tripeptides

↓

PepT carries this into the intestinal cells along with H^+

↓

H^+ is transferred out by exchange with Nat using Na^+ H^+ exchanger

↓

Cytoplasmic proteases act on dipeptides/tripeptides and convert them in to amino acids

↓

Amino acids are transported into blood vessel by basolateral end of intestinal epithelium

Vitamin absorption :

~~Fat soluble (Vit A,~~ D, E, K) → Carried in micelles → Absorbed into mucosal cell.

Water soluble vitamins → Absorption by Na^+ dependent transporters (except folate, Vit B_{12}).

Folate absorption is in upper small intestine : Duodenum, jejunum.

Vitamin B_{12} is absorbed in terminal ileum.

Water :

The GIT has a daily total secretion of 9 litres.

Out of it, 8.8 liters is reabsorbed. 200 ml is lost in feces.

The maximum water absorption in GIT : Jejunum (5.5 L/day).

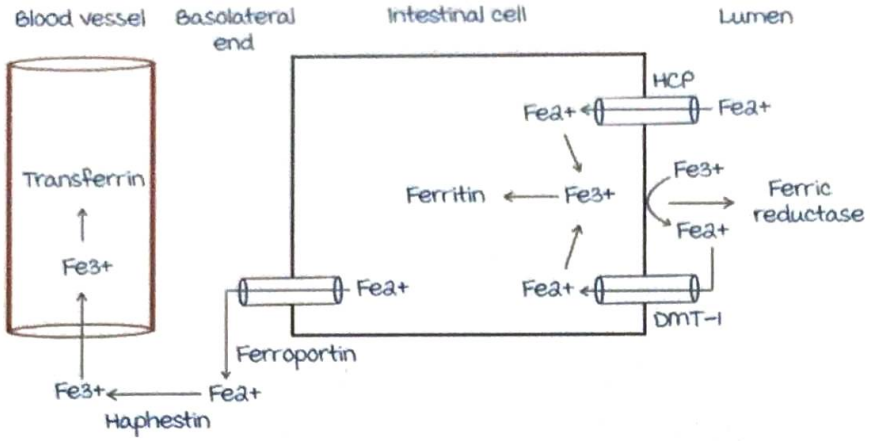
Active space

Iron absorption

00:33:43

Diet : Present as Ferric (Fe^{3+}) form.

Absorbable form : Ferrous (Fe^{2+}) form.



Ferric reductase converts Fe^{3+} to Fe^{2+}

↓

Divalent metal transporter/DMT-1, transports Fe^{2+} into intestinal cells

↓

Heme carrier protein also carries Fe^{2+} into the intestinal cell

↓

Inside intestinal cells, Fe^{2+} is converted to Fe^{3+} and stored as ferritin

↓

The remaining Fe^{2+} is transported out through the basolateral end by ferroportin

↓

Converted to Fe^{3+} by haphestin

↓

Fe^{3+} moves into the blood vessel and is transported with transferrin

Factors that increase iron absorption :

Vitamin C (ascorbic acid).

Factors that decrease iron absorption :

- Antacids.
- Tannins.
- Phytates.
- Oxalates.

Iron absorption depends on :

- Dietary iron intake.
- Body iron stores.
- State of erythropoietic activity in bone marrow.

Regulation of iron absorption : Hepcidin.

- It decreases iron absorption.
- Acts by internalization and destruction of ferroportin.
- Iron is trapped in the mucosal cells and is shed off, thus decreasing iron absorption.
- Hepcidin mutation leads to iron overload (hemochromatosis).

Questions

00:45:33

Q. Following is given with iron to increase its absorption ?

A. Milk.
B. Antacids.
C. Citrus fruits.
D. Alkalis.

Q. A 12 year old boy presented to the hospital with a 3-day history of watery diarrhoea and fever. Rehydration and electrolytic balance were restored with intravenous fluid therapy by oral rehydration solution (ORS). The basis of ORS action is ?

A. GLUT-5.
B. SGLT-1.
C. SGLT-2.
D. GLUT-4.

Q. Which protein mutation is associated with hemochromatosis ?

A. GM-CSF.
B. Thrombopoietin.
C. Erythropoietin.
D. Hepcidin.

Active space

GASTRO INTESTINAL MOTILITY

Movement of food particle → Gastro intestinal (GI) smooth muscle.

Contraction and relaxation → works as a single unit with gap junction.

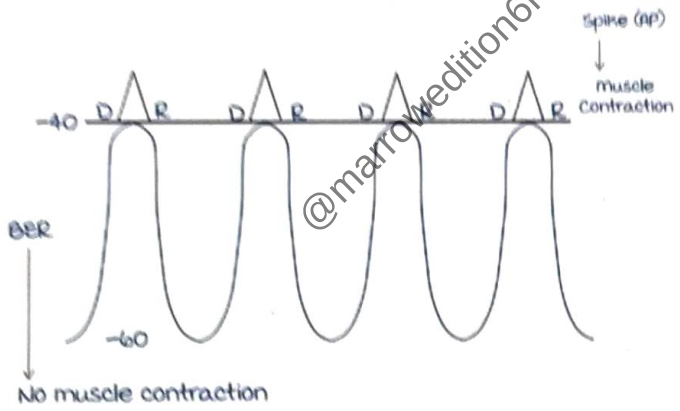
Skeletal muscles are voluntary.

Smooth muscles are involuntary.

Involuntary actions controlled by Pacemakers (Pm).

Pacemakers (Pm) for GI smooth muscles are Cajal cells (interstitial cells of Cajal).

Pm is characterised by Restless Membrane Potential (RMP) oscillating between -60 mV to -40 mV called as Basal Electrical Rhythm (BER).



BER is not an action potential (AP) hence there is no muscle contraction.

Only action potential can cause muscle contraction.

On crossing the threshold, it becomes Action Potential (AP) and causes spikes (spike potential)

The AP have Depolarisation (D) and Repolarisation (R).

Ca^{2+} influx causes depolarisation.

K^{+} efflux causes repolarisation.

Increase in spikes

↓

Increase in muscle contraction

↓

Increase in tension generation :

Under influence of Parasympathetic Nervous System (PNS) with Acetylcholine (Ach).

Decrease in spike

↓

Decrease in muscle contraction.

↓

Decrease in tension generation :

Under influence of Sympathetic Nervous System (SNS) with Norepinephrine (NE).

Frequency of BER

00:07:47

Duodenum : 12 oscillations/min (Highest).

Ileum : 8 oscillations/min.

Stomach : 4 oscillations/min.

Caecum : 2 oscillations/min (lowest).

Intertitial Cells of Cajal (ICC) : Located in mid body of stomach along the greater curvature.

Clinical significance :

Tumor arising from ICC : Gastrointestinal Stromal Tumor(GIST).

Food → mouth

↓

Swallowing /deglutition : Oral stage (Voluntary)

↓

Pharyngeal stage (Involuntary)

↓

Oesophageal stage (Involuntary)

Deglutition reflex

00:11:58

Deglutition reflex : Required for coordination of swallowing.
Afferent : 5th cranial nerve (CN), 9th CN and 10th CN.

↓

Centre : Nucleus Tractus Solitarius (NTS) of medulla.

↓

Efferent : 5th CN, 7th CN, Hypoglossal nerve.

↓

Pharyngeal muscles and tongue → Swallowing of food.

Peristalsis

00:14:06

Oesophageal motility pattern is peristalsis.
Peristaltic contraction :

1. Primary : Progressive.
   Helps in movement of food downwards.
   Physiological.
2. Secondary : Progressive.
   Seen during irritation of oesophagus.
3. Tertiary : Non progressive.
   Seen during oesophageal spasm.

Peristalsis initiation is by local stretch of gut (usually food).

↓

Serotonin released.

↓

Activates myenteric plexus.

↓

Controls peristalsis.

The segment before the food undergoes contraction and segment after food undergoes receptive relaxation.
Contracting segment pushes food forward.
Relaxing segment receives food.

Agents for contracting segment :
Acetyl Choline.
Substance P.

Agents for relaxing segment :

Nitric oxide.

Vasoactive Intestinal Peptide (VIP).

In lower esophageal sphincter region,

Absence of nitric oxide.

↓

Unopposed action of Ach.

Sustained contractions → Achalasia cardia.

Treatment : Botox (Botulinum toxin) inhibits release of Ach.

Gastric motility 00:21:54

Movement of food from esophagus to stomach is by gastric motility.

With food intake → Proximal part of stomach undergoes receptive relaxation to recieve food → Once it is received → Storage of food (also called gastric accommodation).

Retropulsion : Food in stomach is pushed back into the stomach due to contracted state of the pylorus.
This cycle helps in mixing and grinding of food.

Gastric emptying (GE) : Food eventually crosses pylorus after it relaxses, stomach empties its content into the small intestine (1st part of duodenum).

Factors affecting gastric empyting :

Increase in GE :

1. Increased gastric volume.
2. Gastrin.
3. Ach.
4. Substance P.
5. Substance K.
6. Motilin.
7. Serotonin.

Decrease in GE :

1. In duodenum, presence of :
   - Carbohydrate
   - Proteins.
   - Fats.
   - Acid.
   - Hyperosmolar.

   } Indicates incomplete digestion leading to enterogastric reflex which decreases gastric empyting.
2. Cholecystokinin (CCK).
3. Secretin.
4. Nitric oxide.
5. VIP.
6. Somatostatin (universal inhibitor).
7. Dopamine.
8. Encephalin.

Enterogastric reflex is an enteric reflex regulated at the level of gastro intestinal tract.

Defecation in newborn :

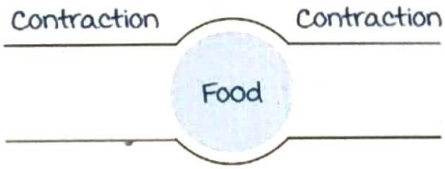
Defecation following a meal is a rule in newborn due to gastro colic reflex.

Increase in stomach distention → Increase colonic motility → Defecation.

This reflex is amplified by gastrin.

Motility in small intestine 00:33:08

1. Peristalsis movement pattern.
2. Segmentation :



Both ends undergoes contraction → Aids in slowing down the movement of food → Ensures adequate time for digestion and absorption.

Exclusively seen in small intestine.

Factors affecting small intestine motility :

Increase :

1. Gastro enteric reflex.
2. Gastro ileal reflex.
3. Gastrin.
4. CCK.
5. Parasympathetic nervous system.
6. motilin.
7. Serotonin.
8. Insulin.

Decrease :

1. Sympathetic nervous system.
2. Secretin.

Large intestine motility

00:37:18

Proximal colon : Absorption of water and electrolytes.
Distal colon : Storage of faeces and eventually defecation.
Maximum motility in sigmoid colon.

Motility patterns :

- Haustrations :
  Seen in proximal colon.
  Combined contraction of longitudinal and circular muscles.
  Aids in absorption of water and electrolytes.
- Mass movement :
  The content in one segment of colon travels a long distance into another segment.
  Movement is segment wise.
  The content eventually moves into rectum and causes rectal distention.

Rectal distention → Increased motility in distal colon → Defecation.

Transit time

00:41:38

Oesophagus : 2-3 seconds.
Stomach : 2-5 hours.
Small intestine : 3-6 hours.
Caecum : 4 hours.
Proximal 1/3rd of colon : 6 hours.

Distal 2/3rd of colon : 9 hours.

Sigmoid colon : 12 hours.

Defecation :

Control by sphincters :

- Internal anal sphincters (IAS) :
  Made of smooth muscle.
  Involuntary.
  Parasympathetic nervous system → Relaxation of IAS → Defecation (D).
  PNS is facilitatory for defecation.

  Sympathetic nervous system → Contraction of IAS.
  SNS is inhibitory to defecation.

- External anal sphincter (EAS) :
  Made of skeletal muscle.
  Voluntary.
  Under the control of pudendal nerve.

Defecation reflex :

Rectal distention → Afferents
↓
Centre : Spinal cord
↓
PNS : Relax IAS
↓
If situations favourable for defecation voluntary relaxation of EAS occurs
↓
Powerful contraction of abdominal muscles, rectum, colon.
↓
Defecation.

1st urge to defecate : Rectal pressure is 18mm Hg
↓
When Rectal pressure reaches 55mm Hg
↓
Cannot voluntarily hold defecation
↓
Violent relaxation of both IAS and EAS
} Soiling

Active space

Dietary fibres 00:48:48

It is advised to consume food rich in dietary fibre content.
Plant materials resistant to enzymatic digestion.
Also called as roughage.

Examples :

- Lignin.
- Pectin.
- Cellulose.
- Hemicellulose.
- Foods rich in cereal grains.
- Fruits
- Vegetables.

Functions :

- Add bulk to diet thereby decreases appetite.
- Slows absorption of glucose.
- Reduce total and LDL cholesterol.
- Microflora in GI tract convert fibres into Short Chain Fatty Acids (SCFAs).
- Hold water thereby adding bulk to stool.
- Prevent colonic diverticula.

Migratory Motor Complex (MMC) 00:52:38

Occurs during fasting (or interdigestive stage).
A contraction originating in stomach migrates all over the GI tract to end in the colon.

Functions :

- Helps in clearing :
  Foreign body.
  Accumulation of bacteria.
  Undigested food particle.
  } To colon, hence MMC considered as sweeper

For example, when children swallows coin/foreign body, parent is advised to keep child in fasting for MMC.

- Keeps GIT clean.
- Prepares GIT for next meal.

One MMC occurs in every 90 min and moves at rate of 5cm/minute.

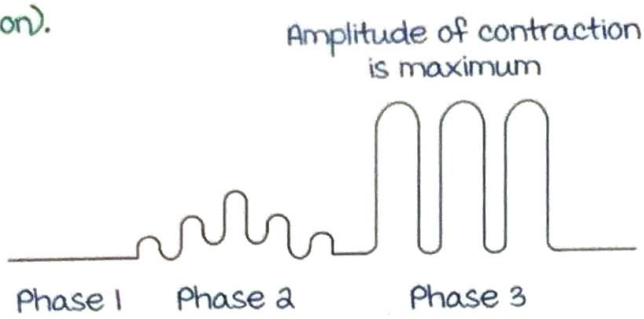
Active space

Phases of MMC :

Phase 1 : Quiescent state / no activity.

Phase 2 : Irregular contractions.

Phase 3 : Regular activity (maximum amplitude of contraction).



MMC is regulated by motilin hormone (from Mo cells), hence it is called the time keeper.

Motilin acts through the motilin receptor.

Erythromycin also can act through the motilin receptor, hence it increases motility.

Erythromycin is therefore used in gastroparesis (where there is reduced gastric motility).

Gastroparesis is commonly seen in Diabetes.

MCQs

Q. In infants, defecation often following meal. The cause of colonic contraction in this situation is ?

A. Gastroileal reflex.
B. Enterogastric reflex.
C. Increased circulation levels of CCK.
D. Gastrocolic reflex.

Amplified by Gastrin hormone.

Q. Mass movement of the colon would be abolished by ?

A. Extrinsic denervation.
B. Distension of the colon.
C. Gastrocolic reflex.
D. Destruction of Auerbach's plexus.

Myentric plexus also called Auerbach's plexus

Q. What is responsible for clearing and flushing food from the intestinal lumen in the interdigestive period ?

A. Segmentation.
B. Migrating motor complexes.
C. Haustrations.
D. Peristalsis.

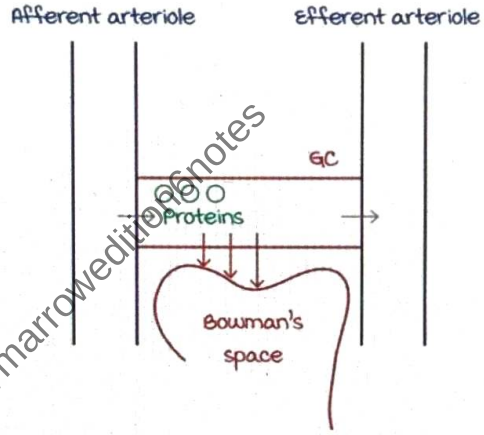
Active space

GLOMERULAR FILTRATION RATE

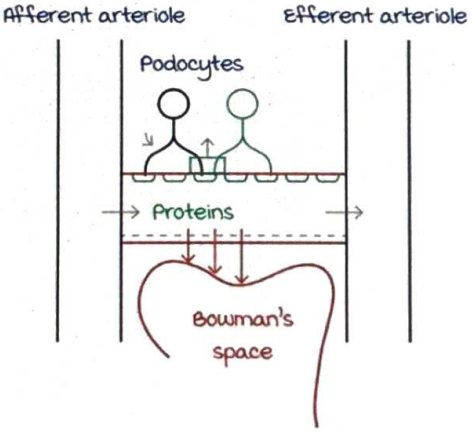
Functional Units

00:00:58

- Key unit : Nephrons (1 million nephrons/kidney).
- Function : Glomerular filtration.
  (Glomerular : Begins in the glomerular capillaries (GC).
  Filtration : Most important function of the kidneys).
- Unique feature of GC : The only capillary which lie in between 2 arterioles.
- GFR = 125ml/min or 180L/day.



Proteins not filtered :



1. Charge : Proteins are anions.
   GC is lined by a negatively charged substance (heparan sulphate).
   Proteins and GC thus repel each other.

2. Size : GC cells have a small gap in between called Fenestrations(4-8nm), thus restrict protein passage.
   If negative charge in GC is lost (any disease process) → Proteins will get filtered.
3. Foot processes of podocyte touch each other to form the slit diaphragm.

3 Structural proteins are responsible for the integrity of slit diaphragm :

Protein	mutation
1. Nephrin (coded by NPHS1 gene)	Congenital Finnish type nephrotic syndrome
2. Podocin	Steroid resistant nephrotic syndrome
3. Alpha actinin	Focal Segmental Glomerulosclerosis

GFR determinants : Starling forces 00:14:08

- Forces required for filtration.
- Types :

Favoring forces	Opposing forces
1. Hydrostatic pressure in GC (P_c). P_c = 60 mmHg.	1. Oncotic pressure of GC (π_c) π_c = 32 mmHg.
	2. Hydrostatic pressure in Bowman's space (P_b). P_b = 18 mmHg.

- Net Filtration Pressure (NFP) :
  = Favoring − Opposing forces
  = $P_c - (\pi_c + P_b)$
  = 60 − (32+18)
  NFP = 10 mmHg

Proteins are not filtered in healthy individuals.

Thus oncotic pressure in Bowman's space (π_b) = 0.

Hydrostatic pressure in Bowman's space (P_b) raised in renal stones → Decrease GFR.

Measurement of GFR

00:21:18

- Gold standard for estimating GFR is inulin due to following factors :
  1. Freely filtered.
  2. No reabsorption.
  3. No secretion.
  4. Non toxic.
- Procedure : Inulin IV → Plasma inulin concentration (P) → Kidneys → Filtration

$$GFR = \frac{\text{Urine concentration(U)} \times \text{Volume of urine(V)}}{\text{Plasma inulin concentration(P)}}$$

GFR= (U x V)/P.

- Inulin completely cleared.
- Inulin clearance : 125ml/min (Gold Standard).
- Clinical estimation of GFR : Plasma creatinine value. if Plasma Creatinine level rises, GFR falls. (inversely proportional)
- New marker : Cystatin C.

If Clearance (C) = GFR → No reabsorption/secretion (inulin).

If C > GFR → Net secretion (Para Amino Hippuric acid-PAH).

If C < GFR → Net reabsorption (Glucose).

Renal Plasma Flow

00:29:38

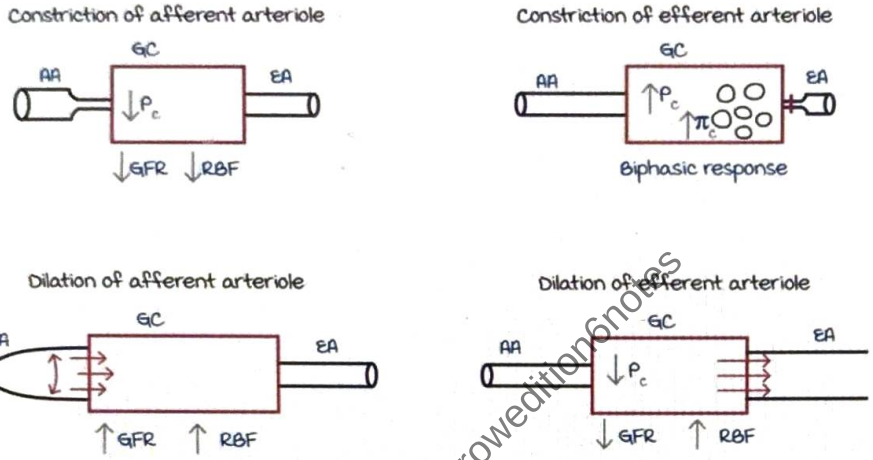
- Renal circulation required to perform glomerular filtration.
- Renal blood flow (RBF) : 1250 ml/min (1-1.5 L/min).
- Kidneys receive 20-25% of cardiac output.
- Only plasma is filtered : Renal plasma flow (RPF).
- RPF : 625 ml/min (55% of RBF).
- Estimation of RPF : Para Amino Hippuric acid (PAH).

- Effective RPF (ERPF) : 625ml/min (Low because only 90% of PAH is extracted). Extraction ratio = 0.9.
- True RPF= 625/Extraction Ratio = 625/0.9 = 700ml/min.
- GFR/RPF = Filtration fraction (FF) = 20%.
- Substances needed to measure FF : Inulin and PAH.

Changes in GFR

00:38:02

- Constriction decreases blood flow.
- Dilation increases blood flow.



Arteriole		Agents	GFR	RBF
Afferent	Constriction	Norepinephrine (in shock).	↓	↓
	Dilation	PG's (PGE_2) : • Increase blood flow to renal cortex. • Decrease blood flow to renal medulla.	↑	↑
Efferent	Constriction	Angiotensin-II	Biphasic response ↑ GFR by ↑ P_c (initially) ↓ GFR by ↑ π_c (later)	↓
	Dilation	ACE inhibitors	↓	↑

Source of PGE2 : Renal Medullary Interstitial Cells (RMICs).

Active space

Regulation of GFR

00:52:46

1. Autoregulation : GFR remains constant in BP range of 80-180 mmHg.
   - mechanism 1 (myogenic mechanism) : Increase in blood flow → Stretch vascular smooth muscles(VSM) → Ca^{2+} channels open → vasoconstriction → Decreased blood flow.

     myogenic mechanism abolished in paralysis of VSM.

   - mechanism 2(Tubulo- Glomerular feedback) : Increase in GFR → more NaCl filtered → Activates macula densa (GFR sensor) → Adenosine release → Afferent arteriole constriction → Decrease in GFR.

     Macula densa is found in tubules.

   - High protein intake : Increase in amino acid → more amino acids and Na+ reabsorbed in PCT → macula densa receives less Na^+ → Activates RAAS (Renin angiotensin aldosterone system)→ Increases GFR.

2. Mesangial cells (MC) :
   - Glomerular capillaries(GC) surrounded by MC.
   - Constriction of MC compresses GC → Less blood flow to GC → Decrease in GFR.
   - Relaxation of MC → Expansion of GCs → more blood flow → Increase in GFR.

Mesangial cells	Agents	GFR
Constriction	• Endothelin • Angiotensin – II • Nor-epinephrine	↓
Relaxation	• Nitric oxide • Natriuretic peptide (ANP) • cAMP • Dopamine	↑

Questions

01:06:00

Q. During Hypovolemic shock which of the following action of norepinephrine is seen?

A. Constriction of efferent arterioles.

B. Constriction of afferent arterioles.

C. Dilation of efferent arterioles.

D. Dilation of afferent arterioles.

Answer : B. Constriction of afferent arterioles.

Q. High protein diet increases GFR because amino acids are coupled with resorption of?

A. Calcium.

B. Potassium.

C. Magnesium.

D. Sodium.

Answer : D. Sodium.

Q. Urine flow rate is 10 ml/min, plasma inulin is 2 mg/ml and urine inulin is 20 mg/ml. Calculate GFR?

A. 125 ml/min.

B. 225 ml/min.

C. 50 ml/min.

D. 100 ml/min.

Answer: D. 100 ml/min.

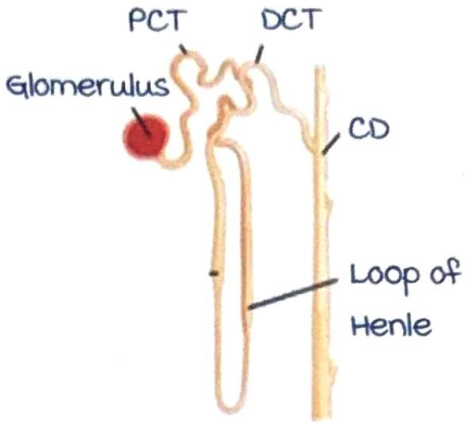
PROXIMAL CONVOLUTED TUBULE

Nephron

00:00:30

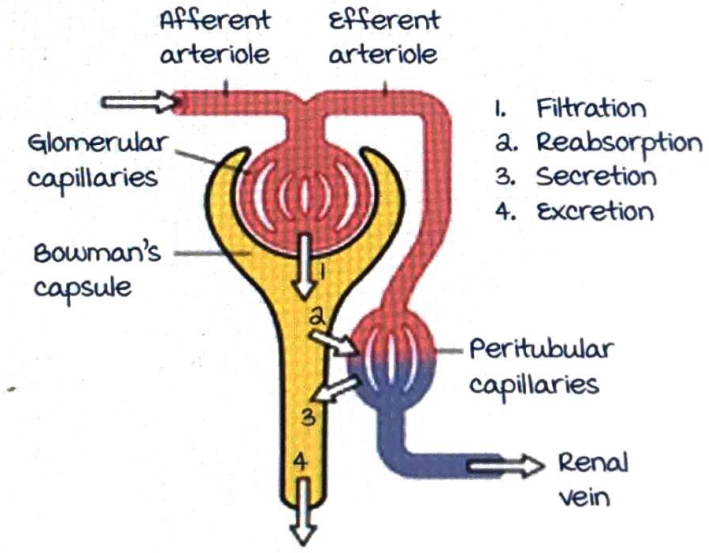
Parts of a nephron :

- Glomerulus.
- PCT/Proximal Convoluted Tubule.
- Loop of Henle.
- DCT/Distal Convoluted Tubule.
- Collecting duct.



Basic renal processes :

- Filtration : Shift of fluid from glomerulus to PCT.
- Reabsorption : Mainly from PCT to peritubular capillaries.
- Secretion : From peritubular capillaries into the tubules.
- Excretion : Filtration − reabsorption + secretion.



Excretion = Filtration − Reabsorption + Secretion

Proximal convoluted tubule/PCT 00:03:48

microvilli (finger-like projections) are present which increase the surface area for reabsorption.
Abundant mitochondria, as majority of the reabsorption processes are through active transport mechanisms.
PCT is the site of maximum reabsorption.
Leaky tight junctions between cells.
(DCT : Tight junctions between cells are tight).

Components of Proximal tubule :

- Proximal convoluted tubule.
- Proximal straight tubule.

Segments of PCT :

- S1 : 1st half of PCT.
- S2 : 2nd half of PCT + 1st half of proximal straight tubule.
- S3 : 2nd half of proximal straight tubule.

  This site is more prone for ischemia and injury.

Percentage of reabsorption occurring in PCT out of the filtered load from glomerulus :

- Na^+ : 2/3rd of filtered load (67%).
- Water : 67%.
- K^+ : 67%.
- Ca^{2+} : 70%.
- PO_4^{3-} and HCO_3^- : 80%.
- Glucose and amino acids : 100%.
  (Complete effective reabsorption).

Na^+ reabsorption 00:11:07

Channel proteins for Na^+ reabsorption in PCT :

- Na^+ H^+ exchanger.
- $Na^+PO_4^{3-}$ cotransporter.
- Na^+ amino acid cotransporter.
- Na^+ glucose cotransporter.

1st half of PCT :
Na^+ is reabsorbed along with PO_4^{3-}, amino acids and glucose.
Hence, corresponding Cl^- rise in the lumen of tubules.
2nd half of PCT : Na^+ is reabsorbed with Cl^-.

Water reabsorption 00:14:17

Reabsorbed along with Na^+ by osmosis.
There is equal amounts of Na^+ and water reabsorption.
Obligatory water reabsorption : [illegible] control.

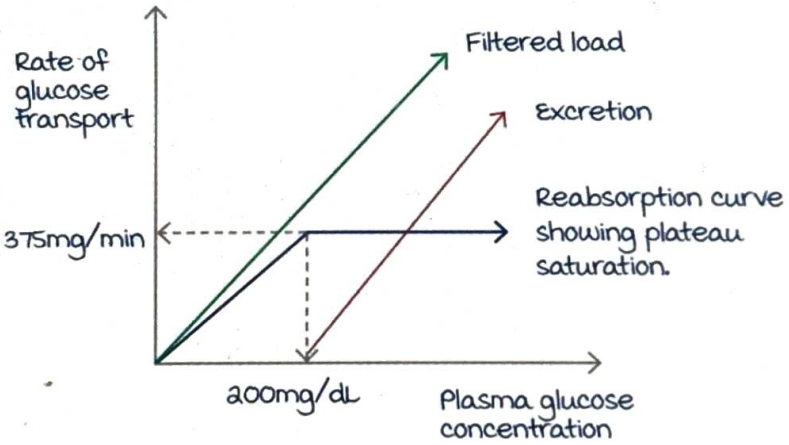
Facultative water reabsorption : Anti-diuretic hormone (ADH) regulates water reabsorption only in collecting ducts.

Glucose reabsorption 00:17:43

Complete effective reabsorption (100%) of glucose reabsorption in PCT through SGLT-2 (Na^+ glucose cotransporter)
SGLT-2 blockers :

- Gliflozin group of drugs : Canagliflozin, Dapagliflozin.
- Used in the treatment of diabetes mellitus.
- Side effects (due to the excretion of glucose in urine) : Urinary tract infections (UTIs).

SGLT-2 channel protein :
Secondary active transport process.
Exhibits saturation.



Maximum rate of transport of glucose is 375 mg/min (TMG Transport Maximum for Glucose).
200mg/dL : Plasma concentration of glucose, beyond which there is excretion of the excess glucose.
(Renal glycosuria/ renal threshold for glucose).
Splay : Deviation seen in reabsorption curve from the filtered load curve because each nephron has different TM.

Active space

Tubular fluid plasma ratio (TF/P) 00:29:16

Substances which are filtered → Tubules (PCT) → Reabsorption → Plasma

more reabsorption of substances from the tubules → Decrease in concentration in tubules (TF ↓ /P ↑).
If TF/P ratio of any substance is equal to 1, reabsorption of that substance is equal to water reabsorption.

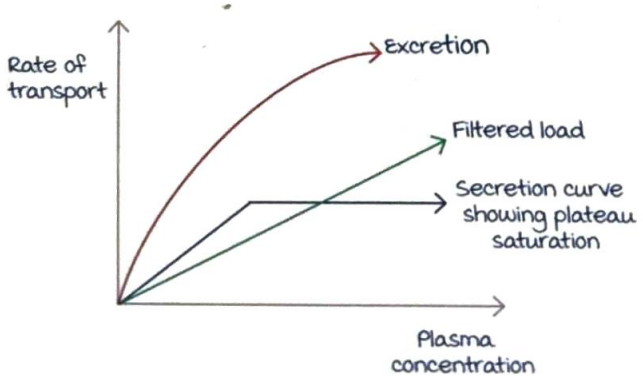
TF/P = 1 for Na^+,
Both Na^+ and water are reabsorbed in same amounts → Osmolarity remains unaffected → Fluid is isotonic in PCT.

TF/P < 1 : Reabsorption of the substance is more than the reabsorption of water.
Examples : HCO_3^-, glucose, amino acids.

TF/P > 1 : Reabsorption of the substance is less than that of water.
Examples : Inulin, para-amino hippuric acid (PAH), Cl^-.

PCT : Secretion 00:35:28

Secretion of para-amino hippuric acid (PAH) occurs via carrier proteins which show saturation.
The final excretion of PAH = Filtered load + Secretion.
Early part of excretion is more steep (Excretion = Filtered load + Secretion).
Later part of excretion is less steep (Excretion = Filtered load).



Q. Which refers to the point where glucose carrier proteins in PCT are fully saturated?

A. Renal threshold for glucose.
B. Transport maximum for glucose.
C. Renal glycosuria.
D. Renal splay.

Answer : Transport maximum for glucose.

Q. Important transporters for sodium reabsorption in PCT are all except ?

A. Na Glucose symport.
B. Na phosphate cotransporter.
C. Na H symport.
D. Na amino acids cotransporter.

Answer : Na H symport. (Na H exchanger should have been there.)

Q. mutation in which channel protein leads to isolated renal glycosuria ?

A. SGLT- 1.
B. GLUT- 4.
C. Aquaporin - 1.
D. SGLT- 2.

Answer : SGLT- 2.
Aquaporin - 1 is the channel for water reabsorption in PCT.

LOOP OF HENLE & DCT

Loop of Henle/LOH

00:00:16

Loop of Henle receives isotonic fluid from PCT having osmolarity of 300mOsm/L.

Helps in :

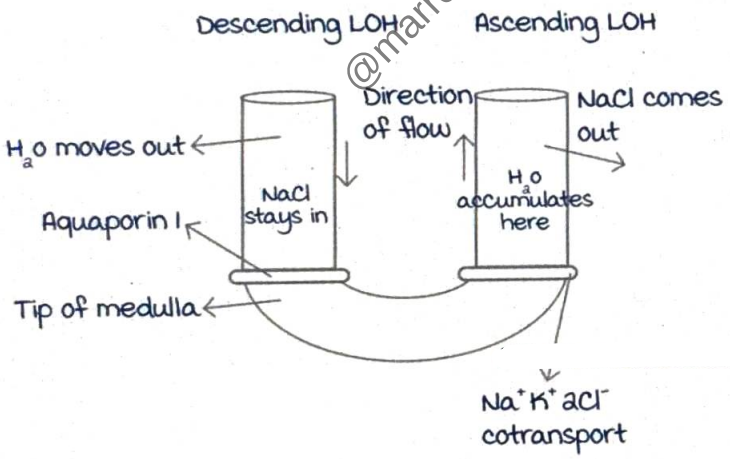
- Concentration of urine.
- Diluting the concentration of urine.

Counter current system :

2 tube like structures close to each other known as descending and ascending loops of Henle have opposite direction of fluid movement known as Counter Current System.

Seen in :

- Kidneys (LOH).
- Intestines.
- Testis.



Descending loop of Henle :

Descending LOH is only permeable to water, (only H_2O can move out) & impermeable to solutes like sodium chloride.

Isotonic fluid from PCT having osmolarity of 300mOsm/L is received by descending LOH.

Since Na^+ cannot move out, concentration occurs inside descending LOH → 1200 mOsm/L (max) at tip of medulla.

Aquaporin I helps in H_2O movement outside from descending LOH.

Active space

Descending LOH is considered the concentrating segment of nephron or counter current multiplier.

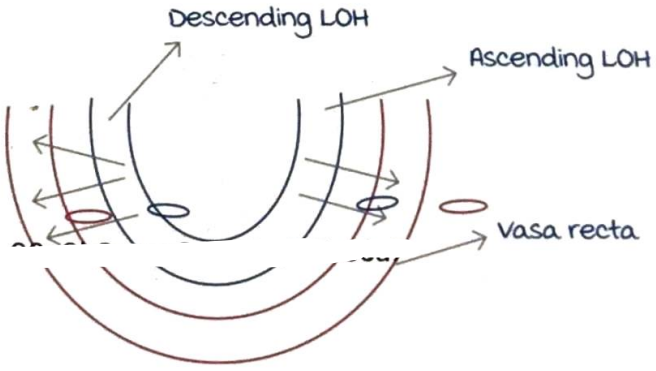
Ascending loop of Henle :
Thick Ascending LOH is only permeable to solutes like NaCl, totally impermeable to water.
NaCl comes out of ascending LOH through $Na^+K^+2Cl^-$ cotransporter.
Ascending LOH undergoes dilution as H_2O accumulates inside → Back to 300 mOsm/L.
Ascending LOH is considered diluting segment of nephron.
$Na^+K^+2Cl^-$ cotransporter can be blocked by loop diuretics (Furosemide) which will inhibit Na^+ reabsorption and cause Na^+ excretion.

Medullary hyperosmolarity → Na^+ coming out through cotransporter gets accumulated in the tip of medulla leading to hyperosmolarity → Required for anti-diuretic hormone (ADH) to act on collecting duct/CD for H_2O reabsorption.

It depends on the length of loop of Henle
(more length = more osmolarity).

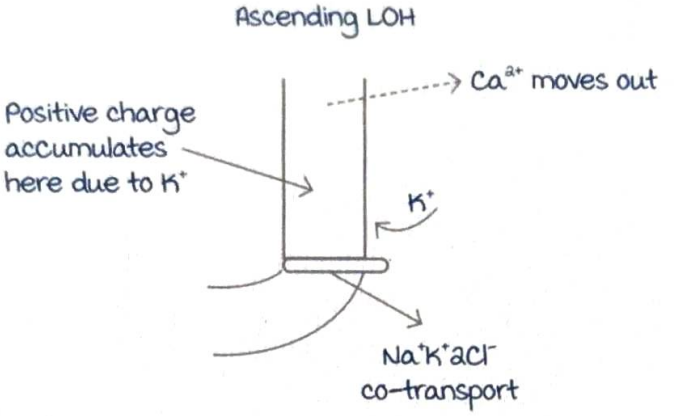
Counter current multiplier (Descending LOH) 00:12:16

Vasa recta (blood vessel) follows loop of Henle closely through its entire length.
It exchanges the developed osmolarity (to prevent wash out) → Counter current exchanger.



Calcium reabsorption in thick ascending LOH :
K^+ coming out through cotransporter gets recycled back into the ascending LOH.

The inside of the loop accumulates the positive charge resulting in reabsorption of Ca^{2+} as it moves out.
Loop diuretic which is a blocker for the cotransporter inhibits the recycling of K^+ and hence increases excretion of Ca^{2+} by preventing calcium reabsorption.



Classification of nephrons based on LOH

Cortical nephrons	Juxta-medullary nephrons
Short LOH.	Long LOH.
85% of nephrons.	15% of nephrons.
	Used for concentration and dilution.

Single effect in loop of Henle:
Unlike PCT where Na^+ and H_2O go together, in descending loop of Henle, the walls are impermeable to solutes but 100% permeable to water whereas, ascending loop of Henle is permeable to solutes like Na^+ and impermeable to H_2O.
Since Na^+ & H_2O behave separately in loop of Henle, this is known as the single effect.

medullary hyperosmolarity in LOH is due to Na+/ solutes (50%) and urea (50%).

The urea is derived from collecting duct under the influence of anti diuretic hormone.
ADH uses specific urea transporter UTA_1 and UTA_3.

We tend to pass concentrated urine whenever there is an intake of high protein diet as the end result of protein metabolism is urea which is responsible for 50% of medullary hyperosmolarity.

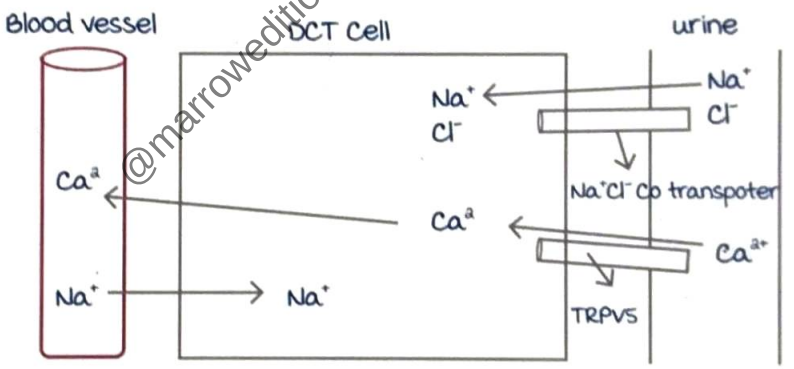
Active space

Urine osmolarity :
Range → 50-1400 mOsm/L.
Average → 100-800 mOsm/L.

Distal convoluted tubule/DCT 00:25:05

NaCl reabsorption and Ca^{a+} reabsorption occurs here.
When DCT comes near its own glomerulus it forms a special apparatus known as juxta-glomerular apparatus /JGA.
Na^+Cl^- cotransporter in DCT helps in sodium and chloride reabsorption.
This Co transporter is blocked by thiazide diuretic, sodium chloride reabsorption is inhibited and thus sodium is excreted in urine.
Na^+Cl^- cotransporter mutation DCT → Gitelman syndrome.

Calcium is reabsorbed in DCT by a specific transporter known as Transient Receptor Potential Vanilloid 5/TRPV 5.

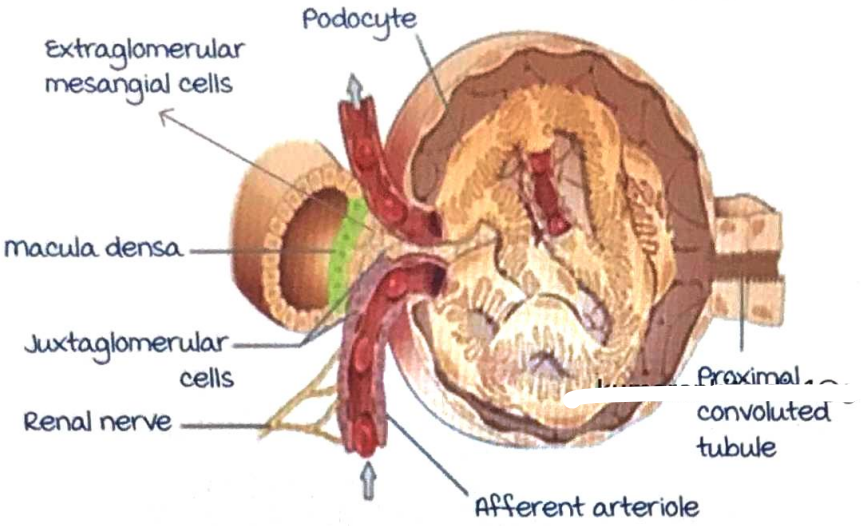


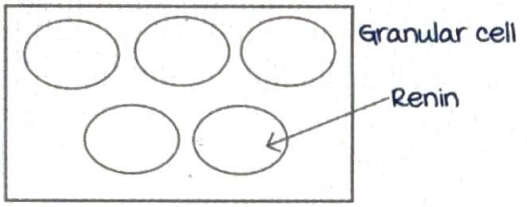
TRPV 5 is upregulated by PTH , vitamin D for calcium reabsorption.
For calcium to move to blood usually sodium is exchanged back to DCT → By Na^+ Ca^{a+}exchanger (channel protein).

Juxta-glomerular apparatus /JGA 00:30:43

3 cell types forming JGA :

- Juxta glomerular cells/JG cells :
  Seen in walls of afferent arterioles.
- Macula densa.
- Extra glomerular mesangial cells :
  Outside the glomerulus.





Juxta glomerular cells/JG cells :
Also called as granular cells.
The granules present in the cells store renin.
Renin will be released from the cells in afferent arterioles if hypotension or hyponatremia occurs activating RAAS (Renin Angiotensin Aldosterone System).

RAAS always increases sodium and blood pressure.
Whenever RAAS is overactive, hypertension occurs.
Renin blockers (Aliskiren) are used to treat hypertension.

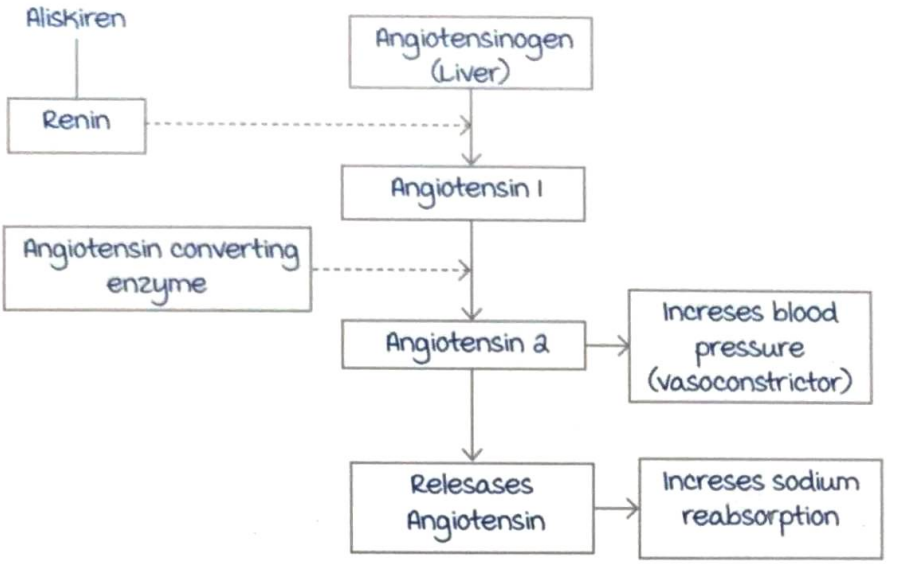
Causes of increase in renin levels :

- Low sodium.
- Low blood pressure.
- Sympathetic stimulation.
- Diuretic intake.
- Haemorrhage.

Causes of decrease in renin levels :

- Increase in afferent arterial pressure.
- Angiotensin 2 inhibits renin.
- Anti diuretic hormone inhibits renin.

Active space



Macula densa :

Location : Seen exactly where ascending LOH ends and DCT begins.

Considered as GFR sensor.

GFR increases → Increase in filtered NaCl → Filtered NaCl in macula densa → Adenosine released → Constriction of afferent arterioles → GFR decreases.
(negative feedback/tubulo-glomerular feedback/TGF).

Extra glomerular mesangial cells :
Also called as lacis cells/Polkissen cells.
Primary function is of a supportive cell.

Clinical scenarios

Q. Which of the following agents inhibits calcium reabsorption and increases calcium excretion?

A. Thiazide diuretics.
B. Carbonic anhydrase inhibitors.
C. Loop diuretics.
D. Aquaretic.

Answer : Loop diuretics (furosemide).

Q. Mutation in the thiazide sensitive NaCl co-transporter leads to?

A. Bartter syndrome.
B. Liddle syndrome.

COLLECTING DUCT AND MICTURITION REFLEX

2 parts : Cortical and medullary collecting duct.

2 hormone : Aldosterone and Anti-Diuretic Hormone (ADH)/ Vasopressin.

Aldosterone

00:02:07

It is an adrenal steroid hormone.

Functions : Reabsorption of Na^{a+} and H_aO and Excretion of K^+ and H^+.

Major hormone for K^+ excretion.

2 cell types for its action :

- Principal cell/P cell.
- Intercalated cell/I cell (H^+ excretion).

Principal cell is involved in :

- Sodium reabsorption.
- Water reabsorption.
- Potassium excretion.

Aldosterone controls ENac H^+- K^+ exchanger.

In the parietal cell, aldosterone enters cytoplasm

↓

Binds to Mineralocorticoid Receptor (MR)

↓

Forms aldosterone–MR complex

↓ moves to nucleus

Epithelial Na^{a+} channels (ENac) is incorporated

↓

Na^{a+} reabsorption

↓

Water follows Na^{a+}, reabsorbed

Renal outer medullary (ROMK) channels are incorporated by aldosterone for K^+ excretion.

Active space

Liddle syndrome :

Overactive ENac channel → Increased Na^{a+} reabsorption → Increased BP.

Blocker of ENac : Amiloride (diuretic).

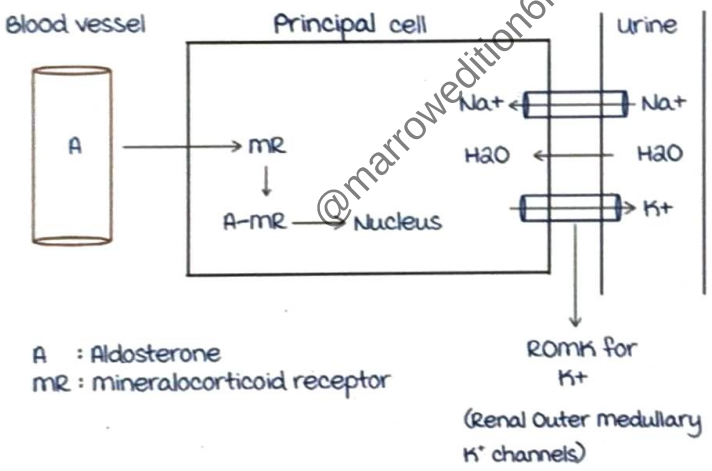
Blocker of MR : Spironolactone (K^+ sparing diuretic).

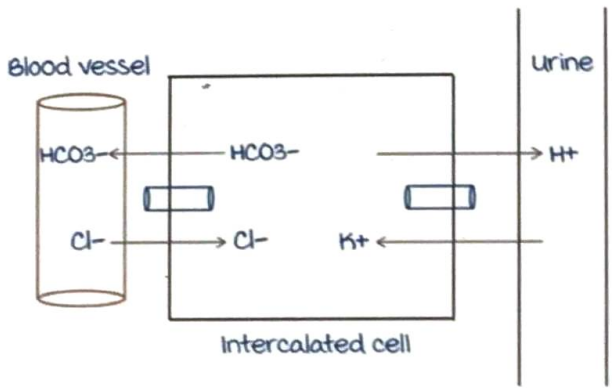
Spironolactone prevents Na^{a+} and H_aO reabsorption, does not excrete K^+.

In intercalated cells, H^+ excretion to urine occurs in exchange of K^+ ion via $H^+ - K^+$ exchanger.

Aldosterone plays significant role in acidosis.

In acidosis, along with H^+ excretion, I HCO_3^- moves into blood in exchange for Cl^- via $HCO_3^- - Cl^-$ exchanger.

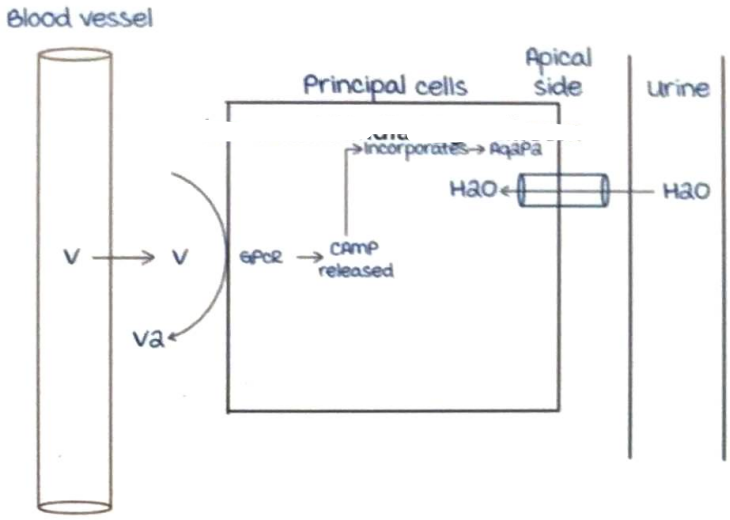




Active space

Anti-diuretic hormone (ADH)

00:13:18



Exclusively for H_2O reabsorption.

It acts in Principal cell (P) and medullary collecting duct.

Protein hormone cannot cross cell membrane (CM) of parietal cell hence binds on V_a receptor on cell membrane.

V_a receptor (V_a R) : G protein coupled receptor (V_a GP_c R).

Vasopressin binds on V_a GP_c R → 2nd messenger cAMP released → Aquaporin 2 synthesized and incorporated to apical side → H_2O reabsorption.

Inhibitors of vasopressin :

V_aR : Aquaretics (causes selection water excretion into urine). Also called vaptans.

Drug : Conivaptan.

Facultative water reabsorption : Hormone dependent water reabsorption occuring in the collecting duct.

Obligatory water reabsorption : 67% water reabsorption occuring in the PCT via osmosis and not under hormonal influence.

Active space

Factors affecting vasopressin release 00:19:49

Increase in vasopressin :

- Increase in osmotic pressure.
- Decrease in ECF volume.
- Any painful stimulus, nausea, vomiting.
- Angiotensin II.

Decrease in vasopressin :

- Decrease in osmotic pressure.
- Increase in ECF.
- Alcohol.

Receptors for vasopressin :

V_1R :

Vasoconstriction.

Minimise blood loss used as treatment for oesophageal varices.

V_1R analogue : Terlipressin.

V_2R :

Abundant in collecting duct.

Associated with water absorption.

Also found in the vascular endothelium.

Vasopressin releases Von Willebrand factor in blood vessel hence used for treatment of von willebrand disease.

Analogue : Desmopressin (intranasal administration).

V_3R :

Abundant in anterior pituitary.

Enhances ACTH release.

Free water clearance :

Vasopressin is associated with solute free water reabsorption.

Negative free water clearance : Less water in urine (concentrated urine).

Very high level of ADH like SIADH.

Positive free water clearance : more water in urine (diluted urine).

Low level of ADH classically seen in diabetes insipidus.

Zero free water clearance : Kidney has completely lost concentrating and diluting ability.

In case of hyponatremia (low sodium levels) : RAAS is activated to enhance sodium reabsorption.

In case of hypernatremia (high sodium levels) : Natriuresis is done by natriuretic peptides.

Natriuretic peptides 00:31:08

3 types based on the source of production :

ANP : Atrium.

BNP : Cardiac ventricles.

CNP : Vascular endothelium.

Actions of ANP :

Decrease Na^{a+} reabsorption.

Increase Na^{a+} excretion in late DCT and collecting duct.

Dilation of afferent arterioles → Increase in GFR.

Stimulus for increase in ANP :

- Atrial stretch by excess fluid overload.
- Increase in ECF volume.

Decrease in ANP :

- Hypovolaemia.
- Decrease in central venous pressure.

RAAS and natriuretic peptides are physiological antagonist.

Increase in aldosterone

↓

Increase in Na^{a+} reabsorption

↓

High BP

↓

Very high level of Na^{a+} in the body (stimulus for ANP)

↓

ANP comes into play (physiological antagonism)

↓

Na^{a+} excretion

Aldosterone escape phenomenon :

Na^{a+} excretion occurs even in the presence of aldosterone due to physiological antagonistic action of ANP to the stimulus of high Na^{a+}.

Micturition

00:37:26

Kidney

↓

Ureter

↓

Pacemaker activity of smooth muscles

↓

Peristalsis of ureter

↓

Urinary bladder

↓

Micturition

Bladder innervation :

Parasympathetic supply : Facilitator for micturition.

Root value : S2, S3, S4.

Leads to contraction of detrusor muscle.

Relaxation of Internal sphincter.

Sympathetic supply : Least role.

Root value : L1, L2, L3.

Least role in micturition.

Primary role : Prevents retrograde ejaculation.

Carry pain signals from bladder.

Active space

Somatic supply :

Comes from Onuf's nucleus.

Nerve involved is pudendal nerve with root value S2, S3, S4

Pudendal nerve cause contraction of external sphincter.

Voluntary action : External sphincter helps to withhold urination.

Micturiton reflex controlled by highest centre :

Facilitatory :

- Pons (Barrington centre).
- Posterior hypothalamus : Response to cold.

Inhibitory :

- Midbrain.

Cortex : Paracerebral lobule supplied by anterior cerebral artery. Any lesion leads to urinary incontinence.

Increase in bladder filling

↓

Stretch of bladder

↓

Afferent information via pelvic nerve

↓

Spinal cord (micturition centre)

↓

Para sympathetic action of S2, S3, S4

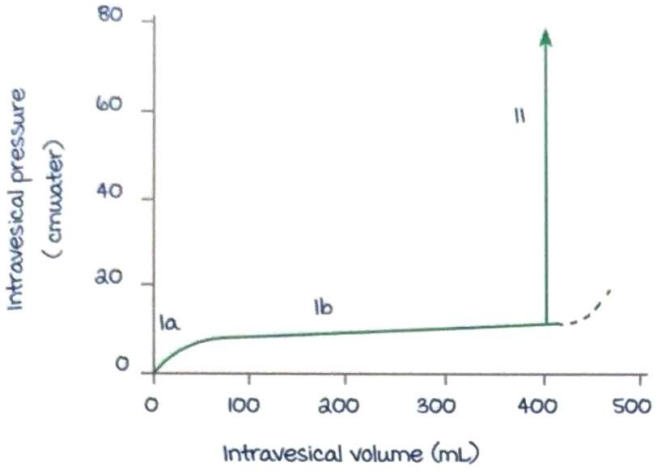
↓

Contraction of detrusor muscle → micturition.

Relaxation of internal sphincter

Bladder filling leads to changes in volume and pressure. Relation between pressure and volume changes are studied with cystometrogram.

3 segments of cystometrogram :



Ia : Bladder filling starts.

Small rise in pressure.

Ib : Bladder filling increases.

Volume increases but pressure is maintained as per Laplace's law.

Tension = Pressure x Radius.

Pressure = Tension/Radius.

Therefore, increase in wall tension and increase in radius with bladder stretching doesn't change the pressure.

II : Sharp increase in pressure leading to micturition.

The 1st urge to void occurs at 150 ml.

marked sense of bladder fullness at 400 ml.

MCQs :

Q. Which drug causes release of FVIII and von Willebrand factor (VWF) and is useful in treatment of hemophilia ?

A. Terlipressin.

B. Desmopressin.

C. Spironolactone.

D. Amiloride.

Answer : B

Q. If the Uosm is 70 mosm/Kg, Posm is 280 mosm/Kg and the total urine output is 12 L/day. Calculate the free water clearance ?

A. 12 L/day.

B. 2 L/day.

Active space

C. 3 L/day.

D. 9 L/day.

Answer : D.

Total volume of urine (TV) : Clearance of osmoles (C_{osm}) + Clearance of H_2O (C_{H2O}).

$C_{osm} : \frac{U_{osm} \times TV}{P_{osm}} = \frac{70 \times 12}{280} = 3$ L/day

$C_{H2O} = TV - C_{osm} = 12-3 = 9$ L/day.

Q. Destruction of sensory afferents from urinary bladder is seen in?

A. Listeriosis.

B. Brucellosis.

C. Gonorrhoea.

D. Syphilis.

Answer : D.

Explanation : Tabes dorsalis can lead to destruction of sensory nerves.

ACID BASE BALANCE

$CO_2 + H_2O \xrightarrow[\text{Anhydrase (CA)}]{\text{Carbonic}} H_2CO_3$ (carbonic acid).

$H_2CO_3 \longrightarrow H^+$ (acid) & HCO_3^- (base).

Acid base balance is important to maintain the pH.

When there is an increase (↑) in CO_2, the acid level H^+ also increases (↑).
Counter-acted with the help of the base HCO_3^-.
This process is called buffering ⟶ happens within seconds ⟶ first line control.
When pH changes the first step is buffering.

Excess (↑) CO_2 ⟶ removed through lungs ⟶ by hyperventilation ⟶ CO_2 wash out.
This is respiratory control ⟶ happens within minutes ⟶ second line control.

The kidneys take days to correct pH.

Kidneys 00:03:30

Kidneys are the last line of control for monitoring pH changes, but it usually takes days to correct.
Role of kidneys in acid-base balance :

- H^+ ion excretion (in acidosis).
- HCO_3^- excretion (in alkalosis).
- Reabsorption of HCO_3^- ions.
- Generation of new HCO_3^- ions.

Normal pH = 7.35 – 7.45
pH > 7.8 and pH < 6.9 ⟶ Death is inevitable.

Increase in H^+ ion causes protein denaturation.
most proteins ⟶ critical enzymes ⟶ denaturation ⟶ reduction in enzyme activities.

Active space

Alkalosis ⟶ CNS more excitable.
Acidosis ⟶ CNS less excitable.

First line control :

$$CO_2 + H_2O \xrightarrow{CA} H_2CO_3 \longrightarrow H^+ \text{ (acid) \& } HCO_3^- \text{ (base).}$$

Most important buffer system exclusively in the extra cellular fluid and overall also : Bicarbonate buffer system.
Because, two of its components CO_2 and H^+ levels are tightly regulated (CO_2 ⟶ at the level of lungs and H^+ excretion ⟶ at the Kidneys).

Protein buffers :
Proteins are most plentiful intracellular buffer.
E.g. Hb inside RBC is an excellent buffer.
For proteins to act as buffer, they need amino acid histidine.

Phosphate buffer system :
Intracellular buffer and excellent urinary buffer.

Ammonia buffer system :
Important urinary buffer.

Second line control

00:11:11

Lungs act as 2nd line control with CO_2 being the sole target.
Alveolar ventilation $\propto \frac{1}{pCO_2}$.
Hyperventilation (increased alveolar ventilation) ⟶ CO_2 washout ⟶ decreased pCO_2.
Hypoventilation ⟶ CO_2 retention.
Lungs can do 75% correction, targeted towards regulating CO_2 levels.

Role of kidneys

00:13:06

Kidneys play the last role in regulation of pH, starting from Proximal Convoluted Tubule/PCT.

- Kidneys help in reabsorption of HCO_3^- ions (80% of filtere HCO_3^- ions are reabsorbed) at the level of PCT.

In the PCT, $CO_2 + H_2O \xrightarrow{CA\ II} H_2CO_3$.

$H_2CO_3 \longrightarrow H^+ \& HCO_3^-$.

H^+ ion $\longrightarrow$ secreted into urine.

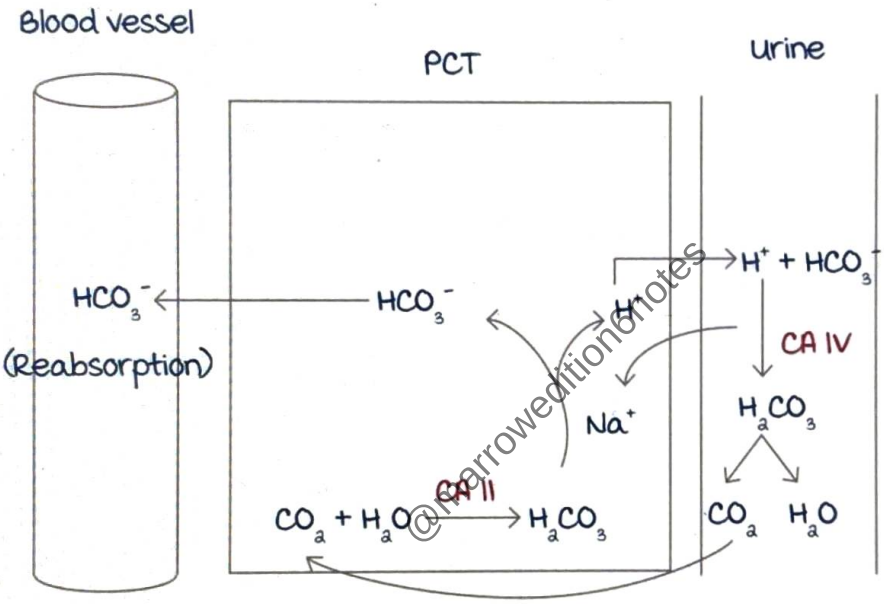
Na^+ ion $\longrightarrow$ reabsorbed into PCT.

This is facilitated by the Na^+- H^+ exchanger seen in the PCT.

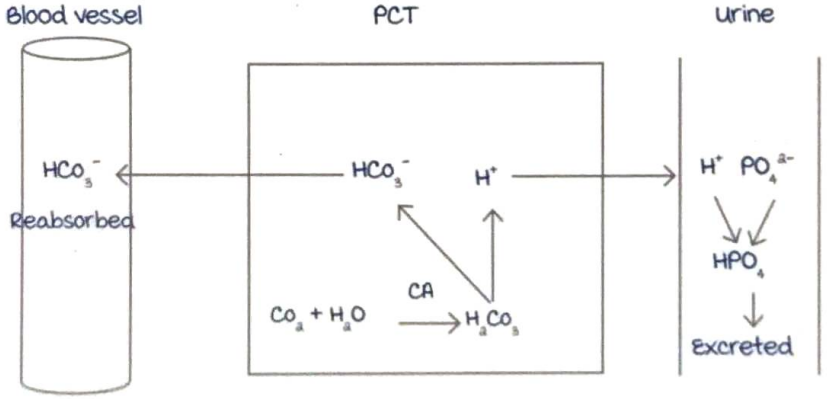
In urine $\longrightarrow H^+ + HCO_3^-$ (filtered from glomerulus) $\xrightarrow{CA\ IV}$ H_2CO_3

$H_2CO_3 \longrightarrow CO_2 + H_2O \longrightarrow$ re-enters PCT $\longrightarrow$ cycle continues.

HCO_3^- ion is reabsorbed into the blood vessels.



- Generation of new HCO_3^- in the PCT by:
  1. Phosphate buffer:
     Following H^+ secretion into urine,
     $H^+ + PO_4^{2-} \longrightarrow HPO_4 \longrightarrow$ excreted in urine.
     HCO_3^- in PCT $\longrightarrow$ newly generated $\longrightarrow$ reabsorbed into the blood vessel.



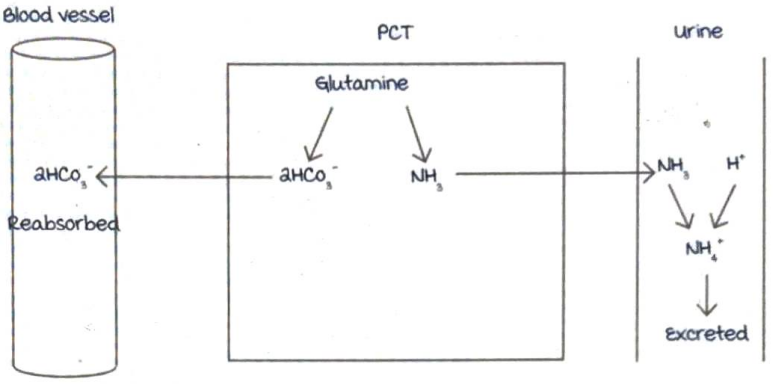
2. Ammonia buffer :

metabolism of glutamine in PCT → two HCO_3^- ions, one NH_3 molecule (ammonia) → ammonia diffuses into urine.

$H^+ + NH_3$ → ammonium ion (NH_4^+) → excreted in urine.

Two newly generated HCO_3^- ions → reabsorbed into blood vessel.

Titratable acids → HPO_4 & NH_4^+ (acids excreted in urine).



Limiting pH

00:22:43

If Limiting pH (4.5) is reached → no more H^+ ion excretion.

All H^+ ions are buffered in PCT → excreted continuously → limiting pH not reached.

Acidification of urine occurs in collecting duct, limiting pH reached.

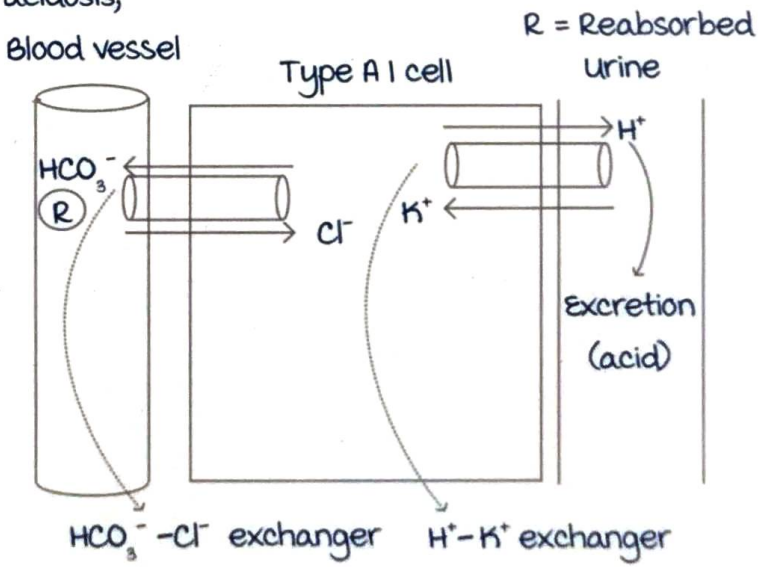
Role of collecting duct in acid-base balance :

Intercalated cells or I cells are of two types :

Type A (acid excreting cells) : Required exclusively during acidosis.

Type B (base/bicarbonate excreting cells) : Required exclusively during alkalosis.

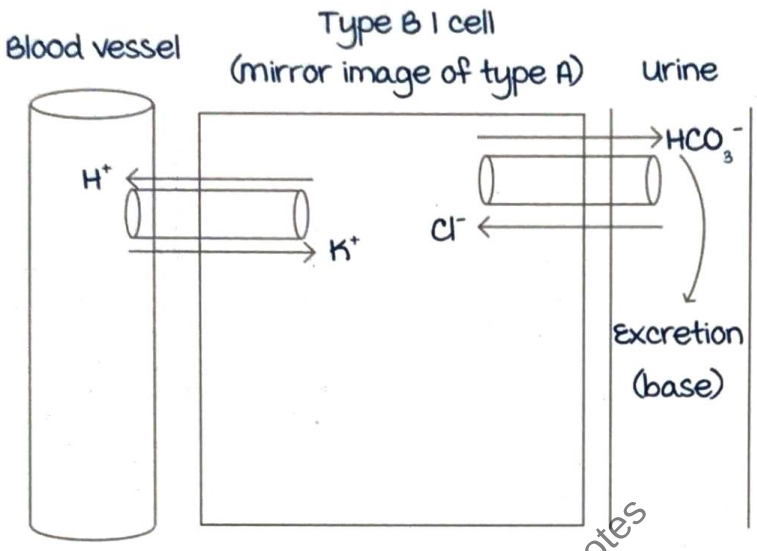
In acidosis,



Active space

Type A cells → H^+-K^+ exchanger protein → H^+ into urine and K^+ into cell → H^+ ion/acid excreted in urine.
HCO_3^- - Cl^- another exchanger protein → HCO_3^- into blood vessel and Cl^- into cell → HCO_3^- ion reabsorption replenishes buffer.

In alkalosis,



Type B cells → HCO_3^- - Cl^- exchanger channel → HCO_3^- into urine and Cl^- into cell → H^+-K^+ another exchanger protein → H^+ ion reabsorption into blood vessel and K^+ ion into cell.

Interconversion between type A and type B cell depending on acidosis or alkalosis is facilitated by a protein Hensin.

Acid-base disorders :
Normal pH = 7.35 – 7.45
Normal pCO_a = 35 – 45 mmHg.
Normal HCO_3^- = 22 – 26 mEq/L.

Metabolic acidosis 00:33:04

Fall in pH/rise in H^+ ions due to accumulation of acids like :

- Lactic acid : Lactic acidosis.
- Keto acid : Diabetic Ketoacidosis.
- Salicylate poisoning/ingestion.

Fall in HCO_3^- ions due to loss of HCO_3^- ions as seen in diarrhea (loss of intestinal contents with HCO_3^-).

Excess acid is eliminated by respiratory compensation.
Hyperventilation → CO_a washout.
metabolic acidosis → fall in CO_a (compensatory).

Renal compensation → $H^+ - K^+$ exchanger → excess acid/H^+ excretion. K^+ enters circulation → hyperkalemia in any state of acidosis.

Kidney reabsorbs HCO_3^- ions and generates new HCO_3^- ions.

Anion gap (AG):

This is due to unmeasured anions like SO_4^{a-}, protein anions, lactate anions or ketoacids.

$AG = Na^+ - [Cl^- + HCO_3^-]$.

$AG = 144 - [108 + 24]$.

$AG = 144 - 132$.

$AG = 12$ mEq/L.

Normal AG = 8 – 16 mEq/L.

Acidosis:

Low pH, rise in H^+ ions.

Anion rises to maintain electroneutrality.

If the anion rise is unmeasured like lactate or keto acid, there will be a high anion gap.

This is called HAGMA: High anionic gap metabolic acidosis.

Causes of HAGMA:

- Diabetic ketoacidosis.
- Lactic acidosis.
- Salicylate poisoning/ingestion.

If the anion rise is measured like chloride (Cl^-), the anion gap will be normal.

This is called NAGMA: Normal anion gap metabolic acidosis.

Also called hyperchloremic metabolic acidosis, as chloride levels rise.

Causes of NAGMA:

- Diarrhea.
- Renal tubular acidosis.
- Hypoaldosteronism.

Metabolic alkalosis 00:51:24

Rise in pH, fall in H^+ ions: Loss of H^+ ions due to vomiting of stomach contents (gastric acid).

Primary cause is rise in HCO_3^- ions: Ingestion of sodium bicarbonate/$NaHCO_3$.

Also seen in hyperaldosteronism. Aldosterone increases H^+ ion excretion.

Patient on Diuretics → excessive water loss → state of volume contraction → activates Renin-angiotensin-aldosterone system (RAAS) → aldosterone secretion → increased H^+ ion excretion → volume contraction alkalosis.

Respiratory compensation → hypoventilation → CO_2 retention & accumulation.
metabolic alkalosis → rise in pCO_2.
Renal compensation → increases HCO_3^- excretion.
Type B Intercalated cells will be more predominant.

Respiratory acidosis 00:57:19

Fall in pH, rise in pCO_2 as hypoventilation causes retention of CO_2. This may be due to :

- Respiratory depression due to drugs like opioids, barbiturates.
- Respiratory muscle weakness/paralysis as seen in Guillain-Barre syndrome, Polio etc.
- Airway obstruction.
- Any gas diffusion disorders like COPD.

In respiratory disturbances there is no respiratory compensation, only renal compensation.
This is achieved by :

- Increased H^+ excretion.
- Increased HCO_3^- reabsorption.
- Generating new HCO_3^- ions.

Therefore there will be increase in HCO_3^- in respiratory acidosis because of renal compensation.

Respiratory alkalosis 01:01:10

This is seen with hyperventilation which may be due to :

- Hysteria/hysteric hyperventilation.
- High altitude : Free Ca^{a+} level falls in alkalosis and the seindividuals are prone for hypocalcemic tetany.

- Hypoxemia : Peripheral chemoreceptors are stimulated which induces hyperventilation.

Renal compensation is achieved by :

- Increased HCO_3^- excretion.

Therefore in respiratory alkalosis, there will be increase in pH, fall in pCO_a and fall in HCO_3^-.

MCQs :

Q. Uncompensated metabolic acidosis shows ?

A. Increased pH with increased HCO_3^-.
B. Increased pH with decreased HCO_3^-.
C. Decreased pH with increased HCO_3^-.
D. Decreased pH with decreased HCO_3^-.

Q. Importance of maintenance of pH are all except ?

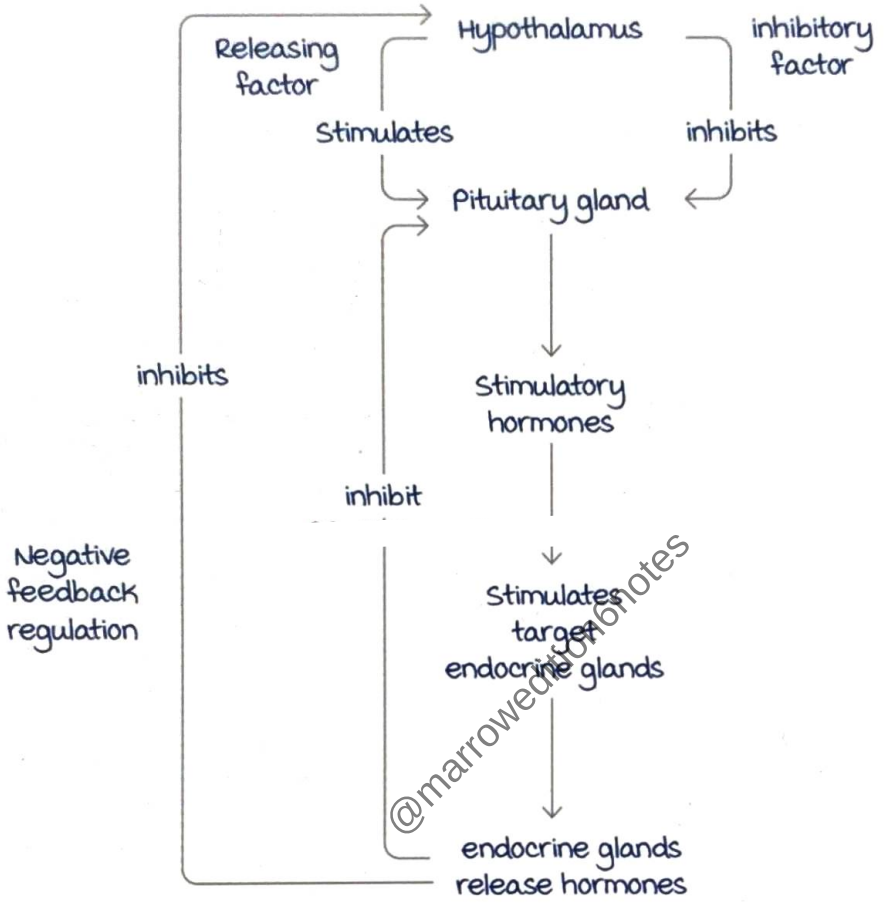
A. Enzymatic activity and protein structure are very sensitive to pH.
B. pH changes can denature proteins.
C. High pH (alkalosis) : CNS becomes less excitable.
D. Reduced enzyme activity.

Q. All of the following are causes of metabolic alkalosis except

A. Vomiting of gastric contents (loss of H^+).
B. Hypoaldosteronism.
C. Excessive ingestion of antacids.
D. Volume contraction alkalosis : Administration of thiazide diuretics.

PITUITARY GLANDS

Endocrine hormone regulation 00:02:00



Pituitary gland (master gland) is divided into :

- Anterior pituitary → 2 cell types.

  6 hormones released by it.

  1. Growth hormone (GH).
  2. Prolactin.
  3. Thyroid stimulating hormone (TSH).
  4. Adreno-corticotrophic hormones (ACTH).
  5. Follicle stimulating hormone (FSH).
  6. Luteinizing hormone (LH).

- Posterior pituitary → Produces no hormones, but stores 2 hormones (Vasopressin & oxytocin).

Active space

Anterior pituitary :

- Acidophilic cells :
  Release GH and Prolactin.
  (twin hormones : Common source, similar receptors and similar change in levels w.r.t. each other).
- Basophilic cells :
  Release FSH, LH, ACTH & TSH.

Corticotrophs : Special type of cells in the anterior pituitary.
Precursors → Pro Opio Melano Cortin (POMC) release Endorphins, Melanocyte Stimulating Hormones (MSH) & ACTH.
Excess of ACTH (pathological) → Performs actions similar to MSH → Hyperpigmentation.
(Addison's disease where ACTH is in excess.)

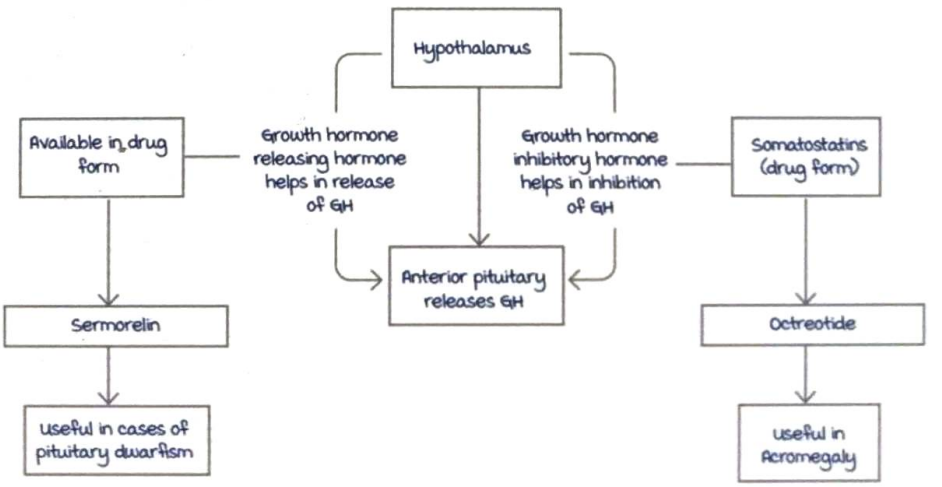
Posterior Pituitary :
Vasopressin and oxytocin are produced from hypothalamus → travel to posterior pituitary for storage →
Herring bodies store and release vasopressin and oxytocin.

Growth hormones

00:14:26

GH levels vary with age of the individual.
Maximum level of GH → Adolescence.
Minimum level of GH → Senescence.

Regulation of GH secretion :



Active space

Factors increasing growth hormone 00:19:08

- Hypoglycemia (low blood glucose) → Release GH → GH increases blood glucose (hyperglycemic/ diabetogenic hormone).
- Fasting.
- Starvation/ long fasting.
- Exercise.
- Stress.

} Cause Hypoglycemia

- Sleep → Non - Rapid Eye Movement (NREM) sleep.

Factors decreasing growth hormone 00:22:42

- Somatostatins and its analogues.
- Hyperglycemia.
- Sleep → Rapid Eye Movement (REM) sleep.

Actions of GH :

- Direct actions : Performed by GH itself → anti-insulin like (lipolysis).
- Indirect actions : mediated through Somatomedins. Source for somatomedins / insulin like growth factors (IGF) → exclusively produced from Liver. Indirect actions are insulin-like (anti-lipolysis).

Bone growth : Both direct and indirect actions.

Direct action : Prechondrocytes → Chondrocytes (by GH).

Indirect action : All further actions related to bone growth are mediated through somatomedins.

Growth hormone disorders 00:28:56

Dwarfism : Fall in levels of GH.

Gigantism : Elevated GH levels in children.

Acromegaly : Elevated GH levels in adults.

Dwarf despite normal GH levels → GH receptor problem → Jak - stat receptor pathway (Janus Kinase) → Low levels of IGF (Laron's Dwarfism).

Prolactin

00:31:48

Regulation :

Hypothalamus has inhibitory factor → Dopamine (prolactin inhibitory factor PRIF) → always inhibits prolactin release.

Factors increasing prolactin :

- Pregnancy & lactation.
- Sexual intercourse.
- Suckling of nipples.
- Sleep → Rapid Eye Movement (REM) sleep.

Factors decreasing prolactin :

- Dopamine.
- L-Dopa.
- Bromocriptine.

Actions of prolactin :

- Produces milk during lactation.
- Negative regulator of reproduction as it inhibits Gonadotropin releasing hormones(GnRH) :
  During lactation → GnRH inhibited by prolactin → lactational amenorrhea (contraception).

Clinical scenarios

00:37:51

Q. A 24 year old woman presents with discharge of milk from her breasts & also has experienced irregular periods. Imaging studies reveals a mass in her pituitary. Which of the following hormones is elevated in her?

A. Dopamine.

B. Melatonin.

C. Somatomedins.

D. Prolactin.

Q. Failure of GH suppression within (1 – 2) hours of an oral glucose load is a test done for?

A. Cushing syndrome.

B. Addison's sidease.

C. Acromegaly.

D. Pituitary dwarfism.

Explanation :

Increase in glucose → Inhibits GH but here there is failure → tumor secreting excess GH.

Q. All of the following are seen in hypopituitarism except?

A. Fatigue.

B. Weight gain.

C. Increase in basal metabolic rate (BMR).

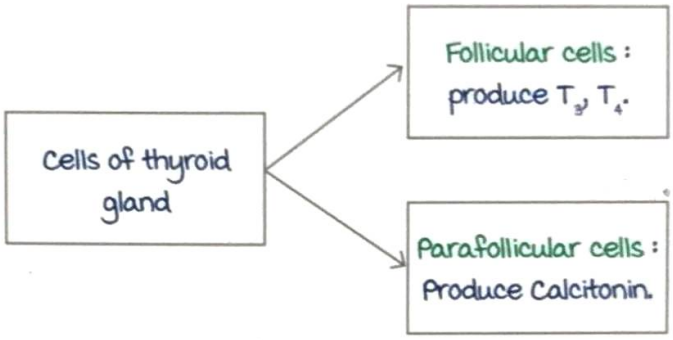
D. Irregular periods.

Explanation :

TSH normally regulates BMR which is affected in hypopituitarism → decrease in BMR.

THYROID GLAND

Cells of thyroid gland :



Follicular cells :

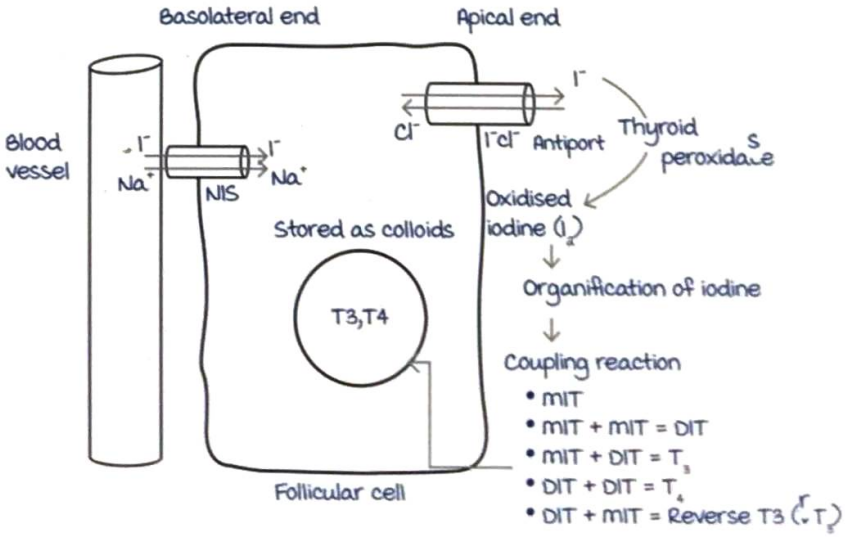
For the production of thyroid hormones T_3 and T_4 :

- Tyrosine → Derived from thyroglobulin (Tg).
- Iodide → Reduced form of iodine that is obtained from dietary sources.

Synthesis of thyroid hormones 00:03:26

Basolateral end of follicular cell : Close to blood vessel.

Apical end : Away from blood vessel.



Active space

$Na^+ I^-$ symporter (NIS):

- Found in the basolateral end of follicular cells.
- Transports Na^+ and I^- ions from the blood vessel to the follicular cell.
- Symporter → secondary active transport processes.
- Found in:

  Thyroid gland.
  Parotid gland.
  Mammary gland.
  Placenta.
  } Capable of iodide uptake.

- If excess levels of iodide come in the follicular cells via the symporter, it inhibits thyroid hormone synthesis → Wolff Chaikoff effect.

The I^- is flushed out as soon as it comes in, as it is in the reduced form.

- To balance it a Cl^- ion comes inside via $I^- Cl^-$ antiport.

The iodide is oxidized by thyroid peroxidase (TPO).

- TPO Enzyme is a cell membrane bound enzyme, which is why iodide is flushed out of the cell.

I_2 is incorporated into tyrosine: organification of iodine.
Coupling reactions occur following organification.

- Monoiodotyrosine (MIT).
- MIT + MIT = diiodotyrosine (DIT).
- MIT + DIT = T_3.
- DIT + DIT = T_4.
- DIT + MIT = reverse T_3 (rT_3).

Once the hormones are synthesized, it is taken into the follicular cells and stored as colloid.
Colloids can supply thyroid hormones up to 2 - 3 months.

- Released by breaking the colloid.
- The hormones are released directly to the blood vessel → endocrine.

$I^- Cl^-$ antiport:
Locations: Thyroid gland and inner ear.

Active space

Also called as pendrin.

Mutation causes : Pendred syndrome.

- Goiter : enlargement of thyroid hormone.
- Sensorineural hearing loss.

Thyroid peroxidase (TPO) :

Reduced form of iodine (I^-) —(Thyroid peroxidase)→ Oxidized iodine (I_2).

Important in thyroid hormone synthesis.

TPO blockers → decreases thyroid hormone synthesis → anti thyroid drugs.

- Propylthiouracil.
- methimazole.
- Carbimazole.

Thyroid hormones :

Hormones released into blood vessels.

Free form (1%) : Responsible for all actions.

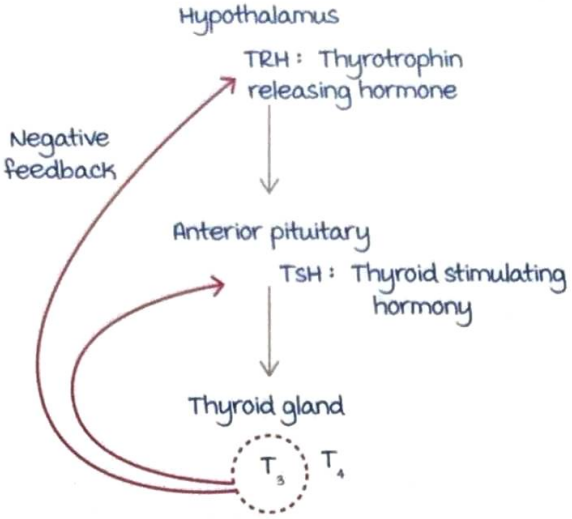
Bound form (99%) : Bound by proteins.

- Albumin.
- Globulin : Thyroid hormone binding globulin (TBG). Highest affinity to bind thyroid hormones.
- Transthyretin : Can bind thyroid hormones and vitamin A.
  Also called prealbumin.

Regulation of thyroid hormones synthesis 00:21:19

The thyrotrophin releasing hormone (TRH) from hypothalamus stimulates the anterior pituitary.

Anterior pituitary releases thyroid stimulating hormone (TSH).



Action of TSH on thyroid gland :

- Increases vascularity.
- Increases iodide trapping.
- Increases thyroid hormone synthesis.

T_3 formed exerts negative feedback on :

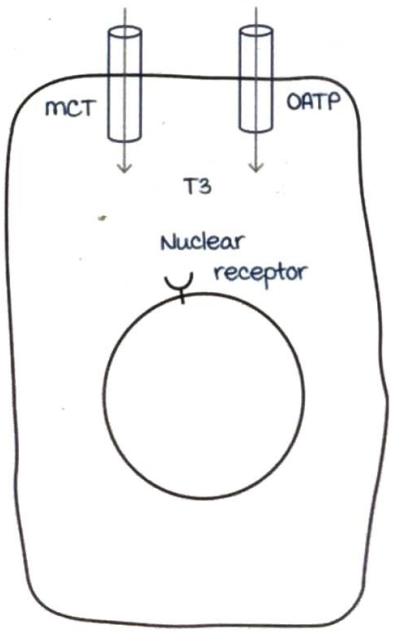
- TSH from anterior pituitary.
- TRH from hypothalamus.

Receptors of thyroid hormones :

Transporters in cell membrane helps in transporting the thyroid hormones despite being amino acid derivatives.

- MCT : mono carboxylase transporter.
- OATP : Organic anion transporting polypeptide.

Thyroid hormones act via nuclear receptors.

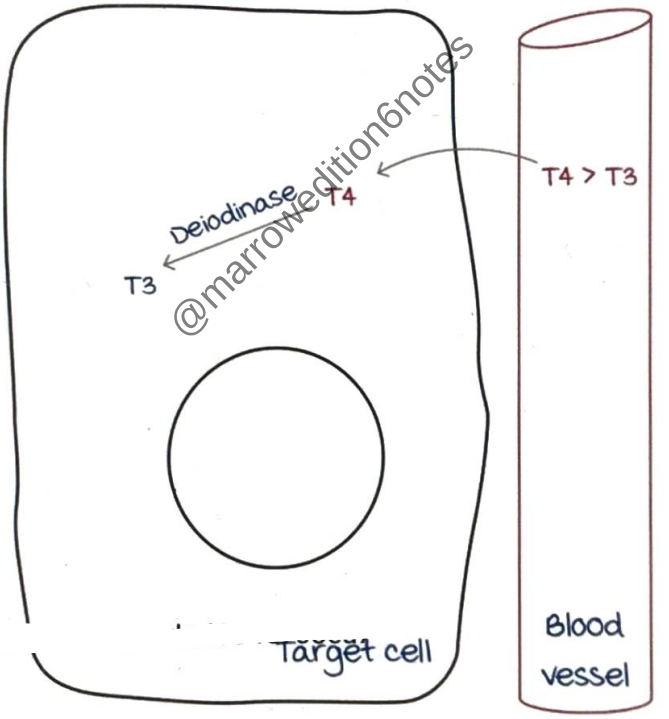


T_3	T_4
most potent.	Less potent.
Active : responsible for physiological actions.	Less active.
Rapid action	Slow acting.
Short half life.	Long half life : used as pharmacological form for hypothyroidism.
Circulating level is less.	Circulating level is more.

Peripheral conversion :

T4 hormone abundantly present in blood gets taken up by the target cell.

It gets converted to T3 by the enzyme deiodinase.



Actions of thyroid hormone : T_3 00:31:10

1. Increases Basal metabolic rate (BMR), i.e., increases oxygen consumption.
   metabolism at rest.
2. Physiological uncouplers of electron transport chain (ETC).
   Increases body heat → thermogenic action.

Active space

Patients with hypothyroidism cannot tolerate cold → cold intolerant.

Patients with hyperthyroidism cannot tolerate heat → heat intolerant.

3. Catabolic in nature.

Carbohydrate metabolism : glycogenolysis → increases blood glucose.

Lipid metabolism : lipolysis → increase in free fatty acids.

Protein metabolism : proteolysis.

Cholesterol : lowers blood cholesterol levels.

In hypothyroidism, increase in blood cholesterol → more prone to atherosclerosis.

4. During development.

Growth of brain : increase myelination in CNS.

Growth of bone.

- Congenital hypothyroidism: mental retardation and stunted growth.

5. Increases the responsiveness of heart to circulating catecholamines like norepinephrine.

Norepinephrine increases :

- Heart rate.
- Stroke volume.
- Myocardial contractility.

These are beta receptor mediated actions of norepinephrine.

For management of thyroid storm, beta blockers like Propranolol are used.

Q. A 64 year old male has a 3 year history of fatigue, depression, weight gain, and cold intolerance . Which of the following will be increased in the patient?

A. Heart rate.

B. Myocardial contractility.

C. Stroke volume.

D. Cholesterol levels.

Q. Myopathy seen in hyperthyroidism is due to?

A. Catabolic effects on carbohydrates.

B. Catabolic effects on lipids.

C. Catabolic effects on proteins.

D. Catabolic effects on vitamins.

Q. Euthyroid sick syndrome is characterized by?

A. Increase in T3.

B. Increase in T4.

C. Increase in reverse T3.

D. Increase in T3 and T4.

Euthyroid sick syndrome:

- Seen in prolonged starvation.
- T_3 is catabolic, which can cause detrimental effects.
- Decreased T3 and T4, and increased rT3.

PANCREAS

Endocrine pancreas 00:00:11

Majority of the endocrine part is present in tail of pancreas.

Tail of pancreas is collection of isolated cells (looks like island of cells) → Islets of Langerhans.

Cells :

- A cell or α cell : Glucagon production → Increase blood glucose.
- B cell orβ cell :

a) Insulin production → Decreases blood glucose.

b) Amylin production → Potentiates the action of insulin. (amylin analogue : Pramlintide : Rx of DM).

c) C-peptide : Insulin = 1 : 1 ratio (equimolar proportion). C-peptide a.k.a endogenous insulin marker → C-peptide assay.

- Delta cells : Somatostatin → Universal inhibitor (inhibits insulin, glucagon).
- F cells : Pancreatic polypeptide (PP).

Maximum population of cells i.e., 55% of cells : β cells.

Insulin 00:07:33

Discovered by Banting and McLeod.

Insulin contains 51 amino acids which was sequenced by Sanger.

- Insulin was the first protein to get completely sequenced.
- Insulin was the first protein produced by recombinant DNA technology.

Insulin is always stored along with zinc in β cell because zinc stabilizes the structure of insulin.

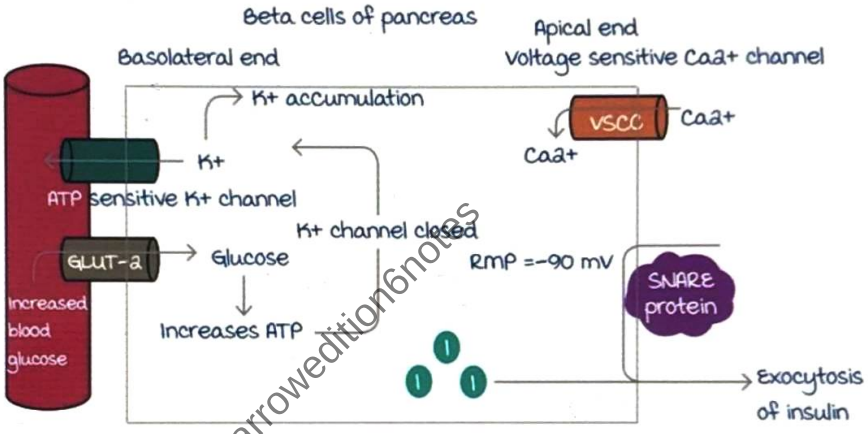
Transcription factor : Hepatocyte Nuclear Factor (HNF) is required for insulin production.

HNF mutation can lead to Maturity Onset Diabetes of the Young (MODY).

Synthesis and release of insulin 00:12:00

Increase in blood glucose → Insulin release → Decreases the blood glucose levels.

Classical example of negative feedback.



Beta cells of pancreas contain storage granules with insulin at resting membrane potential of -90 mV which is maintained by ATP sensitive K^+ channels by releasing K^+ into systemic circulation.

When blood glucose levels are increased : GLUT 2 facilitates all the glucose into the β cells → Increase in ATP → K^+ channels are closed → K^+ accumulation.

When K^+ are accumulated → VSCC facilitates Ca^{2+} inside the cell.

Snare protein → Exocytosis of insulin by releasing the insulin stored granules into circulation.

With help of ATP, Ca^{2+} and snare protein insulin is released.

Summary :

1) GLUT 2 sensing.
2) Closure of ATP sensitive K^+ channels (sulfonylurea receptors).

Active space

3) Opening of voltage sensing Ca^{2+} channels.
4) Exocytosis of insulin.

ATP sensitive K^+ channels closure → Insulin release (important step).

- Drugs closing ATP sensitive K^+ channels : Insulin secretogogues → Sulfonylureas.

ATP sensitive K^+ channels opens → Decrease insulin release.

- Used in Rx of insulinoma : Diazoxide.

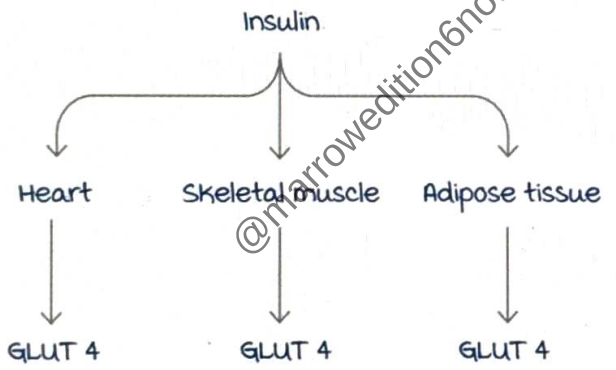
Actions of insulin

00:22:20

Receptors : Tyrosine Kinase receptor : 2 α sub units and 2 β sub units.

Tyrosine Kinase enzyme activity : 2 β sub units.

Increase in glucose.



- From blood, glucose moves to heart, skeletal muscle, and adipose tissue via GLUT 4 → Decrease in blood glucose levels (GLUT 4 mediated).
  GLUT 4 : Facilitated diffusion.

  In insulin resistance → Down regulation of GLUT 4.

- Decreases K^+ levels.

Rapid actions of insulin : Decrease in blood glucose and decrease in potassium levels.

- Therefore insulin along with dextrose is used in the treatment of hyperkalemia.

Dextrose is used to avoid hypoglycemia.

Long term actions of insulin 00:28:38

Hours to days to manifest.

Insulin :

Major anabolic hormone (storage).

Hormone of insurance.

- Glycogenesis.
- Lipogenesis.

Metabolic pathways :

Stimulated by insulin	Inhibited by insulin
• Glycogenesis • Lipogenesis • Increases glucose metabolism : Glycolysis	• Glycogenolysis • Neoglucogenesis • Lipolysis • Ketogenesis from liver

In fetus insulin secretion starts by 5th week of intrauterine life.

Factors affecting insulin secretion 00:33:00

Increase insulin secretion :

- High blood glucose
- Glucagon
- Amino acids : Arginine, leucine
- GI Hormones : most significant
  Glucagon Like Peptide (GLP) and Glucose dependent Insulinotropic Peptide (GIP) → Incretins.

a) Incretin analogues : Exenatide (Rx of DM).

DPP-4 : Primary function is to destruct incretin.

b) DPP-4 inhibitors : Increases the levels of GLP and GIP : used in the treatment of DM.

E.g., Sitagliptin.

- Gastrin.

- Cholecystokinin
- Secretin

Decrease insulin secretion :

- Somatostatin
- Diazoxide
- Streptozocin,
  Alloxan : Used to create models of experimental diabetes.

Effects of autonomic nervous system in relation with insulin secretion :

Para sympathetic nervous system : Increases insulin secretion.

- Ach.
- Vagal stimulation.

Sympathetic nervous system :

α : Decreases insulin.

β : Increases insulin.

Dominant is alpha mediated action : Decrease in insulin.

Glucose homeostasis

00:42:30

Hypoglycemic hormone : Insulin	Counter regulatory hormones
Blood glucose < 30 mg/dl → Coma is inevitable. Protein rich meal → Increases both insulin and glucagon. To prevent hypoglycemia	Increase blood glucose → Hyperglycemic hormone. 1) Growth hormone : Hyperglycemic hormone. Elderly diabetic patient took night dose of insulin → hypoglycemia → GH release → Hyperglycemia (early morning). This phenomenon : Dawn phenomenon. 2) Glucagon 3) Thyroid hormones 4) Cortisol 5) Epinephrine

Q. A 24 year old man who is a known case of type I diabetes injects insulin for treatment. Which aspect of glucose transport is enhanced by insulin?

A. Transport into RBCs.

B. Transport into brain.

C. Transport into spleen.

D. Transport into adipocytes.

Q. Which of the following is useful in differentiating endogenous and exogenous sources of insulin in the evaluation of hypoglycemia ?

A. Glucagon.

B. Epinephrine.

C. C-peptide.

D. Cortisol.

Q. Compared to iv glucose infusion, increase in insulin after oral glucose load is greater. This effect is because of ?

A. Growth hormone.

B. Cortisol.

C. Incretins.

D. Peptide YY.

ADRENAL GLAND

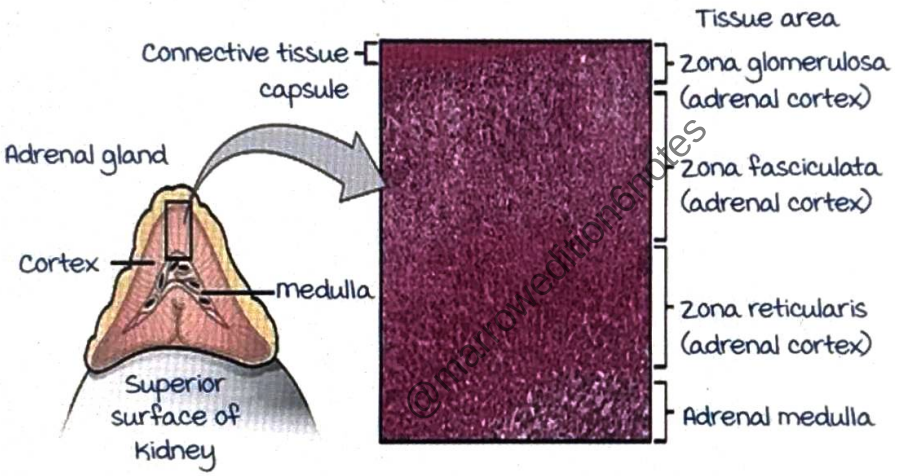
Anatomy 00:00:49

Adrenal gland consists of:

1. Cortex (78%).
2. Medulla (22%).

Adrenal medulla is the source of catecholamines :

1. Epinephrine (90%).
2. Norepinephrine.
3. Dopamine.



Adrenal cortex (3 layers. Mnemonic : GFR) :

- Produces Mineralocorticoids : Aldosterone.
- Contains stem cells to produce new cortical cells.

2. Zona Fasciculata

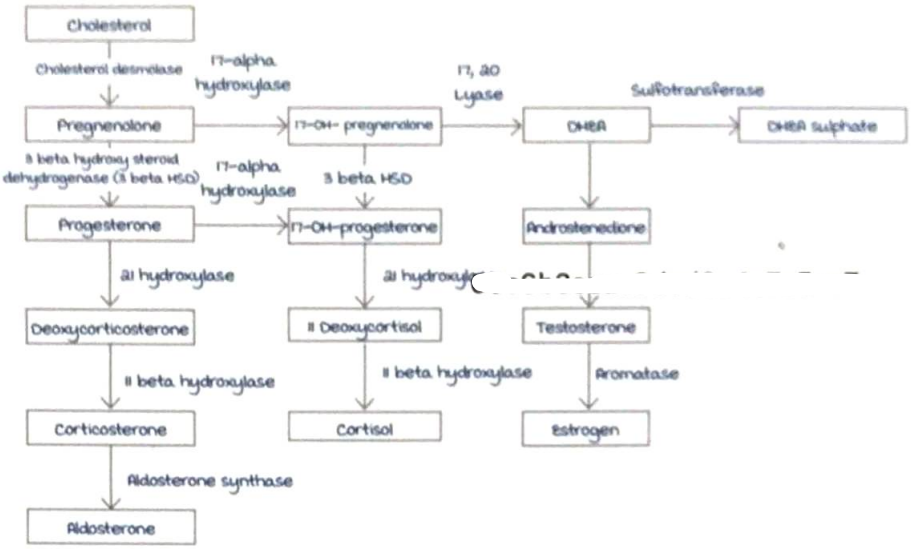
- Occupies 50% of cell population.
- Produces Glucocorticoids : Cortisol.

3. Zona Reticularis

- Produces adrenal sex steroids : Dihydro epiandrosterone (DHEA) and Androstenedione.

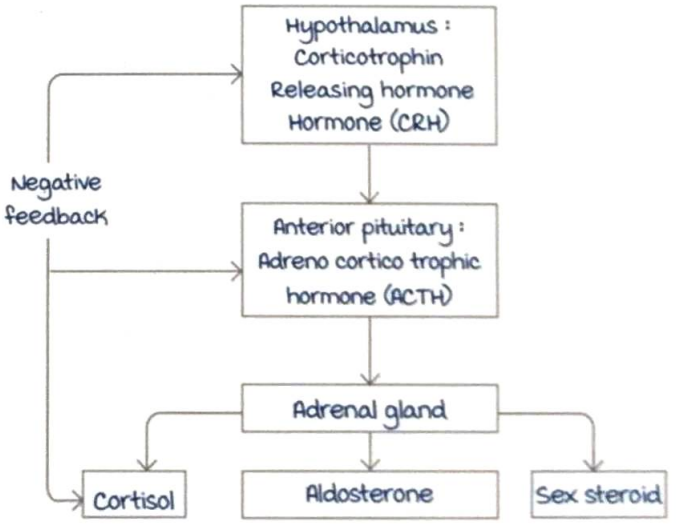
Adrenal cortical hormone synthesis 00:05:12

For all adrenal cortical hormones, the precursor is Cholesterol. Deficiency in any of these hormones produces Congenital adrenal hyperplasia.



Aldosterone synthase enzyme : Only in Zona Glomerulosa.
17-alpha-hydroxylase: Vital enzyme for Cortisol synthesis.
90% DHEA comes from adrenal cortex and rest from ovay.
Sulfotransferase enzyme : Only in Zona reticularis, hence DHEA sulphate is exclusively produced from adrenal cortex.

Adrenal hormone regulation 00:12:35



Cortisol has negative feedback over CRH and ACTH release.
ACTH regulates all adrenocortical hormones, but has no influence over adrenal medulla.

Active space

Aldosterone

00:15:05

Produced by zona glomerulosa.

It's a mineralocorticoid.

4 vital functions:

Reabsorption	Excretion
1. Sodium reabsorption.	1. Potassium excretion.
2. Water reabsorption.	2. Acid excretion (H^+ excretion).

Major life saving hormone.

Receptors : Mineralocorticoid receptor (MR).

Location of the receptors : Cytoplasm.

Aldosterone is a steroid hormone.

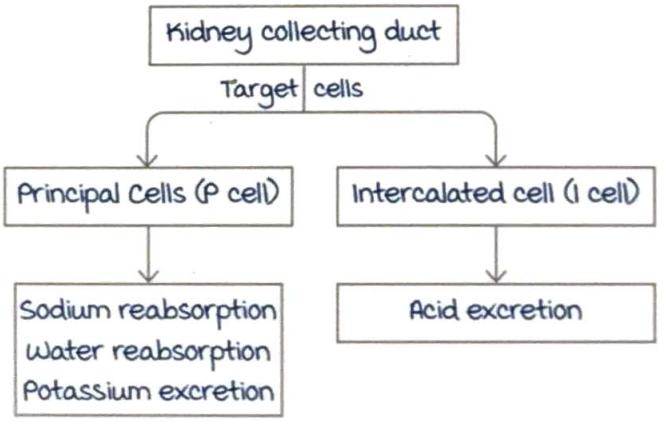
All steroid hormones can cross membrane easily.

Aldosterone-MR complex is moved to nucleus for all its actions.

MR is exclusively found in :

- Kidneys.
- Colon.
- Hippocampus.
- Salivary glands.
- Sweat glands.

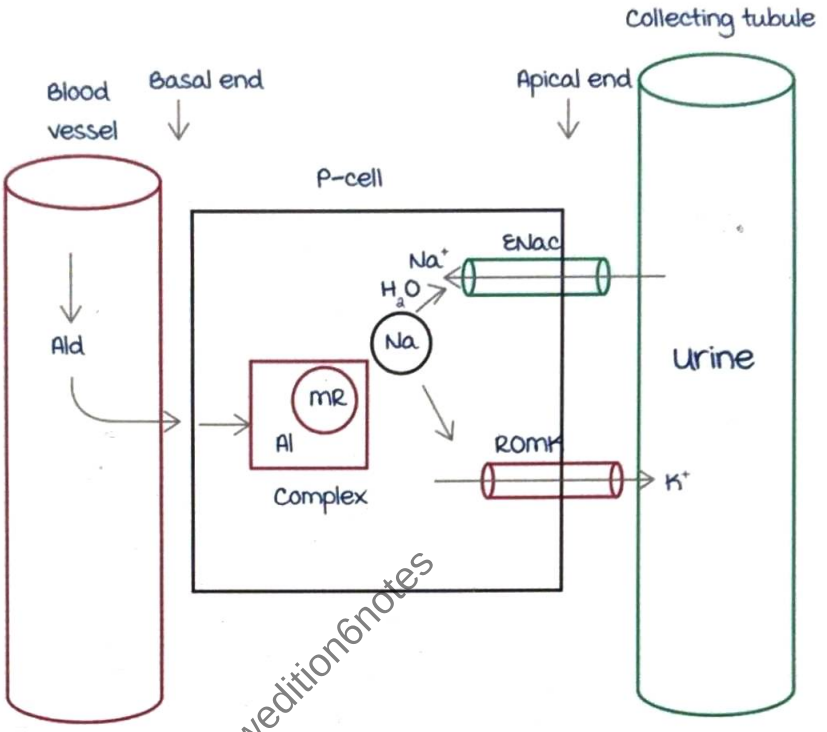
Action of aldosterone on Kidney :



Aldosterone on P cell :

Aldosterone (blood) attaches to MR in cytoplasm of P cell.

1. The MR-Aldosterone complex moves to the nucleus for the transcription of a ENaC protein.
(ENaC : Epithelial Sodium Channel)



This protein incorporated into the apical end serves as a channel for reabsorption of Na^+ from urine.

Once Na^+ is reabsorbed, water is also absorbed through osmosis.

Liddle Syndrome :
Overactive ENaC → Excessive Na^+ and water absorption → Hypertension.

Amiloride :
Blocks ENaC → Loss of Na^+ and water in urine → Diuretic action.

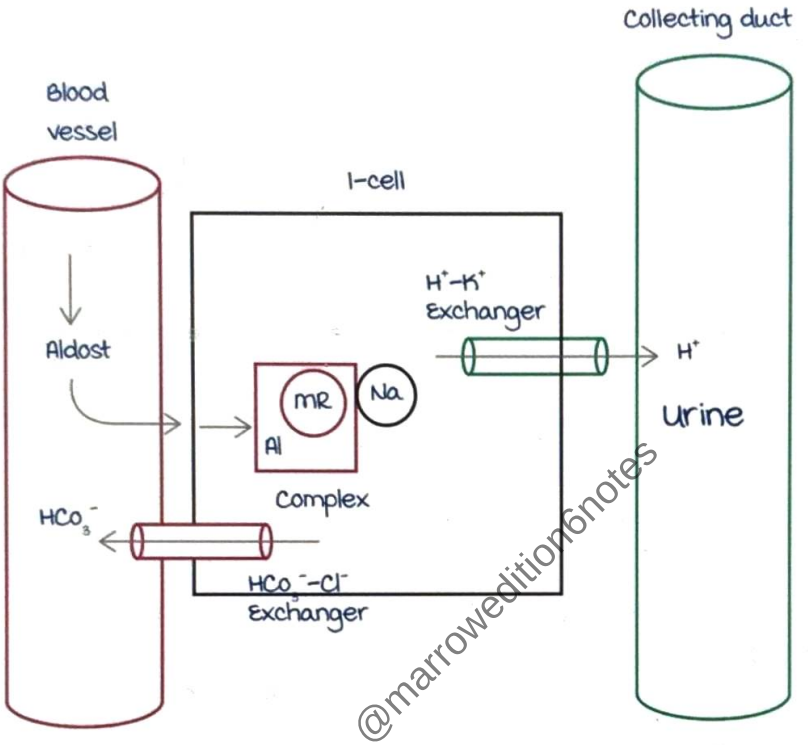
2. MR-Aldosterone complex moves to the nucleus for the upregulation of transcription of a ROMK protein.
(Renal Outer Medullary potassium channels)

This protein incorporated into the apical end serves as a channel for excretion of potassium ions.

Aldosterone on I-cell :

1. Aldosterone regulates the H^+-K^+ exchanger channel protein at the apical side which leads to the excretion of H^+ ion into urine.

2. In the intercalated cell, there is a $HCO3^-$ - Cl^- ion exchanger on the basal side. This helps to bring in bicarbonate ions into blood.



Intercalated cells are upregulated during acidosis and called as Acid-base cell.
During acidosis, intercalated cells help to push acid out into urine and at the same time reabsorb bicarbonate into blood.

Regulation of aldosterone 00:30:44

Most important regulating factor : Hyperkalemia.
It is part of [illegible] Angiotensin Aldosterone System, which primarily functions to increase sodium reabsorption.
ACTH can transiently increase aldosterone level.

60% of Aldosterone is bound to protein.
$T_{1/2}$ of Aldosterone is 20 mins.

Active space

Glucocorticoids

00:33:32

Cortisol : 90–95% is protein bound.

Binding protein : CBG (Cortisol Binding Protein)/ Transcortin.

$T_{1/2}$ is 60–90 mins.

Receptor : Glucocorticoid receptor (GR).

Location : Inactive receptor is present in the cytoplasm.

When combined with cortisol, the active complex moves to the nucleus for all actions.

Actions :

1. Protein metabolism :
   - Muscle :
     - Proteolysis → Alanine release (Gluconeogenesis).
     - Excess cortisol → Excess proteolysis → Muscle weakness (may be the presenting feature of Cushing's syndrome).
   - Liver : Increases plasma protein synthesis.
2. Carbohydrate metabolism :
   - Increases blood glucose levels (Hyperglycemic) by neoglucogenesis. Cushing's syndrome → High risk to develop diabetes mellitus (Adrenal diabetes).
3. Lipid metabolism :
   - Causes lipolysis → Increases free fatty acid levels.
   - But chronic excess cortisol → Lipogenesis → Weight gain and obesity.
4. Anti inflammatory action : Only in large doses.
   - Reduces prostaglandin synthesis.
   - Reduces histamine.
   - Increases lipocortin → Inhibits phospholipase A2.
   - Reduces interleukin 2 levels.
5. On blood cell :
   - Decreases eosinophils : Anti allergic action.
   - Decreases lymphocytes.
   - Increases neutrophils (transient).
   - Increases RBCs.
6. On Bone :
   - Activates osteoclasts.
     - Therefore, excess leads to fractures.

7. On GIT :

   Increases acid production.

   Excess level of cortisol can lead to peptic ulcer.

8. Reproductive functions :

   Inhibits GnRH, therefore negative regulator for reproductive functions.

9. Permissive action on catecholamines.

   Lipolysis and bronchodilation become more pronounced.

Clinical scenarios

00:49:36

1. Patients with Liddle's syndrome usually present with?

   A. Hyponatremia.
   B. Hypertension.
   C. Hyperkalemia.
   D. Metabolic Acidosis.

Explanation: Liddle's syndrome presents with increased ENaC activity leading to hypertension.

2. Clinical consequences of excess aldosterone are all except?

   A. Muscle weakness.
   B. Metabolic alkalosis.
   C. Hypertension.
   D. Hyperkalemia.

Explanation: aldosterone increases excretion of potassium and hence causes hypokalemia.

3. All of the following are seen in Cushing's syndrome except?

   A. Muscle weakness
   B. Eosinopenia.
   C. Weight gain.
   D. Hypoglycemia.

Explanation : Cortisol leads to hyperglycemia.

CALCIUM HOMEOSTASIS

Introduction 00:00:33

Calcium level is regulated completely by hormones.
Normal Ca^{2+} level : 8.7–10.2 mg/dL.

Total calcium exists in 2 forms :
Free Ca^{2+}/ionic Ca^{2+} : Most active form responsible for all the actions of Ca^{2+} (eg : muscle contraction, vasoconstriction, exocytosis, 2nd messenger etc).
Bound form/inactive form : Binding protein is albumin.

The ratio of free and bound Ca^{2+} is altered by :

- pH of blood.
- Serum Albumin levels.

Acidosis : Low blood pH, high H^+ ions.
H^+ ions competes with Ca^{2+} to bind to albumin.
Acidosis → increased H^+ ions → binds to albumin → decrease in bound Ca^{2+} → increase in free Ca^{2+} → hypercalcemia.

Alkalosis → fall in free Ca^{2+} levels → hypocalcemia.
Respiratory alkalosis → hypocalcemia → tetany (hypocalcemic tetany).

Tetany is characterized by hyperexcitability.
State of low Ca^{2+} → frequent opening of Na^+ channels → increased frequency of action potentials → hyperexcitability.

Tetany occurs at Ca^{2+} levels ~ 6mg/dL.
Chvostek's sign : Tapping of facial nerve leads to twitching of facial muscles because of hyperexcitability.
Trousseau's sign : Find systolic BP → Rise pressure above systolic BP for 5 mins → development of carpopedal spasm.
Calcium regulation :

Active space

Three hormone three organ model :

Three hormones :

1. Parathormone : Increases Ca^{2+} levels.
2. Vitamin D : Increases Ca^{2+} levels.
3. Calcitonin : Decrease Ca^{2+} levels.

Three organs :

1. Bone : Bank for Ca^{2+}.
2. Gastrointestinal tract (dietary calcium absorption).
3. Kidneys (excretion of excess calcium).

Parathormone/PTH 00:12:04

Secreted by chief cells of parathyroid gland.

It is a peptide hormone containing 84 amino acids in its structure.

Actions of PTH :

1. Bone :

   Osteoblasts help in bone formation while osteoclasts help in bone resorption.

   PTH receptor is found in the osteoblast.

   - PTH → Acts on PTH receptors on osteoblasts → RANK ligand released → Induces differentiation of osteoclasts for bone resorption.

   RANK ligand blocker : Denosumab (prevents bone resorption - osteoclasts don't differentiate) is used in the treatment of osteoporosis.

   - Osteoprotegerin/OPG is produced by osteoblasts which prevents bone resorption (protects bone).
   - PTH inhibits OPG and causes bone resorption.
   - Osteoclasts act by dissolving calcium phosphate crystals in bone (Hydroxyapatite crystals), leading to increase in Ca^{2+} and PO_4^{2-} levels in the blood.

   Continuous administration of PTH → Bone resorption.

   Intermittent administration of PTH → Bone formation.

Teriparatide (drug form of PTH) : Intermittent administration is used to treat osteoporosis.

2. Kidneys :

PTH increases Ca^{2+} reabsorption from distal tubules.

PTH acts at proximal convulated tubule causing PO_4^{2-} excretion by inhibiting Na^+-PO_4^{2-} cotransporter.

Overall action of PTH : Increases Ca^{2+} ; Decreases PO_4^{2-}.

Hence, PTH is also called Phosphatonin & Phosphate terminating hormone.

3. Gastrointestinal tract :

Increases Vitamin D levels in GIT. Only Vitamin D helps in the absorption of Ca^{2+} from GIT.

PTH indirectly acts on GIT through vitamin D.

Most important stimulus for PTH release is hypocalcemia.
High levels of Ca^{2+} suppresses PTH release.

Low calcium induces CaSR, while high calcium suppresses CaSR (Calcium Sensing Receptor) present in chief cells of parathyroid glands.
CaSR inactivating mutations : PTH is not suppressed, leading to Familial hypocalciuric hypercalcemia.

Vitamin D/sunshine vitamin 00:30:14

Lab investigations assess Vitamin D status by estimating levels of 25-OH Vitamin D3 in the liver.

Formation of 1, 25 di-hydroxy vitamin D3 will be impaired in chronic renal failure/CKD (no action of 1α-hydroxlase).

1-α-Hydroxylase (rate limiting enzyme) is always stimulated by low levels of Ca^{2+} and increase in PTH.

In high levels of calcium, Kidneys will produce 24, 25 di-hydroxy vitamin D_3. This does not have vitamin D activity.
Vitamin D activity is not required in high levels of calcium.

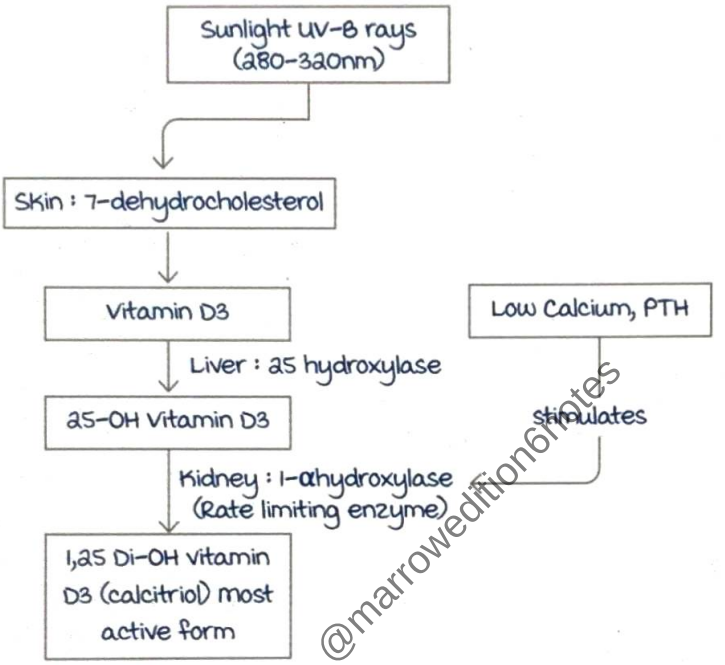
Actions of Vitamin D :

1. It is the only hormone which acts in GIT for Ca^{2+} regulation.

   Ca^{2+} is absorbed exclusively from duodenum by :

   - Upregulating Calbindin protein.
   - Increased expression of Ca^{2+} ATPase.
   - Increased expression of alkaline phosphatase.

   All these mechanisms increase calcium absorption.



2. Bone :

   If Ca^{2+} levels are high in the blood, Vitamin D helps in bone formation.

   If Ca^{2+} levels are low in blood, vitamin D favors bone resorption.

   mechanism of bone resorption is similar to PTH.

   Vitamin D → Vit. D receptor on osteoblast → releases RANK ligand → differentiation of osteoclasts → bone resoprtion.

3. Kidneys :

   Vitamin D increases the reabsorption of both Ca^{2+} and PO_4^{2-}.

Overall action of Vitamin D : Increases Ca^{2+} and PO_4^{2-}.

Active space

Calcitonin 00:42:16

Formed by parafollicular C cells of thyroid gland.
Calcitonin is the only hormone having a direct receptor on osteoclasts.

Calcitonin inhibits osteoclasts → prevents bone resorption → decreases Ca^{a+} levels.
Also decreases absorption of Ca^{a+} from both GIT and Kidneys.
Drug form of calcitonin : Salcatonin (derived from salmon fish) mimics the action of calcitonin.

Pregnant and lactating mothers → increased loss of Ca^{a+} stores → to meet fetal demands.
Calcitonin prevents excess bone loss → protect bones.

In Medullary carcinoma of thyroid (tumor of parafollicular C cells), calcitonin is used as a tumor marker.

Paraneoplastic syndrome :
Hypercalcemia occurring as a part of malignancies.
For example :

- Squamous cell carcinoma of lung.
- Small cell carcinoma of lung.

This is due to the secretion of PTH_{RP} (PTH Related Peptide) from these malignancies.

Markers of bone formation and resorption 00:50:31

Bone formation markers :

- Osteocalcin.
- Alkaline phosphatase.
- Pro-peptides of type I collagen.

Bone resorption markers :
In blood :

- Tartrate resistant Acid Phosphatase (TRAP).
- matrix metalloproteinases (mmps)
- Cathepsin K.

In urine :

- N and C telopeptides of collagen cross links (NTX and CTX)

MCQs :

Q. Which of the following hormone inhibits bone resorption ?

A. Parathormone.

B. Vitamin D.

C. Parathormone related peptide.

D. Estrogen.

Explanation : Estrogen inhibits bone resorption by stimulating OPG (osteoprotegrin).

Q. Familial Hypocalciuric Hypercalcemia (FHH) is due to inactivating mutation of ?

A. Vitamin D receptor.

B. Calcitonin receptor.

C. Calcium sensing receptor.

D. Thyroxine receptor.

Q. Most specific test for diagnosis of Vitamin D deficiency is ?

A. Osteoprotegerin levels.

B. 1 alpha hydroxylase levels.

C. 25 OH vitamin D levels.

D. 1,25 Di OH vitamin D levels.

Active space

MALE REPRODUCTION

Introduction 00:00:45

The gonads develop into male gonads if there is presence of Y chromosome.

Short arm of Y chromosome has SRY gene (Sex determining Region in Y chromosome).

SRY gene codes for a transcription factor called testes determining gene product.

This transcription factor influences the following cells in the testes :

- Leydig cells : To secrete testosterone, which induces wolffian duct stimulation.
  Leads to development of male sex structures.
- Sertoli cells : Secretes Anti-Mullerian Hormone (AMH) which inhibits mullerian derivatives which leads to the suppression of development of female structures.

Only in the absence of SRY gene, the gonads develop into female.

SRY estimation is important for sex differentiation and identification.

Puberty 00:06:09

Hypothalamus : Secrets Gonadotrophin Releasing Hormone (GnRH).

Before puberty :

GnRH secretion is continuous which results in the inhibition of FSH and LH release.

Pulsatile secretion of GnRH marks the onset of puberty.

This pulsatile release of GnRH leads to the release of FSH and LH from anterior pituitary.

The pulsatile release of GnRH is inhibited by GABA and melatonin before the onset of puberty.

During puberty :

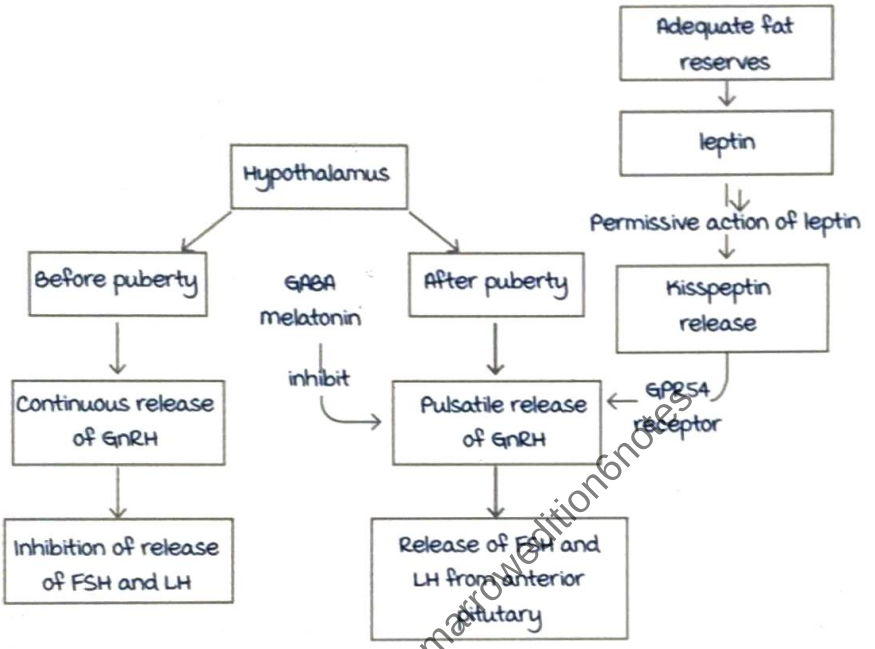
There is increase in the level of Kisspeptin, which acts on GnRH neurons through G-protein coupled receptors (GPR54).

This leads to the onset of pulsatile secretion of GnRH.

Puberty begins when there is adequate body fat reserves.

Peripheral signals (leptin) increase Kisspeptin levels.

This action of leptin is called permissive action to initiate puberty.



Spermatogenesis

00:12:27

Site : Seminiferous tubules of testes.

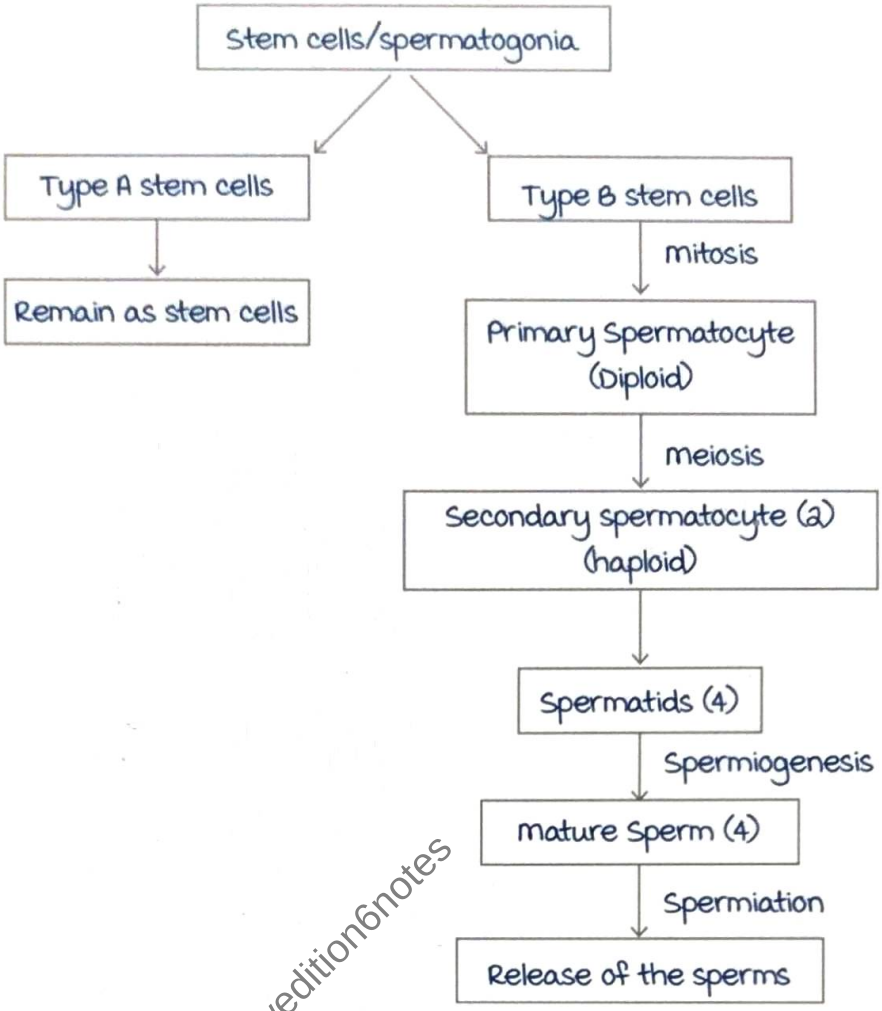
It takes 74 days for the entire process to complete.

Testicular temperature is 1 to 2° lower than the body temperature because of the requirement of low temperatures for the process of spermatogenesis.

Regulation of spermatogenesis is by the following hormones :

- Testosterone.
- FSH/Follicle Stimulating Hormone.
- LH/Luteinizing Hormone.
- Growth hormone : It promotes early division of spermatogonia.

Active space



Cells in the testis

00:19:57

Leydig cell : Source of testosterone.

Sertoli cells.

Functions of sertoli cells :

- Provides nutrition to the developing sperms, hence called nurse cells.
- Forms the blood testes barrier (formed by the tight junctions between the two adjacent sertoli cells).
- Produces androgen binding protein (binding protein of testosterone).
- Anti-Mullerian hormone secretion.
- Source of aromatase, required to form estrogen.
- It produces inhibin (negative feedback regulation for FSH).
- Phagocytic function : Phagocytosis of the dead sperm cells.

Semen

00:25:15

Contains sperms and fluid component.

pH : 7.4.

Number of sperms : 90 – 120 million/ml.

Sperm acquires motility in epididymis.

Sperm maturation : Occurs in epididymis.

- Increase in forward motility : Due to Ca^{2+} channel called catsper.
- Increased ability to fertilize ovum.
- Maturation of acrosome.

Sperm capacitation : Occurs in the female genital tract following ejaculation.

- Acrosome reaction occurs which gives the ability for the sperms to penetrate zona pellucida (ovum) leading to fertilization.
- Vaginal secretions are also known to increase sperm motility.

Fluid component of semen :

Seminal vesicles :

- 60 % of the volume of semen is contributed by seminal vesicles.
- Fructose (energy source) : GLUT-5 is the transporter for fructose uptake in sperms.
- Antioxidants (vitamin C).
- Prostaglandins (PGs) : Reacts with cervical mucus and make it penetrable by sperm.

  Also induces peristaltic contractions in the female genital tract and thus propel the sperms further.
- Phosphoryl choline : It is estimated in Florence test to detect seminal stains in rape victims.

Prostate gland :

- 30% of the volume of semen is contributed by it.
- Fibrinolysin : Liquefaction of semen when it is left for 15 to 30 min is due to fibrinolysin.

- Acid phosphatase.
- Spermin : It can also be estimated in Barberio's test to detect seminal stains.

Vas deferens :

- 10% of the volume of semen is contributed by it.
- Bicarbonate buffer.
- Phosphate buffer.

Stages of male sexual act

00:37:13

- Erection of penis :
  1. Parasympathetic nervous system (S2,S3,S4) : Acetyl choline.
  2. NANC system (Non Adrenergic Non Cholinergic system) : NO (Nitric Oxide).
  3. These 2 systems cause dilation of arterioles leading to compression of veins which eventually leads to engorgement of the penis with blood.

NO acts through cGMP (2nd messenger).
cGMP is degraded by phosphodiesterase enzyme.
Phosphodiesterase inhibitors : Sildenafil (increases NO levels).

- Ejaculation of semen :
  1. Emission : Movement of semen into urethra.
  2. Ejaculation proper : Release of semen from urethra.

  It is under sympathetic control (T12 – L2).

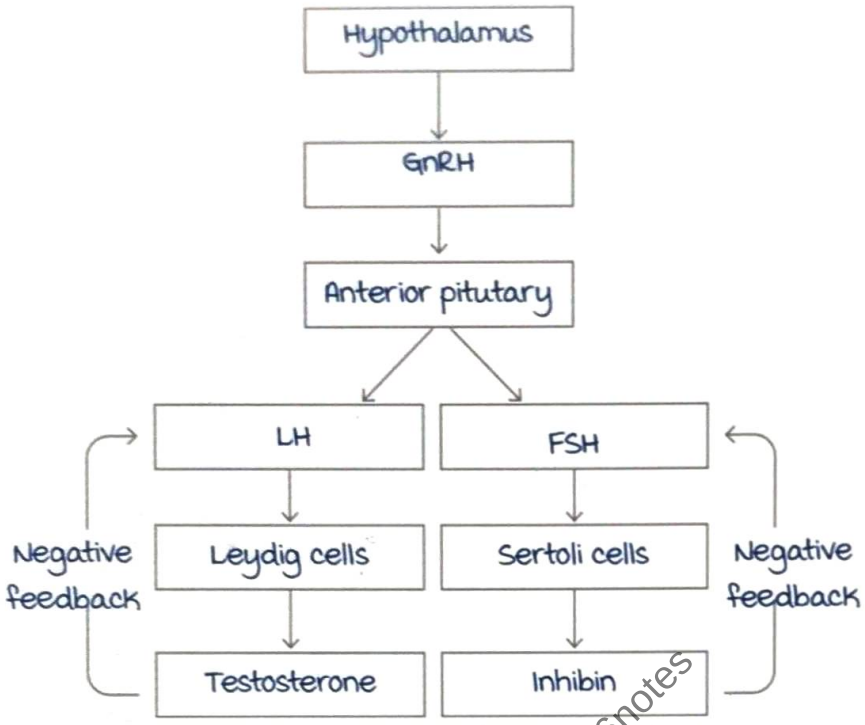
- Resolution (detumescence) :

  Constriction of arterioles occurs due to :
  1. Norepinephrine.
  2. Endothelin.

Life span of sperms following ejaculation : 24 to 48 hours.

Regulation of male reproduction 00:44:46

Two cell two gonadotrophin model :



Male sex hormone : testosterone 00:47:40

Important functions of testosterone :

- Development of gonads : Wolffian stimulation.
- Helps in the growth of internal genital organs.
- Protein anabolic effect : To increase the muscle mass in men.
- Increases RBC count in men.
- Libido.

$$\text{Testosterone} \xrightarrow[\text{Reductase}]{5\alpha} \text{DHT.}$$

(more potent)

DHT level raises during puberty and has the following actions :

- External genital organ growth
- Facial hair growth in men.
- Acne development in men.

Active space

- Temporal recession of hairline.
- Prostrate growth.

Benign prostatic hyperplasia is treated with 5α Reductase inhibitor (Finasteride) which decreases the formation of DHT.

Q. Children fail to enter puberty when mutation is found in ?

A. Serotonin receptor.
B. Dopamine receptor.
C. GPR 54.
D. Glycine receptor.

Q. Reduced sperm motility in Kartagener syndrome is termed as :

A. Aspermia.
B. Azoospermia.
C. Necrozoospermia.
D. Asthenospermia.

Aspermia : Absence of sperms in semen.
Azoospermia : Reduced sperm count.
Necrozoospermia : Presence of dead sperms.
Asthenospermia : Reduced sperm motility.

Q. All of the following are seen in androgen insensitivity syndrome except ?

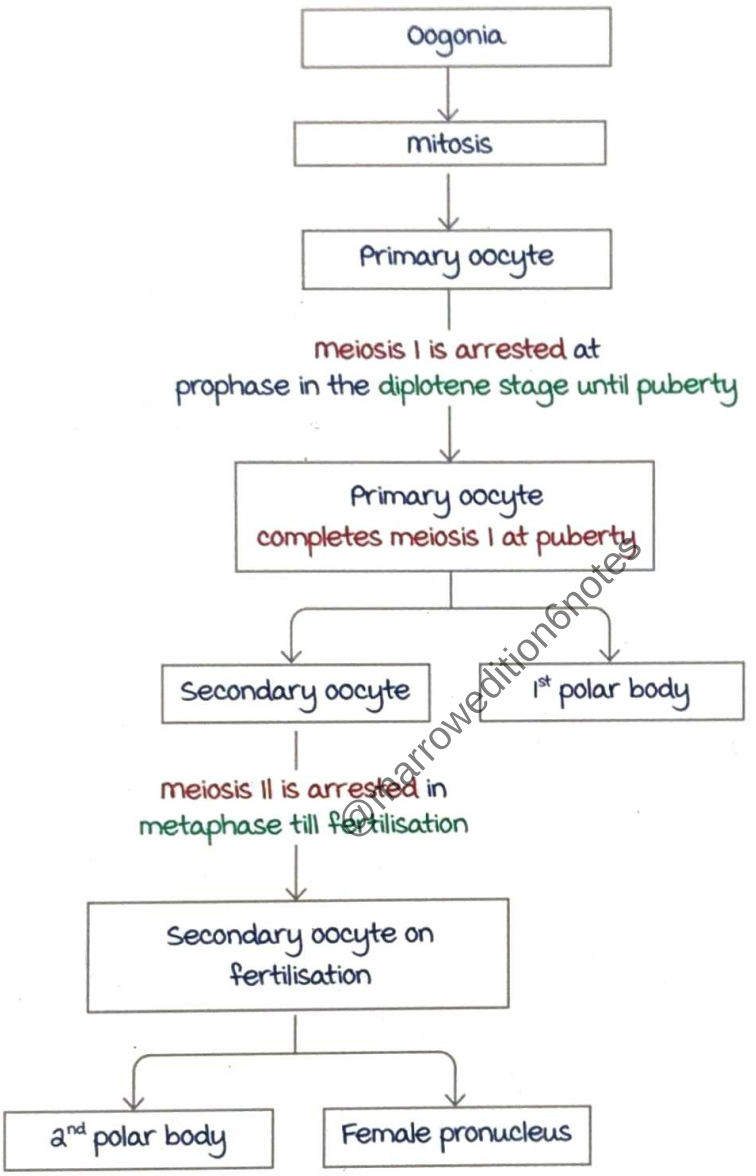
A. Female phenotype.
B. Normal breast development.
C. Short vagina.
D. Well developed uterus.

AIS is due to mutation in androgen receptor leading to development of resistance to testosterone and DHT.

FEMALE REPRODUCTION

Oogenesis

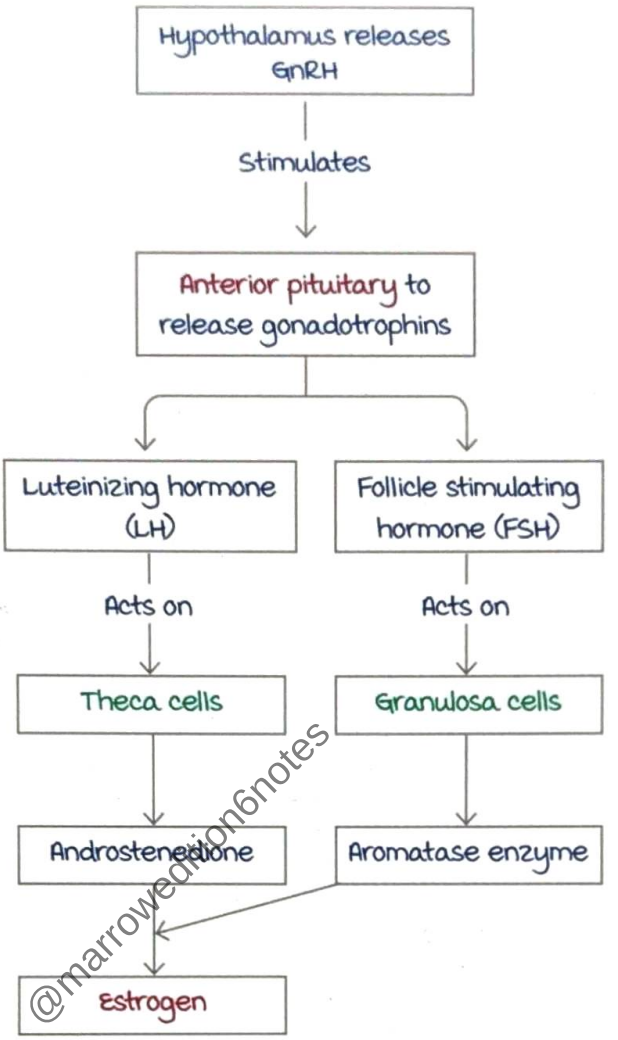
00:00:39



Active space

Two cell two gonadotrophin model

00:04:38



Menstrual cycle

00:07:24

menstrual cycle happens in humans.

mammals other than humans do not menstruate.

They have estrous cycle.

Ovarian cycle :

Average of 28 day cycle.

Follicular phase :

Pertains to follicular growth.

Active space

FSH : 1st hormone to rise in the menstrual cycle.

- Under its influence, 10 – 15 follicles grow.
- Only one becomes dominant follicle → Graaffian follicle.

  Highest number of FSH receptors.

  Maximum aromatase activity.

  Maximum estrogen production.
- FSH surge : Lyses follicular wall.

  Helps in ovulation.

Estrogen : 2nd hormone whose levels rise.

- Level is highest just before ovulation.
- Responsible for the rise of LH (positive feedback).

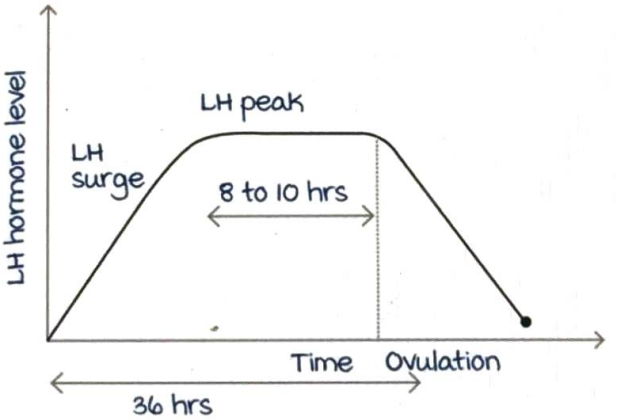
LH : Rises due to rising levels of estrogen. 3rd hormone to rise.

- LH surge → Happens around 36 hours before ovulation.

  Aids 1°oocyte to complete meiosis I → Ovulation.

  Progesterone formation.

  Synthesis of prostaglandins.
- LH peak → 8 – 10 hours before ovulation.



Luteal phase

00:17:22

Graaffian follicle bleeds inside → Forms Corpus hemorrhagicum.

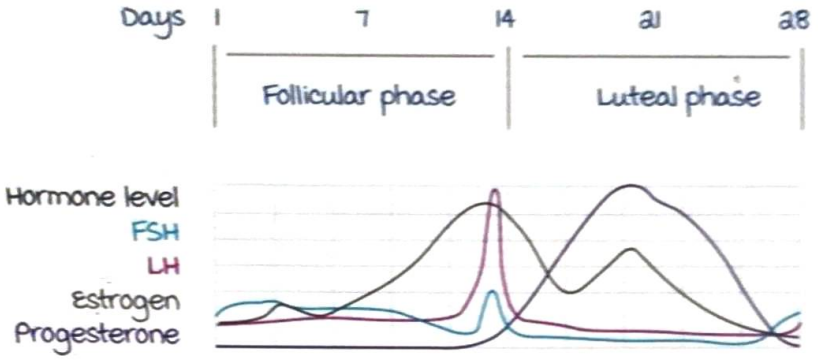
The clots within are converted to yellow coloured luteal cells by LH hormone.

Progesterone : 4th hormone to rise.

- Secreted from luteal cells of corpus luteum aided by LH hormone.

On the 10th day after ovulation (24th day of the menstrual cycle) :

- Corpus luteum degenerates.
- Leads to menstrual blood loss.



Endometrial cycle

00:22:29

1. Proliferative phase : 6 – 14 days.
2. Secretory phase : 15 – 28 days.
3. Menstrual phase : 1 – 5 days.

Proliferative phase : Restoration of lost epithelium.
Under the influence of estrogen,

- Uterine endometrial thickness increases rapidly.
- Uterine glands lengthen, but do not secrete.

Secretory phase : Preparation for implantation.
Also called progestational phase.
Under the influence of progesterone,

- Uterine endometrial thickness reaches its maximum.
- Uterine glands secrete clear fluid.
- Blood vessels undergo spiralling.

Menstrual phase :

- Shedding of endometrium.
- Superficial 2/3rd is lost.

- Spiral artery undergoes constriction, ischemia and degeneration → PGF_{2} alpha → menstrual blood loss.

Cervical changes 00:28:07

Affects the cervical mucus.

Estrogen → Thin and watery → Easy movement of sperm.

- more elastic.
- Highly stretchable : Spinnbarkeit effect.
- Microscopically : High sodium chloride & low protein content → Fern pattern.

Post ovulation, under the influence of progesterone,

- Cervical mucus becomes thick.
- Elasticity is lost.

Vaginal changes 00:30:56

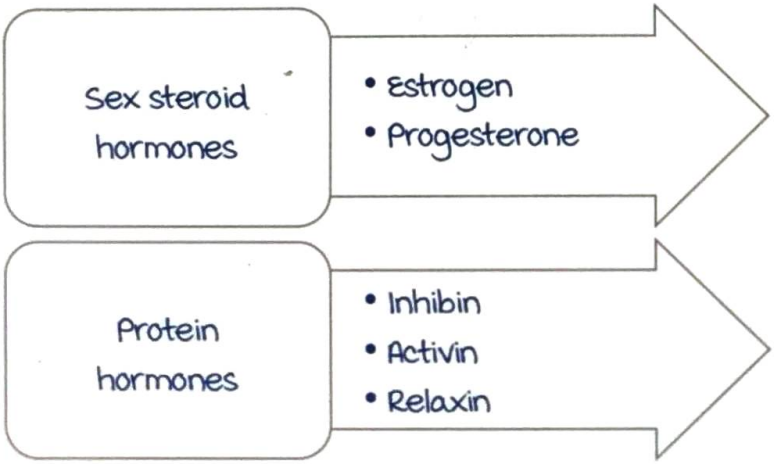
Parabasal cells : Lack of hormonal activity.

Intermediate cells : Predominant under the influence of progesterone.

Superficial cells : Predominate under the influence of estrogen.

Ovum survives up to 24 hours following ovulation (sperm survives for 24 – 48 hours).

Hormones 00:32:58



Active space

Estrogen :

Sources :

- Granulosa cells : Primary source.
- Corpus luteum.
- Placenta.

It is a C_{18} steroid.

Depending on the age, the form of estrogen varies :

- Estradiol (E_2) seen in reproductive age group.
- Estriol (E_3) seen in pregnancy.
- Estrone (E_1) seen in menopause.

Actions of estrogen :

On uterus :

Estrogen primed uterus : Increased number of gap junctions make it more contractile, i.e., more excitable → more sensitive to oxytocin.

Favors delivery in normal labour.

On breast :

- Considered the growth hormone of breast.
- Promotes ductal growth in breast.

On bone :

- Considered bone friendly → Produces Osteoprotegerin → Inhibits bone resorption by binding to RANK-L.

On heart : Heart friendly.

- Produces vasodilation by increasing NO levels.
- Inhibits platelet activation.

On liver : Plasma LDL cholesterol lowering effect.

On brain : Neuroprotective.

On kidneys : Conserve salt and water.

Progesterone

00:41:54

In uterus : Anti estrogenic.

- Less excitable.
- Less contractile.

On breast : Favors lobular & alveolar growth.

On brain :

- CNS depressant.
- Alters set point for thermogenesis → basal body temperature assessed for ovulation. Basal body temperature rises by 0.5 – 1°F, due to thermogenic action.

On respiratory system :

- Stimulates ventilation.
- Increase in respiration → In luteal phase, alveolar pCO_a is lower.

On Kidneys : Salt & water excretion (steroids are usually water and salt retainers).

Estrogen receptors :

1. ER alpha : Uterus and heart.
2. ER beta : Ovaries and prostate gland.

Protein hormones 00:47:21

Inhibin :

Inhibin A :

- From corpus luteum.

Inhibin B :

- From granulosa cells.
- Inhibitor for FSH (negative feedback system).

Activin : Activates the synthesis and secretion of FSH.

Follistatin : Decreases FSH levels.

Relaxin :

- Produced from uterus, placenta.
- Relaxes the pubic symphysis.
- Helps in dilation of uterine cervix.
- Aids in normal labor.

Placental hormone 00:50:39

Human chorionic gonadotrophin (HCG).

Glycoprotein hormone.

Two subunits : α and β.

α : Similar to LH, FSH & TSH.

β : Specific (β HCG).

Actions resemble LH.

Produced from syncytiotrophoblast.

Functions of HCG :

- Maintains corpus luteum following fertilization.
- Increases progesterone levels.
- Increases placental steroid hormone synthesis.
- Increases synthesis of relaxin.
- Prevents fetal rejection.

Lactation 00:54:37

Mammogenesis : Breast growth.

- Estrogen → Ductal growth.
- Progesterone → Lobulo alveolar development.

Lactogenesis : Production of milk.

- Prolactin.
- Insulin.
- Growth hormone.

Galactokinesis :

- Suckling → Hypothalamus activation → Release of Oxytocin → Posterior pituitary → Oxytocin release → milk let down reflex (neuroendocrine reflex).
- Inhibited by anxiety, pain and depressive disorders.

Galactopoiesis :

- Maintenance of lactation by prolactin.

Q. Inadequate growth and function of the corpus luteum leading to inadequate progesterone secretion is seen in ?

A. Follicular phase defect.
B. Proliferative phase defect.
C. Before puberty.
D. Luteal phase defect.

Ans : D.

Q. Drug that blocks the enzyme aromatase which is required for estrogen synthesis is ?

A. Clopidogrel.
B. Anastrozole.
C. Amphotericin B.
D. Aspirin.

Ans : B.

Q. Which of the following hormone is responsible for milk let down reflex ?

A. Prolactin.
B. Estrogen.
C. Oxytocin.
D. Progesterone.

Ans : C.

EXERCISE PHYSIOLOGY

Impotance of exercise :

Used as CPET/ Cardio Pulmonary Exercise Testing.
AKA Exercise Stress test & is used to diagnose cardiovascular and respiratory disorders.

Exercise as a form of lifestyle modification and treatment in diabetes.

Exercise causes release of endorphins which are mood enhancers.

Changes in skeletal muscle during exercise 00:02:40

Force generation by shortening / tension generation.
Maximum contractile force = 3-4 Kg/cm^2.

Types of exercise:

- Isotonic exercises / dynamic exercises
  - Tension → Remains same.
  - Length (of muscle) → Changes.
  - E.g. : Treadmill running.
- Isometric exercises / static exercises.
  - Tension → Changes.
  - Length (of muscle) → Remains same.
  - E.g : Pushing a wall.

System	Energy source	Duration
Phosphogen system.	Creatine phosphate.	(8–10) seconds. Short bursts of activity like 100m sprints.
Glycogen lactic acid system.	Anaerobic glycolysis (causes pain and fatigue)	(1.3 to 1.5) minutes.
Aerobic system.	ATP.	Unlimited time (depending upon [illegible] in blood)
Long standing activities (endurance activity).	Carbohydrate rich diet causes increased muscle glycogen storage.	Upto 4 hours.

Type I muscle fibres are slow, small, red and are more suitable for long standing activities.

Changes in skeletal muscle during exercise 00:13:38

Blood flow at resting state = 2–3 ml/100gm/min → Lowest.

Blood flow during exercise = 80 ml/100gm/min → Increases more than 20 times.

Redistribution of blood flow :

- Decreased blood flow → Kidneys, splanchnic circulation (diverted).
- Increased blood flow (to exercising muscle) → Heart, exercising skeletal muscles.
- No change in blood flow → Brain (autoregulation).
- Initially decreases, later increases → Cutaneous circulation /skin (heat dissipation).

Active space

Exercise Hyperemia :

During exercise, muscle blood flow increases due to increased metabolism, leading to accumulation of end products like H^+, K^+ & lactate, which are vasodilators.

Changes in CVS during exercise 00:20:30

Increase in cardiac output (CO) :

Untrained individuals → Increases 4 fold.

well trained individuals→ Increases is 7 fold.

Cardiac output = Heart rate x Stroke volume.

Increase in cardiac output during exercise is mainly due to increase in heart rate.

Anticipatory tachycardia :

Thinking about exercise → Increased heart rate.

Due to proprioceptors in joints.

Blood pressure changes :

Isotonic exercises	Isometric exercises
Increase in SBP. Decrease in DBP. Cause: Local accumulation of vasodilators. Relaxation of blood vessels. Total peripheral vascular resistance/TPR decreases causing decrease in DBP.	Increase in SBP. Increase in DBP. Cause : Sustained muscle contraction. muscle of blood vessels are compressed. Increase in TPR.

Exclusively during exercise, we see increase in MSFP/ mean Sympathetic filling pressure because :

Sympathetic stimulation causes venoconstriction.

Skeletal muscle contraction causes muscle blood vessels compression.

Increase in MSFP, increases the blood going to heart.

Respiratory changes during exercise 00:29:15

1. Due to increase in respiratory rate → Increase in pulmonary ventilation.

Anticipatory tachypnoea :

Increase in respiratory rate even before onset of exercise due to impulses generated from proprioceptors.

pO_a, pCO_a, and pH in blood → Normal.

Stimulation of respiration is due to :

- Release of K^+ ions produced by muscle → Stimulate chemoreceptors → Increase in respiratory rate.
- Increase in body temperature.

2. Increase in oxygen consumption :

Resting O_a consumption = 250 mL/min = 1 MET (metabolic equivalent).

During exercise, MET value increases :

maximum O_a consumption → VO_a max.

At the end of exercise → O_a consumption → Peak VO_a.

O_a consumption :

At the onset of exercise → O_a supply comes from O_a stores (hemoglobin / myoglobin).

At the end of exercise → O_a debt incurred that is repaid by increased respiratory rate, fed O_a consumption & EPOC (Excess Post exercise O_a Consumption).

3. Increase in diffusion capacity of lungs → Increases diffusion of gases in lungs.

4. Release of oxygen to tissues :

Oxygen dissociation curve → Shift to the right.

5. Tissues extract more oxygen which is reflected as Increase in arterio-venous oxygen difference.

Effects of Smoking → Decreased work capacity due to :

- Constriction of bronchioles : Increase in resistance.
- Cilia are paralyzed.
- Swelling of epithelial cells.
- Increase in fluid secretion into the bronchial tree.

Q. To dissipate body heat generated during exercise which of the following circulation increases?

A. Splanchnic circulation.

B. Cerebral circulation.

C. Renal circulation.

D. Cutaneous circulation.

Answer : Cutaneous (Initially decreases later increases).

Explanation : Splanchnic circulation decreases.

Cerebral circulation is maintained.

Renal circulation decreases.

Q. All of the following are true regarding dynamic exercise except?

A. Systolic BP increases.

B. Heart rate rises.

C. Diastolic BP increases.

D. Stroke volume increases.

Answer : Diastolic BP increases.

Explanation : Diastolic BP decreases.

Q. If a person stops doing exercise prematurely due to cardiorespiratory limitations, the highest oxygen uptake by that individual at the end of the test is called?

A. VO_a max.

B. Peak VO_a.

C. metabolic equivalent (MET).

D. Anaerobic threshold.

Answer : Peak VO_a.

Active space

REGULATION OF BODY TEMPERATURE

Introduction :

Normal oral temperature :

36.8 ± 0.4°C or 98.2 ± 0.7° F

Body temperature variation based on circadian rhythm :

- Lowest : 6 am in morning.
- Highest : 4 to 6 pm in evening.

Humans are homeotherms :

Even if the environmental temperature fluctuates, our body temperature is maintained because of temperature regulation system.

Poikilotherms/cold blooded animals : Body temperature is governed by environmental temperatures.

Heat

00:03:46

Increase in body heat causes protein denaturation.

The proteins which are critical enzymes lose their function.

Cold :

Results in formation of crystals (e.g., ice crystals) cause mechanical tissue damage.

Transient Receptor Potential Channels (TRPs) :

Sensors/receptors for detection of heat & cold

For heat : $TRPV_1$ (V-Vanilloid), $TRPm_2$ and m_3, $TRPA_1$

For Cold : $TRPm_8$ (m-menthol).

Calorie (Kilocalorie) is unit of heat measurement :

It is the amount of heat required to rise the temperature of 1 Kg of water by 1°C.

Active space

Source of heat generation :

Metabolism : O_2 consumption & CO_2 production.

For measurement, we use indirect calorimetry.

Respiratory quotient (Rq) :

Volume of CO_2 produced for given volume of O_2 consumed.

$$Rq = \frac{\text{Volume of } CO_2 \text{ produced}}{\text{Volume of } O_2 \text{ consumed}} = \frac{VCO_2}{VO_2}$$

Rq for Carbohydrates : 1.

Rq for Proteins : 0.8.

Rq for Fats : 0.7.

Rq for mixed diet : 0.82.

Respiratory Exchange Ratio (RER) :

If all CO_2 produced is completely expelled by lungs known as steady state. In steady state, Rq = RER.

Sources of heat loss :

Evaporation : Sweating.

Conduction : Direct transfer of heat to cooler objects.

Convection : Loss of heat to air currents.

Radiation : Loss of heat through electro magnetic waves.

Regulation of body temperature 00:14:14

Hypothalamus :

Anterior hypothalamus :

When individual is exposed to heat, anterior hypothalamus (preoptic) regulates :

- Sweating.
- Vasodilation.
- Increase in thirst sensation.

In response to cold, posterior hypothalamus regulates :

- Shivering.
- Vasoconstriction.
- Increase in urinary frequency.

Body temperature regulation is anticipatory control/ feed forward control system.

Skin temperature is known as shell temperature.

Internal organ temperature is known as core temperature.

When shell temperature falls, hypothalamus anticipates that core temperature is about to fall, and thus maintains core temperature. This control is called anticipatory control/ feed forward control system.

Heat disorders

00:18:55

Fever :

Fever is alteration in body temperature set point.
Fever causing agents are known as pyrogens.
Exogenous pyrogens like endotoxins of gram negative bacteria.
Endogenous pyrogens like IL 1, IL 6, TNF, ciliary neurotrophic factor, interferon alpha (used in treatment of hepatitis, side effect : Fever).

As pyrogens cannot cross the blood brain barrier, they use Organum Vasculosum of Lamina Terminalis (OVLT) which is outside the blood brain barrier. OVLT is close to hypothalamic temperature regulating area. Hence pyrogens alter the temperature set point in hypothalamus.

All pyrogens increase the levels of prostaglandin E_a/PGE_a.
PGE_a acts on EP_3 receptors and increases cAMP causing alteration of temperature set point resulting as fever.
PGE_a also causes myalgia, arthralgia.
Antipyretics acts by reducing PGE_a formation.
Body defense mechanism is enhanced by rise in body temperature/fever.

Other heat disorders :

1. Heat cramps is a mild heat disorder.
   Caused by working in hot environment.
   Thermoregulatory mechanism is intact, causes profuse sweating and loss of electrolytes.
   Results in muscle pain and muscle cramps.
   Treatment : Electrolyte replacement fluids.

2. Heat syncope : Is a mild heat disorder.
   Caused by prolonged standing and working in hot environment.
   Thermoregulatory mechanism is intact which causes vasodilation and venous pooling thereby reducing cardiac output, diastolic filling to heart & blood flow to brain.
   This results in syncopal attack and unconsciousness.
   Treatment : Recovered by lying down.

Hot environment

↓

Thermoregulatory mechanism

↓

Vasodilation

↓

Venous pooling

↓

decrease in CO

↓

decrease blood flow to heart and brain

↓

Heat syncope

3. Heat exhaustion/heat collapse :

Symptoms : Dilated pupils, unconsciousness.

Mechanism : Excessive vasodilation causing reduced diastolic filling to heart.

Here the thermoregulatory mechanism is intact.

Treatment : Lie them down + fluid replacement.

4. Heat stroke : Is a severe heat disorder.

Thermoregulatory mechanism is not intact.

No sweating is seen.

Can occur in two forms :

1. Classic form : Seen in old age individuals with chronic disorders.
2. Exertional form : Seen in young athletes and soldiers.

Triad of heat stroke :

It is a medical Emergency.

Treatment :

Move them to a cool place, cold water bath, apply cold cloths (meausres of active cooling).

Fluid replacement.

5. Malignant hyperthermia :

Due to overactivity of ryanodine receptors.

Enhanced release of calcium.

Resulting in increased muscle contraction and heat generation.

Treatment : Dantrolene sodium (ryanodine receptor blocker).

Drugs precipitating Malignant Hyperthermia :

Succinylcholine.

Halothane.

Hypothermia 00:38:53

1. Accidental causes :

In cold environment.

Drugs : Barbiturates.

2. Therapeutic hypothermia :

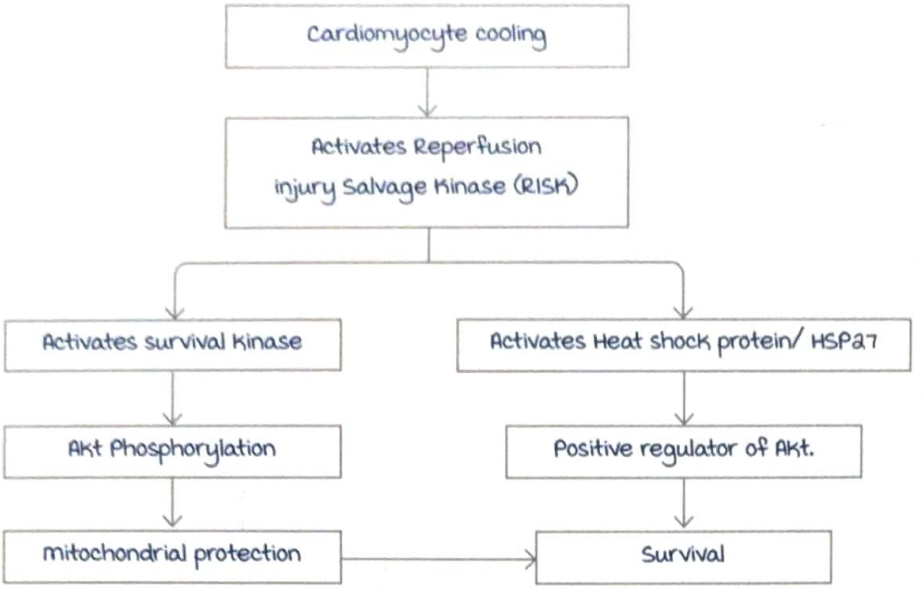
For every 1°C decrease in body temperature, cerebral blood flow reduces by 7%.

This is used during neurosurgical procedures to minimize blood loss.

In acute myocardial infarction, after Return of Spontaneous Circulation (ROSC) can result in death due to oxidative stress.

To prevent this, cardiomyocyte cooling is done.

By reducing the body temperature by 5°C.



Q. Excess calcium release from sarcoplasmic reticulum leading to excessive muscle contraction and increased body temperatures seen in ?

A. Heat cramps.
B. Heat syncope.
C. Heat stroke.
D. Malignant Hyperthermia.

Answer : D. Malignant Hyperthermia.

Q. Which of the following is the most important mediator in altering hypothalamic setpoint during fever ?

A. IL 1.
B. IL 6.
C. PGE2.
D. TNF alpha.

Answer : C. PGE2.

Q. Lesion in which of the following nucleus can cause hyperthermia ?

A. Dorsomedial nucleus.
B. Mamillary bodies.
C. Anterior hypothalamic nucleus.
D. Lateral hypothalamic nucleus.

Answer : C. Anterior hypothalamic nucleus.

Active space